DIETARY AND PHYSICAL ACTIVITY BEHAVIORS, KNOWLEDGE, AND BELIEFS ASSOCIATED WITH POLYCYSTIC OVARY SYNDROME

A Dissertation

Presented to the Faculty of the Graduate School

of Cornell University

In Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

by

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August 2017

OVERVIEW: DIETARY AND PHYSICAL ACTIVITY BEHAVIORS, KNOWLEDGE, AND BELIEFS ASSOCIATED WITH POLYCYSTIC OVARY SYNDROME

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Polycystic ovary syndrome (PCOS) occurs in approximately 7 to 18% of reproductive-aged women worldwide and is characterized by oligo/amenorrhea, hyperandrogenism, and/or polycystic ovaries. Women with PCOS are at higher risk of poor physical and mental health outcomes. Up to 80% of women with PCOS have reported BMI ≥25 kg/m^2, leading researchers to hypothesize that obesity contributes to the development of PCOS. Although poor diet and physical inactivity are known contributors of obesity, it remains uncertain whether these activities can predict the development of PCOS features.

Weight loss interventions are the first recommendation in treating reproductive and metabolic symptoms of PCOS, yet adherence with these interventions varies greatly across PCOS studies. To encourage behavior change, it is essential to understand: 1) the associations between diet and physical activity (PA) behaviors with PCOS and 2) the health-related knowledge and beliefs associated with PCOS. This dissertation addresses these research gaps by investigating the cross-sectional associations between PCOS and dietary and physical activity behaviors, as well as knowledge, and beliefs. Our published narrative review **(Chapter 1)** summarizes the current evidence of the health-related behaviors – PCOS link and identifies gaps in the literature to inform the studies conducted in **Parts 1** and **2** of this dissertation.

Two approaches were used in **Part 1** to investigate the link between health-related behaviors with combined and/or isolated features of PCOS. **Chapter 2** presents a secondary data analysis using data from the longitudinal cohort, Coronary Artery Risk Development in Young Adults (CARDIA) Women's Study. We show that diet quality was associated with PCOS, and that this association varied by race. When macro- or micronutrient intake were considered individually, there were no differences between women with and without PCOS. Similarly, there were no differences in PA by PCOS status. Results from our prospective case-comparison study (Assessment of Dietary Intake and Physical Activity in Women with and without PCOS) in **Chapter 3** confirmed that diet, but not PA, was linked to PCOS status. These findings suggest that some aspects of diet could serve as targets for tailored PCOS interventions.

Part 2 explored associations between health-related knowledge and beliefs with PCOS status. We developed and validated two instruments that were distributed to reproductive-aged women in the United States. Findings from **Chapter 4** (Instrument for PCOS: Knowledge, Health-Related Beliefs, and Self-Efficacy) demonstrate that women with PCOS had less favorable health-related beliefs than the comparison group, but reported similar self-efficacy in performing salubrious diet behaviors. In **Chapter 5** (Instrument for PCOS: Medical Experiences), we report that specific domains of trust and social support directed toward healthcare professionals differed between women with and without PCOS, thereby identifying factors that could improve the physician and PCOS patient relationship. Collectively, this dissertation integrates physiological, sociological and epidemiological concepts with nutrition in order to contribute to the development of effective behavioral interventions for PCOS patients.

BIOGRAPHICAL SKETCH

Annie W. Lin grew up in Chicago, Illinois and completed her undergraduate education in the Department of Food Science and Human Nutrition at the University of Illinois Urbana-Champaign in 2010. After receiving her Bachelor's of Science in Dietetics with a minor in Chemistry, Annie was accepted to the combined Master's in Clinical Nutrition and Dietetic Internship program at Rush University Medical Center in Chicago. She completed her thesis on the validation of a malnutrition assessment tool in hemodialysis patients in 2012, which inspired her research interests and led her to apply to the Ph.D. program in the Division of Nutritional Sciences at Cornell University. She joined Dr. Marla E. Lujan's research group and completed projects that investigated the associations between PCOS with diet, physical activity, and psychosocial constructs. In 2014, she gained further understanding of epidemiology concepts by working with Dr. Patricia A. Cassano. Annie also participated in the 2016 WHO/Cochrane/Cornell Summer Institute for Systematic Reviews in Nutrition for Global Policy Making program to build upon her knowledge regarding translational and multidisciplinary research. In conjunction with her research experiences at Cornell, Annie participated as a Nutrition Evidence Library abstractor for the 2015 US Dietary Guidelines Committee. She served as a graduate mentor for four undergraduate students on research projects related to this dissertation, and as a teaching assistant for a broad scope of nutrition undergraduate courses. In her free time, she participated in the "Baked Goods Free Trade Agreement" among a group of graduate students who exchange baked goods with peculiar ingredient combinations.

This is dedicated to women who struggle with polycystic ovary syndrome.

Also, to my dad Robert Z. Lin, who always sought the best for me.

ACKNOWLEDGMENTS

I would like to thank my **mom, Evelina** (sister)**,** and **Steve** (husband). You are the strongest support system that I could ever have, and I am extremely grateful that you are in my life. I would also like to thank **Aunts Helen** and **Emily,** as well as **Uncles Ken** and **Charles** who have been incredibly supportive during my child- and adulthood. Thanks also to my in-laws **Betty** and **Dan**, who have encouraged Steve and myself. A special thank you to my **friends** for loving to eat food as much as I do.

I could not express enough gratitude for the mentorship I received as I embarked on this journey. I am incredibly inspired by all of you and know that any of my accomplishments are because of your time and care. Thank you to **Drs. Marla E. Lujan** and **Patricia A. Cassano** for their mentorship and aid with research and professional development. They say that actions speak louder than words, but your kindness has been prominent with both words and deeds. I am incredibly lucky to have worked closely with you throughout the last five years. Thank you to my committee members, **Drs. Jamie S. Dollahite, Jeffery Sobal** and **Kimberly O'Brien** for your advice and supervisory roles with my research. There are not enough baked goods in the world that could show my appreciation. To my Master's advisor, **Dr. Kathryn S. Keim** at Rush University, for your encouragement, mentorship and lunch provision throughout the last seven years. It is because of you that I found my passion for research and I am honored to have been one of your students. Thank you to the **Rush University faculty** for being very supportive during this journey. A last thank you to our **collaborators** who helped make these projects possible.

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PART ONE PREFACE

In a published narrative review, we summarized the current evidence on the comparison of health-related lifestyle behaviors between women with and without PCOS **(Chapter 1)**. We recommended three courses of action that build on the previous literature: 1) explore the associations between health-related lifestyle behaviors and features of PCOS; 2) consider the role of race on reproductive status; and 3) use accelerometry to measure and provide objective measures of PA. To address these research gaps, this dissertation used data from a longitudinal cohort study **(Chapter 2)** and a case-comparison study **(Chapter 3)** for the following specific aims:

AIM 1: To investigate the associations between lifestyle behaviors and PCOS.

Chapter 2 *was restricted to analyzing the classic PCOS phenotype (1990 NIH criteria defined as oligo/amenorrhea and hyperandrogenism) and its isolated features due to the available data. To explore whether results may differ based on more current PCOS diagnostic criteria, the Rotterdam consensus criteria (2003) was used in* ***Chapter 3****.*

SUBAIM 1.1. To identify lifestyle predictors of isolated features of PCOS.

This aim was achieved in ***Chapter 2****.*

AIM 2: To investigate whether associations between lifestyle behaviors and PCOS vary by race, while also considering isolated features of PCOS.

This aim was achieved in ***Chapter 2****.*

Accelerometers were used in **Chapter 3** to quantify the PA behaviors of reproductive-aged women. We compared PA estimates from three recently developed algorithms to understand how variations in algorithm development can impact results and to select an approach to analyze our PA data **(Appendix A).** The above projects led to one narrative review and three primary research manuscripts.

CHAPTER 1: REVIEW ON THE COMPARISON OF DIETARY INTAKE AND PHYSICAL ACTIVITY BETWEEN WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME*

Submitted and Accepted: June 2, 2014 by Advances in Nutrition

* Lin AW, Lujan ME. Comparison of dietary intake and physical activity between women with and without polycystic ovary syndrome: a review. Adv Nutr 2014;5:486–96.

ABSTRACT

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting women of reproductive age worldwide. In addition to imparting deleterious effects on fertility, women with PCOS are at increased risk for obesity, diabetes, cardiovascular disease, depression and certain cancers. Hormonal and metabolic aberrations in PCOS have the potential to influence dietary intake and physical activity levels. There are emerging global data that women with PCOS have different dietary energy intake compared to women without PCOS. These alterations in diet may exacerbate clinical symptoms and compound risk for chronic disease for PCOS patients. Few studies have compared physical activity levels among women with and without PCOS. Although comparisons among studies are confounded by several factors, the data point to no differences in activity levels among PCOS and non-PCOS groups. This review provides an assessment of the current literature on dietary intake and physical activity levels in women with PCOS. Future recommendations to strengthen research in this area are provided, given their implications to aid in the development of effective nutrition-focused for PCOS.

INTRODUCTION

As a leading cause of anovulatory infertility and a risk factor for endometrial dysfunction and uterine cancer, polycystic ovary syndrome (PCOS) represents a serious health concern for women across the life span (1,2). PCOS is characterized by a heterogeneous collection of symptoms: infrequent or absent menstrual cycles, biochemical or clinical evidence of androgen excess, and polycystic ovarian morphology (3,4). PCOS occurs in a striking proportion of women of reproductive age, ranging from 6% to 15% worldwide, depending on the diagnostic criteria used (3,5,6). PCOS should be regarded as a broad-spectrum disorder because its consequences for patients extend beyond impairments of the reproductive system to include serious metabolic (i.e., metabolic syndrome, type 2 diabetes, and cardiovascular disease) and psychological sequelae (i.e., depression, anxiety, poor self-esteem, and reduced quality of life) (3,7,8).

Researchers have established that up to 80% of the PCOS population is overweight or obese with obesity prevalence rates, dependent on the ethnicity and geographical location (3,9). Although PCOS can manifest in both normal weight and overweight women, some evidence supports that increased central adiposity is present across all BMI categories (10–12). It is debatable as to whether women with PCOS have a unique predisposition to obesity or whether obesity contributes to the development of PCOS (13). Data supporting lower basal metabolic rate (14) and postprandial thermogenesis (15) in individuals with PCOS compared with age- and weight-matched controls may account for a higher prevalence of obesity among the PCOS population. However, reports on differences in basal metabolic rate among women with or without

PCOS are inconsistent (16). There is also the potential for appetite circuits to be affected by the abnormal hormone profile in PCOS. Testosterone replacement was shown to increase meal frequency in male rodents (17), whereas anti-androgenic pharmaceutical therapy was found to reduce meal-related hunger in women with bulimia (18). The anti-androgenic finding may be particularly relevant because women with PCOS exhibit appetite indications similar to those in women with bulimia (19). Women with PCOS also demonstrated smaller reductions in postprandial ghrelin (i.e., an orexigenic hormone) and lower postprandial cholecystokinin concentrations (i.e., an anorexigenic hormone) compared with age- and/or weight-matched controls (20,21). Collectively, these findings are consistent with the hypothesis that women with PCOS have lower perceived

satiety and greater appetite compared with women without PCOS. These findings are tempered by other studies that showed no differences or a blunted response in ghrelin concentrations among women with or without PCOS (22,23). Last, experimental and clinical evidence supports that testosterone promotes abdominal fat deposition in women (11,24,25). Increased abdominal adiposity has been linked to elevated leptin secretion and leptin resistance, which may result in impaired satiety and increased energy intake (26). Irrespective of whether PCOS causes obesity or a reverse causation exists, it is recognized that obesity, particularly abdominal obesity, worsens clinical and metabolic features of PCOS (3).

Diet and PA interventions are recommended as a first-line treatment in overweight and obese women with PCOS (27). Uncontrolled trials involving hypocaloric diets with physical activity (1200 kcal/d) and low-carbohydrate, ketogenic

diets (<20 g carbohydrate/d, unlimited consumption of high-biologic-value protein and dairy) support improvements in hyperandrogenism, frequency of menses, ovulation, pregnancy rates, insulin resistance, and lipid profile when accompanied by modest weight reductions for women with PCOS (28,29). Randomized controlled trials with reduced-energy diets also support improvements in hyperandrogenism and insulin resistance in women with PCOS. Yet, data on ovulation and other reproductive outcomes are less clear (30–32). There are limited data on the feasibility or effectiveness of long-term weight-loss interventions for this population. Moreover, only a few studies examined diet alterations to improve cardiometabolic risk factors in normal weight women with PCOS (33,34). Understanding the dietary intake and physical activity levels of the PCOS population is essential to aid in the development of effective weight loss interventions in free-living settings. The primary aim of this review was to examine the current literature on dietary intake and physical activity behaviors in women with PCOS. Furthermore, this review provides recommendations for future studies in this area of research.

Studies were identified by searching the electronic databases PubMed, CINAHL, and PsycINFO for studies published after 1990 and before January 2014. A search was performed by using a combination of the following keywords: ‘diet’, ‘polycystic ovary syndrome’, food frequency questionnaire’, ‘food records’, and ‘diet recall.’ Ten studies from various countries were included in the review based on a Population, Intervention, Comparison, Outcome framework established a priori by the authors. In short, studies included for review were limited to original research articles in which 1) the primary objective was to assess diet and physical activity levels between

adult women with and without PCOS, 2) enrollment exceeded 10 participants in each study arm, and 3) diet and physical activity were assessed in a free-living sample. A description and the main findings of each study included for review are summarized in Table 1.1.

Comparison of dietary intake between women with and without PCOS. Two studies compared dietary intake between women with and without PCOS by using case-control study designs in the United States (35,36). Wright et al. (36) assessed dietary intake by using FFQs in mostly middle-aged women undergoing the perimenopausal transition. This was evidenced by the number of women in both control and PCOS groups who reported the absence of menses for 12 mo. By contrast, Douglas et al. (35) assessed the food records of reproductive-aged women who were ~20 y younger than the sample used by Wright et al. Both dietary assessment methods used by these studies have been commonly used to assess dietary intake (37,38), yet each has distinct strengths and weaknesses. Whereas diet records over several days are expected to reflect usual intake and have less reliance on participant memory, this approach may have limited accuracy because participants are aware that their dietary intake would be scrutinized on specific days. This may result in atypical dietary intake and provide misleading dietary information (38,39). The FFQ is an appropriate measure to assess usual dietary composition over a longer period of time; however, the accuracy of the data can be limited by the respondents' abilities to recall their diet habits (38). It is also impossible to discern whether a PCOS diagnosis may have been a catalyst to altered dietary intake due to the study design.

Table 1.1. Cross-sectional study characteristics assessing diet and physical activity in women with and without polycystic ovary syndrome[1]

Author(s)	Sample, Assessments Used	Outcomes[2]	Limitations
Wright et al. 2004 (33)	Groups N=84, PCOS N=79, controls Age (years) 46.7 ± 5.8, PCOS 48.2 ± 5.7, controls BMI (kg/m^2)[3] 32.1 ± 9.3, PCOS 29.0 ± 6.0, controls Location Pittsburgh, US Race Caucasian: 83% PCOS, 90% controls Non-Caucasian: 13% PCOS, 10% controls PCOS definition Oligoamenorrhea plus either hirsutism, hyperandrogenism and/or elevated LH:FSH No specific exclusion criteria were applied Assessments FFQ Physical activity questionnaire	No differences in daily food and nutrient intake or physical activity between PCOS and control groups Lower nutrient intake in lean PCOS (N=21) vs. lean control (N=33) groups*: Total energy/d, CHO (g/d), protein (g/d), fat (g/d), SFA (g/d), MUFA (g/d), PUFA (g/d), cholesterol (mg/d) Lower bread, cereal, rice, pasta, meat, fish, poultry, egg intake in lean PCOS vs. lean control groups (servings)* Lower milk product intake in overweight PCOS (N=15) vs. overweight control (N=19) groups (servings)* Lower meat, fish, poultry, egg intake in obese PCOS (N=48) vs. obese control (N=27) groups (servings)* Higher carbohydrate and lower fat intakes in PCOS group vs. Reaven study recommendations (49)	Diagnostic criteria used yielded a heterogeneous PCOS cohort Population studied used medications known to influence endocrine profile (e.g. oral contraceptive, anti-androgens) No reported exclusion criteria on medications that may influence weight, appetite Older, potentially perimenopausal, populations studied, heterogeneous control group used with 41% reporting oligo-amenorrhea. Low generalizability to younger women with PCOS. Power analysis not provided for post-hoc comparisons among BMI-matched groups Did not report energy expenditure or energy balance Did not compare with US DRI
Douglas et al. 2006 (34)	Groups N=30, PCOS N=27, controls Age (years) 28.9 ± 6.3, PCOS 28.9 ± 6.5, controls BMI (kg/m^2) 29.1 ± 4.8, PCOS	No differences in nutrient intake between PCOS and control groups Greater white bread intake in PCOS vs. control groups (servings)*	Population studied used drugs known to influence endocrine profile No reported exclusion criteria on other medications that may influence weight, appetite Comprehensive dietary intake not collected on all days of week

Table 1.1. Cross-sectional study characteristics assessing diet and physical activity in women with and without polycystic ovary syndrome[1]

Author(s)	Sample, Assessments Used	Outcomes[2]	Limitations
	29.7 ± 4.8, controls Location Birmingham, US Race Caucasian: 83% PCOS, 85% controls Black: 13% PCOS, 11% controls Other: 4% PCOS, 4% controls PCOS definition Oligoamenorrhea plus hirsutism and/or hyperandrogenism Exclusion criteria Diabetes, use of insulin sensitizers or glucose-lowering drugs and adherence to a modified diet Assessments 4-day food records (Wed/Thu/Sat/Sun)		Overall study cohorts not matched for BMI Power analysis not provided Data on physical activity not collected Did not compare with US DRI
Alvarez-Blasco et al. 2011 (38)	Groups N=22, PCOS N=59, controls Age (years)[3] 26.3 ± 7.6, PCOS 32.2 ± 7.5, controls BMI (kg/m^2) 35.2 ± 6.7, PCOS 32.2 ± 6.1, controls Location Madrid, Spain Race not reported PCOS definition Oligoamenorrhea plus hirsutism and/or hyperandrogenism Exclusion criteria	No differences in nutrient intake and physical activity between PCOS and control groups PCOS group intake vs. United States dietary recommended intake*: Above: total fat (g/d), SFA (% energy/d), MUFA (% energy/d), dietary cholesterol (mg/d), sodium (mg/d), vitamin C (mg/d), vitamin D (μg/d), calcium (mg/d), magnesium (mg/d) Below: fiber (g/d), potassium (mg/d), vitamin E (mg/d)	Study cohorts not matched for age Power analysis not provided Details on physical activity assessment tool not reported Did not report energy expenditure or energy balance Did not compare intake with EFSA recommended intake which is established for European countries

Table 1.1. Cross-sectional study characteristics assessing diet and physical activity in women with and without polycystic ovary syndrome[1]

Author(s)	Sample, Assessments Used	Outcomes[2]	Limitations
	Use of hormonal contraception and medications that interfere with metabolism, hypocaloric dieting, implausible energy intake, supplement use Assessments FFQ Exercise habits assessed using interview		
Barr et al.2011 (39)	Groups N=198, PCOS Age (years) 32.6 ± 6.3 BMI (kg/m^2) 27.4 ± 7.3 Location London, UK Race Caucasian: 97% PCOS Unknown: 3% PCOS PCOS definition not provided Exclusion criteria Pregnancy, breastfeeding, eating disorders and use of weight loss medications Assessments 7-day food and activity record	Greater daily nutrient intake in PCOS vs. controls (national survey reference)*: Total energy/d, CHO (g/d), protein (g/d), fat (g/d), fat (% energy/d), SFA (g/d), MUFA (g/d), PUFA (g/d), total sugar (g/d), fiber (g/d) Lower daily nutrient intake in PCOS vs. controls (national survey reference)*: CHO (% energy/d) Lower daily glycemic index in lean (N=80) vs. overweight PCOS (N=100) groups* PCOS group intake vs. UK recommended intake*: Above: total energy/d, protein (g/d), fat (g/d), SFA (g/d), MUFA (g/d), PUFA (g/d) Below: CHO (g/d), fiber (g/d) Greater activity in moderate intensity physical activity (min/day) in lean (N=80) vs. overweight (N=100) PCOS groups*	Diagnostic criteria for PCOS not provided, heterogeneous PCOS cohort studied Recruitment based on self-reported diagnosis of PCOS Reference population may contain women with PCOS No reported exclusion criteria on medications that may influence endocrine profile Older, potentially perimenopausal, women included Did not report energy expenditure or energy balance
Toscani et al. 2011 (37)	Groups N=43, PCOS N=37, controls Age (years)[3] 22.7 ± 5.6, PCOS	No differences in nutrient intake between PCOS and control groups PCOS group intake vs. US recommended intake*: Below: fiber (g/d), MUFA (% energy/d), PUFA (% energy/d)	Study cohorts not matched for age No reported exclusion criteria on medications that may influence weight and appetite High reporting bias as participants may

Table 1.1. Cross-sectional study characteristics assessing diet and physical activity in women with and without polycystic ovary syndrome[1]

Author(s)	Sample, Assessments Used	Outcomes[2]	Limitations
	29.7 ± 4.9, controls BMI (kg/m^2) 30.9 ± 5.5 PCOS 29.7 ± 5.2 controls Location Porto Alegre, Brazil Race Caucasian: 90% PCOS; 74% controls African-European: 10% PCOS; 26% controls PCOS definition Oligoamenorrhea plus either hirsutism and/or hyperandrogenism Exclusion criteria Medications known to interfere with hormone levels, BMI>40kg/m^2 and diabetes Assessments 24-hour dietary recall	No associations among androgen status and nutrients	alter diet before scheduled visit Data on physical activity not collected Comparisons with US recommended intake may not be appropriate for Brazilian populations
Tsai et al.2012 (43)	Groups N=45, PCOS N=161, controls Age (years) 32.7 ± 4.2, PCOS 34.7 ± 3.6, controls BMI (kg/m^2)[3] 23.0 ± 4.4, PCOS 21.3 ± 2.9, controls Location Taipei, Taiwan Race not reported PCOS definition	Greater daily nutrient intake in PCOS vs. control groups*: Fat (% energy/d) Lower daily nutrient intake in PCOS vs. control groups*: Total energy/d, CHO (g/d), CHO (% energy/d) Positive associations among hormones and nutrients in PCOS*: FSH and CHO (g/d), FSH and CHO (% energy/d) No differences in daily nutrient intake between hyperandrogenic (N=21) and non-androgenic (N=24) PCOS groups	Diagnostic criteria used yielded heterogeneous PCOS cohort Control group comprised infertile women with various etiologies including unexplained infertility Study cohorts not matched for BMI No reported exclusion criteria on medications that may influence weight and appetite Power analysis not provided for post-hoc comparisons among PCOS phenotypes Data on physical activity not collected

Table 1.1. Cross-sectional study characteristics assessing diet and physical activity in women with and without polycystic ovary syndrome[1]

Author(s)	Sample, Assessments Used	Outcomes[2]	Limitations
	Two of three symptoms: 1) oligoamenorrhea, 2) hirsutism and/or hyperandrogenemia, 3) polycystic ovaries Exclusion criteria Hormonal therapy Assessments 3-day food record (2 weekdays, 1 weekend day)		
Altieri et al. 2013 (49)	Groups N=100, PCOS N=100, controls Age (years) 27.7 ± 5.2, PCOS 28.4 ± 5.8, controls BMI (kg/m^2) 34.7 ± 5.5, PCOS 34.8 ± 5.4, controls Location Bologna, Italy Race not reported PCOS definition Two of three symptoms: 1) oligoamenorrhea, 2) hirsutism and/or hyperandrogenemia, 3) polycystic ovaries Exclusion criteria Endocrine or metabolic disorders, medications that influence appetite, reproduction, glucose or lipid levels, psychoactive drugs, eating disorders, intensive lifestyle interventions Assessments	Greater daily nutrient intake in PCOS vs. control groups*: Fiber (g/d) Lower daily nutrient intake in PCOS vs. control groups*: Lipids (% energy/d) Greater starchy sweets (g/d), cheese (g/d), oil (g/d) in PCOS vs. control groups* Lower cooking fats (g/d) in PCOS vs. control groups* Positive associations among hormones and nutrients in PCOS*: A4 and total energy, A4 and protein (g/d), A4 and cholesterol (mg/d)) Negative associations among hormones and nutrients in PCOS*: SHBG and total energy/d, SHBG and CHO (g/d), SHBG and CHO (% energy/d), SHBG and oligosaccharides (g/d)	Diagnostic criteria used yielded a heterogeneous PCOS cohort Data on physical activity not collected Did not compare intake with EFSA recommended intake which is established for European countries

Table 1.1. Cross-sectional study characteristics assessing diet and physical activity in women with and without polycystic ovary syndrome[1]

Author(s)	Sample, Assessments Used	Outcomes[2]	Limitations
	7-day food records		
Moran et al. 2013 (40)	Groups N=409, PCOS N=7057, controls Age (years)[3] 33.5 ± 1.4, PCOS 33.7 ± 1.5, controls BMI (kg/m^2)[3] 29.3 ± 7.5, PCOS 25.6 ± 5.8, controls Location Australia (national survey) Race not reported PCOS definition not provided No specific exclusion criteria were applied Assessments FFQ Physical activity 1-week recall	Greater daily nutrient intake in PCOS vs. control groups*: Total energy/d, fiber (g/d), folate (µg/d), iron (mg/d), magnesium (mg/d), phosphorus (mg/d), vitamin E (mg/d), sodium (mg/d)[3], zinc (mg/d)[3], calcium (mg/d)[3], potassium (mg/d)[3], niacin (mg/d)[3] Lower daily nutrient intake in PCOS vs. control groups*: SFA (% energy/d), glycemic index, retinol (µg/d) PCOS group reported higher diet quality than control group* PCOS group intake vs. US DRI*: Above: SFA (% energy) No differences in self-reported physical activity between PCOS and control groups PCOS group reported greater amount of sitting time compared to controls*	Recruitment based on self-reported diagnosis of PCOS Control group may contain undiagnosed women with PCOS No reported exclusion criteria on medications that may influence weight, appetite or reproduction Cohorts included women who are pregnant women and using hormones Study cohorts not matched for age or BMI Did not compare intake with Australian nutrient reference values
Graff et al. 2013 (42)	Groups N=61, PCOS N=44, controls Age (years) 22.7 ± 6.2, PCOS 25.0 ± 6.3, controls BMI (kg/m^2) 28.9 ± 5.6, PCOS 27.1 ± 5.7, controls Location Porto Alegre, Brazil Race	Greater daily nutrient intake in PCOS vs. control groups*: Total energy/d, glycemic index[3], glycemic load[3], sodium (mg/d)[3] Higher energy intake/d and glycemic index diet between Classic PCOS (N=39) and control (N=44) groups* Higher glycemic index diet between Classic PCOS (N=39) and Ovulatory PCOS (N=22) groups* No differences in total energy intake and glycemic index diet between Ovulatory PCOS (N=22) and control (N=44) groups	Diagnostic criteria used yielded a heterogeneous PCOS cohort Included both adolescents and adults with PCOS No reported exclusion criteria on medications that may influence weight and appetite Power analysis not provided for post-hoc comparisons among PCOS phenotypes Pedometer may not comprehensively capture physical activity data

Table 1.1. Cross-sectional study characteristics assessing diet and physical activity in women with and without polycystic ovary syndrome[1]

Author(s)	Sample, Assessments Used	Outcomes[2]	Limitations
	Caucasian: 88% of sample African-European: 12% of sample PCOS definition 1) Classic PCOS: oligoamenorrhea, hirsutism and/or hyperandrogenemia with or without polycystic ovaries; 2) Ovulatory PCOS: hirsutism and polycystic ovaries in the presence of regular menstrual cycles and normal androgens Exclusion criteria Diabetes, medications that alter hormone levels, pregnancy, BMI ≥ 40 Assessments FFQ 6-day pedometer use	No differences in physical activity between PCOS and control groups	Did not report energy expenditure or energy balance
Ahmadi et al. 2013 (41)	Groups N=65, PCOS N=65, controls Age (years) 25.1 ± 6.1, PCOS 26.1 ± 6.5, controls BMI (kg/m^2) 23.4 ± 3.6, PCOS 23.1 ± 3.8, controls Location Shiraz, Iran Race not reported PCOS definition Two of three symptoms: 1) oligoamenorrhea, 2) hirsutism and/or hyperandrogenemia, 3) polycystic ovaries	Greater daily nutrient intake in PCOS vs. control groups*: Total kcal/d, fat (% energy/d), SFA (g/d), PUFA (g/d) No significant self-reported physical activity differences between PCOS and control groups No differences in daily nutrient intake between lean (N=49) and overweight (N=16) PCOS groups	Diagnostic criteria used yielded a heterogeneous PCOS cohort Power analysis not provided for post-hoc comparisons among PCOS groups Details on physical activity assessment tool not reported Did not report energy expenditure or energy balance

Table 1.1. Cross-sectional study characteristics assessing diet and physical activity in women with and without polycystic ovary syndrome[1]

Author(s)	Sample, Assessments Used	Outcomes[2]	Limitations
	Exclusion criteria Liver, kidney and heart disease, hormone use, medications that influence metabolism or body composition, incomplete FFQ, implausible energy intake and intensive lifestyle interventions Assessments Three 24-hour recalls (2 weekdays, 1 weekend day) Exercise habits assessed using demographic questionnaire		

[1]A4, androstenedione; CHO, carbohydrates; DGI, Dietary Guideline Index for Australian adults. Possible range 0 to 130 (highest compliance with guidelines); DRI, Dietary Reference Intake; EFSA, European Food Safety Authority; FSH, follicle stimulating hormone; FFQ, Food Frequency Questionnaire; MUFA, monounsaturated fatty acids; PCOS, polycystic ovary syndrome; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acid; SHBG, sex hormone binding globulin; UK, United Kingdom; US, United States.

[2]Only data pertaining to diet and/or physical activity reported

[3]Not significant after adjustment for energy intake or age and BMI

[*]$P < 0.05$

When the data were pooled without regard to body composition, both Wright et al. (36) and Douglas et al. (35) reported no significant differences in micro- and/or macronutrient intake among women with PCOS and controls. The data were consistent with studies conducted in Italy (40,41) and Spain (42), in which researchers either reported no differences in energy and/or nutrient intake among women with and without PCOS as evidenced by 24-h dietary recall, 7-d food records, and FFQ (35,36). However, Douglas et al. (35) noted that the PCOS group consumed more servings of white bread compared with the control group. When dietary intake was assessed with respect to BMI categories, Wright et al. (36) reported that normal weight women with PCOS (BMI <25 kg/m2) consumed significantly lower total energy diets compared with BMI-matched women without PCOS (~400 fewer kcal). This may be attributed to the lower reported intakes of carbohydrates (~43 g), protein (~15 g), total fat (~19 g), saturated fat (~5 g), monounsaturated fat (~7 g), polyunsaturated fat (~6 g), and cholesterol (~60 mg) by the normal weight PCOS group compared with controls. An examination of food servings also revealed that normal weight women with PCOS consumed less bread, cereal, rice, pasta, and meat products compared with BMI-matched controls. This may be considered clinically significant as it provided an energy difference of ≥250 kcal/d between the 2 groups. These findings led Wright et al. to hypothesize that women with PCOS within a normal weight range restricted their daily energy intake to a clinically significant margin to offset weight gain. In the higher BMI categories, Wright et al. noted no differences in overall macronutrient and energy intake among overweight and obese women with PCOS compared with their respective BMI-matched controls. Overweight women with PCOS reported lower intakes of milk products compared with overweight

controls, whereas obese women with PCOS reported consuming more servings of meat, fish, poultry, and eggs than the obese controls. Most of these differences were less than 1 serving apart. This may or may not be considered clinically significant, depending on the type of protein consumed.

By using the 7-d food records from a large cohort of women (n = 198) with a self-reported PCOS diagnosis, Barr et al. (43) reported that women with PCOS in the United Kingdom had higher total energy intakes (~350 kcal) compared with a reference population. They noted that women with PCOS consumed higher amounts of total carbohydrates (229.0 vs. 198.0 g), protein (78.0 vs. 66.3 g), dietary fat (85.0 vs. 61.1 g), saturated fat (26.5 vs. 22.2 g), monounsaturated fat (29.7 vs. 21.7 g), polyunsaturated fat (16.2 vs. 12.6 g), sugar (102.0 vs. 87.4 g), and dietary fiber (16.5 vs. 13.0 grams) compared with a reference population (43). On the basis of these results, it can be recommended that sugar intake should be monitored when conducting dietary assessments in patients with PCOS in the United Kingdom. Barr et al. also reported that overweight women with PCOS consumed higher glycemic index diets compared with normal weight women with PCOS. These findings were consistent with reports from Australia involving a cohort of women (n = 409) with a self-reported diagnosis of PCOS (44). Moran et al. (44) noted a small, but statistically significant difference in total daily energy intake (~50 kcal) between women with PCOS and controls on the basis of a validated FFQ. The PCOS group consumed higher amounts of iron (12.3 vs. 11.6 mg), magnesium (272 vs. 258 mg), phosphorus (1471 vs. 1401 mg), and vitamin E (5.9 vs. 5.6 mg) when adjusted for total daily energy intake and lower amounts of saturated fat (15.1% vs. 15.4% of energy) and retinol (295 vs. 311 mg). Although the studies by Barr

et al. (43) and Moran et al. (44) represent the largest studies that assessed dietary intake in PCOS to date, both were limited by their reliance on a self-reported diagnosis of PCOS. It is possible that the control populations contained women with PCOS and/or other endocrine issues because Barr et al. (43) did not exclude PCOS features from their control population survey. Moran et al. used a diagnostic question within a survey that restricted PCOS diagnosis and treatment to within 3 y. This may have classified women with PCOS who were diagnosed earlier in their lives or not seeking treatment as controls. Collectively, there is the potential for differences in dietary intake between groups to be underestimated by these studies.

Higher energy diets were also reported in Iranian (45) and Brazilian (46) women with PCOS. Ahmadi et al. (45) compared the 3-d, 24-h dietary recalls of Iranian women with and without PCOS and noted that overall daily energy intake was higher (~300 kcal) in women with PCOS. Iranian women with PCOS also reported higher total fat (~2% kcal), polyunsaturated fat (0.6 g), and saturated fat (0.8 g) intakes compared with controls. This was contradicted by Altieri et al. (40), who reported that the Italian PCOS group consumed a lower fat diet (~1% kcal) compared with healthy controls. The 24-h dietary recall used by Ahmadi et al. has similar disadvantages to a FFQ because it relies on participant memory. However, it is a convenient method that can provide accurate dietary information when collected by a trained interviewer using standardized approaches. Similar to Ahmadi et al., Graff et al. (46) reported that Brazilian women with PCOS had higher total daily energy intakes (~250 kcal) compared with controls with the use of an FFQ. Brazilian women with PCOS reported consuming a higher glycemic index (2 units), glycemic load (~33 units), and sodium (~430 mg) diet.

However, these differences disappeared after adjusting for age and BMI. Graff et al. (46) recognized the heterogeneous composition of their PCOS population and performed an assessment of dietary intake on the basis of PCOS phenotypes. They found that women with a classical form of PCOS (i.e., chronic anovulation and hyperandrogenism), but not those with ovulatory PCOS (i.e., hyperandrogenism, polycystic ovaries but regular menstrual cycles), had significantly higher total daily energy intake compared with controls. These differences became negligible after adjusting for age and BMI. Last, Tsai et al. (47) investigated dietary intake in Taiwanese women with PCOS by using 3-d food records. Taiwanese women with PCOS reported lower total daily energy intakes (110 kcal) compared with infertile women without PCOS. The PCOS group consumed more total dietary fat (~3% of energy) but lower amounts of total daily carbohydrates (~4% of energy; 30 g), which likely accounted for the energy difference between groups. Comparing the results of this study with others is challenging because groups were not matched for BMI and their control population comprised infertile women (including those with unexplained infertility).

Comparison with national dietary guidelines. Six of the 10 studies compared nutrient intake in women with PCOS with established dietary guidelines (35,36,41–43,48). Wright et al. (36) noted that women with PCOS in the United States had slightly higher carbohydrate and lower fat intakes compared with the dietary recommendations for insulin resistant individuals established by Reaven (49) (i.e., diet consisting of 45% carbohydrates, 15% protein, 10% polyunsaturated fat, 20% monounsaturated fat, and <10% saturated fat). The Reaven recommendations may not be an optimal comparator for this population because certain PCOS phenotypes may not be prone to insulin

resistance (50) and the low carbohydrate recommendation may be difficult to achieve in a free-living setting. When compared with the 2010 Dietary Guidelines for Americans (51), women with PCOS in the United States consumed excessive saturated fat (12% of total daily energy intake vs. <10% of total daily energy intake). The PCOS group consumed amounts within the Acceptable Macronutrient Distribution Ranges for carbohydrate and protein (51), which was similar to the results of the U.S. study conducted by Douglas et al. (35). Douglas et al. (35) determined that the PCOS group consumed more than the recommended amount of saturated fat as established by the National Cholesterol Education Program (<7% kcal/d). The PCOS group also exceeded American Heart Association recommendations for sodium (≤2400 mg/d) and did not meet dietary fiber recommendations (25–30 g/d). When compared with the 2010 Dietary Guidelines, their reported values are consistent with the conclusion that American women with PCOS consume excessive sodium and insufficient fiber in their diets (35,51). When the PCOS group was stratified by BMI, normal weight and obese women with PCOS exceeded dietary fat Acceptable Macronutrient Distribution Range recommendations by 2% and 5%, respectively, whereas overweight women with PCOS consumed within the normal range (36). This emphasizes the importance of accounting for BMI when assessing nutrient intake within the PCOS population.

Barr et al. (43) used the UK's Reference Nutrient Intake (RNI) guidelines to determine whether their PCOS group met dietary guidelines. On the basis of the results, women with PCOS exceeded the reference intakes for fat (i.e., total fat, saturated fat, polyunsaturated fat) and mean dietary glycemic index but did not meet fiber recommendations. The reported values also indicated that women with PCOS in the

United Kingdom consumed more protein and but did not meet carbohydrate recommendations. The RNI established in the United Kingdom may not be an appropriate measure to determine nutrient adequacy (52). There is significant potential to overestimate the percentage of women with PCOS who are not meeting dietary guidelines because the RNI values are defined as nutrient intakes required to meet the recommendations for 97.5% of a national population.

Álvarez-Blasco et al. (42), Toscani et al. (41), and Moran et al. (44) used DRIs established in the United States to assess nutrient intake in Spanish, Brazilian, and Australian populations, respectively (Table 1.1). The dietary recommendations designed to meet the needs of the American population may not be a useful reference for countries that have different dietary patterns, food environment, and cultural beliefs and the potential for genetic variations in metabolism. The European Food Safety Association has established dietary reference values for the intake of carbohydrates, fats, and water that are likely more appropriate for European countries, including Spain (53). Similarly, the Australian National Health and Medical Research Council and the New Zealand Ministry of Health have established nutrient reference values specifically for the Australian and New Zealand populations (54). To the best of our knowledge, there are no established South American nutrient value recommendations.

When comparing the dietary intake results with the corresponding national dietary guidelines, we concluded that Spanish, British, and Australian women with PCOS exceeded the recommended intakes for total, saturated, and/or monounsaturated fats when compared with women without PCOS (42–44). Álvarez-Blasco et al. (42) reported that women with PCOS in Spain exceeded the U.S. recommended dietary

cholesterol intake, while not meeting the fiber, potassium, and vitamin E recommendations. Both Spanish (42) and Italian (40) women with PCOS consumed excessive total fat but inadequate fiber when compared with European Food Safety Association recommendations. Similarly, Australian women with PCOS had inadequate fiber and vitamin E intakes compared with the Australian nutrient reference values (44). The global data indicate that women with PCOS exceed total fat and saturated fat recommendations, while not meeting recommended amounts of dietary fiber in their diet. Women without PCOS included in these studies appear to have similar results when comparing nutrient intake to national nutrient reference values across countries. Meeting nutrient recommendations may be a key public health issue for clinicians and researchers to resolve across both PCOS and non-PCOS populations.

Biomarkers and diet. Two of the studies included in this review determined associations between biochemical markers and nutrients (Table 1.1). Tsai et al. (47) reported a positive association between carbohydrate intake (g and % of energy) and follicle-stimulating hormone. Follicle-stimulating hormone is a hormone that promotes follicular growth in the ovaries and is typically lower compared with its companion gonadotropin (luteinizing hormone) in a subset of women with PCOS (55,56). Altieri et al. (40) observed positive associations of total energy, protein (g), and cholesterol intakes with androstenedione (a precursor of testosterone). Although androstenedione is not a diagnostic marker of PCOS, a subgroup of women with PCOS exhibit elevated concentrations of this androgen (57). Collectively, these data are consistent with the hypothesis that PCOS symptoms may be related to dietary intake. Further research is

needed to corroborate these findings and to determine the physiologic mechanisms behind these associations.

Physical activity. Six of the 10 studies performed an evaluation of physical activity levels in women with PCOS (36,42–46). By using a validated physical activity questionnaire, Wright et al. (36) did not detect any differences in self-reported physical activity levels between American women with PCOS and healthy controls. Both the PCOS and control groups reported similar amounts of time engaged in various activities, including vigorous, moderate, and light activity, as well as sleeping or reclining, for typical weekdays or weekend days. These findings were consistent with those of Álvarez-Blasco et al. (42), Ahmadi et al. (45), and Graff et al. (46), who also noted no differences in overall physical activity among Spanish, Iranian, and Brazilian women with or without PCOS. Wright et al. (36) noted that women with PCOS reported greater sitting time. Unlike the findings in an Australian cohort (44), this difference did not reach significance ($P = 0.064$). Wright et al. (36) did not detect differences in physical activity among PCOS and control groups when the data were analyzed by BMI categories (i.e., normal weight, overweight, and obese).

By using 7-d activity records, Barr et al. (43) showed that the majority of women with PCOS (74%) in their UK study reported achieving 30 min of daily moderate-intensity activity. This was consistent with the UK national recommendations for healthy living (58). Approximately half of the overweight and obese women with PCOS did not achieve the recommended 60 min of daily moderate-intensity activity (43). The authors admit that a self-selected sample might not have yielded a representative sample of women with PCOS because their approach may have overestimated physical activity

due to the inclusion of highly motivated individuals. This study did not include comparisons with healthy age- and BMI-matched controls. Rather, Barr et al. (43) examined the potential for differences in physical activity among normal weight and overweight women with PCOS. They noted that normal weight women with PCOS reported longer durations of moderate-intensity physical activity compared with overweight and obese women with PCOS of the same age. Coupled with their findings of lower glycemic index diets in normal weight women with PCOS, this study supported that diet and physical activity behaviors were associated with BMI among women with PCOS.

The emerging data about physical activity levels in women with PCOS are challenging to interpret because none of the studies used the same physical activity evaluation tool. The limitations for the methods used merit consideration. Wright et al. (36) used the Paffenbarger Physical Activity Questionnaire, which has been primarily validated in mixed-gender populations (59). It is uncertain whether this tool provides an accurate measure of physical activity for pre- and perimenopausal women with PCOS. Álvarez-Blasco et al. (42) and Ahmadi et al. (45) evaluated physical activity on the basis of an assessment of exercise habits by using interview questions. The validity of this approach is uncertain because the details regarding the validation of their interview tools were not provided. The 7-d activity records used by Barr et al. may be considered a more accurate quantification of physical activity since because is minimal dependence on memory, in contrast to the 7-d self-recall implemented in the Australian study (43). However, 7-d activity records place greater burden on participants, which can impact the reporting accuracy. Graff et al. (46) was the only research group to eliminate recall

bias and use pedometers, which objectively quantified 6 d of physical activity among participants. Graff et al. reported no difference in physical activity levels between women with or without PCOS. Although these data are strengthened by their inclusion of an objective measure of physical activity, we are unaware of any validation study on the pedometer model that was used. Moreover, pedometers may have low accuracy when assessing energy expenditure (60). Future studies would benefit from a combination of objective and subjective instruments in the situation that the objective tool may malfunction in the field. Information on perceptions of physical activity may also have relevance when used in conjunction with objective measures.

SUMMARY AND FUTURE RECOMMENDATIONS

It is important to recognize that studies assessing diet and physical activity of women with PCOS used broad definitions for PCOS. This creates a challenge when interpreting the literature because the PCOS group comprise of several distinct clinical phenotypes. Most research groups used criteria supported by the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology, known as the Rotterdam criteria (61), which yield heterogeneous PCOS phenotypes. Hormonal and metabolic differences exist among these clinical phenotypes, which may serve as confounding factors when examining lifestyle variables (62,63). As Graff et al. (46) demonstrated, there may be distinct differences in dietary intake among clinical phenotypes of PCOS. This is consistent with repeated reports that women with milder variants of PCOS have improved metabolic status and different health risks compared with those with more severe phenotypes (64,65). Researchers must establish

a clear distinction between PCOS status to provide an accurate comparison of lifestyle habits between women with and without clinical variants of PCOS.

Energy balance is an important determinant of weight that has not been adequately explored in women with PCOS. Few studies performed concomitant assessments of physical activity when examining dietary intake in women with PCOS. Future studies would be strengthened by the addition of objective tools to measure physical activity (e.g., accelerometers), which can provide an unbiased account of energy expenditure. Although there are emerging data on the associations between biochemical markers and dietary intake, more of these analyses are needed in PCOS populations to develop hypotheses related to potential predictors of dietary intake and physical activity in women with PCOS. Dietary interventions featuring weight loss were shown to have a positive effect on reproductive outcomes (27,30,31,48). However, methods to maintain weight loss should be further examined. Researchers should consider the interaction between environmental influences, personal beliefs, and biological variables in women with PCOS to fully understand influences on diet and physical activity behaviors. Experts have suggested that depression and/or low self-esteem place women with PCOS at higher risk of emotional eating and decreased exercise, which contribute to a long-term positive energy balance and weight gain (66). By examining and understanding these associations, it may be possible to identify potential key intervention targets with a high likelihood for success in the PCOS population. The roles of race and ethnicity also merit further consideration. There is existing evidence supporting racial disparities in reproductive function among women with PCOS (67,68). Because only a few studies disclosed the race of their participants,

we were unable to draw any conclusions regarding any potential influence of race on dietary intake or physical activity.

CONCLUSIONS

This review is the first to our knowledge to summarize the literature on dietary intake and physical activity in women with and without PCOS and to provide recommendations to strengthen research within this area. There are emerging global data that women with PCOS have different dietary intakes compared with women without PCOS. Although the limited number of studies in the United States suggest that dietary intake is similar to that of women without PCOS irrespective of BMI (35,36), both studies recommend that diet and its effect on metabolic outcomes be more thoroughly examined in this population. These recommendations were based on the observation that differences existed in the consumption of certain foods among women with PCOS (e.g., high glycemic index), despite similarities in overall energy or nutrient intake. Moreover, notable differences in dietary intake were evident in women with PCOS when BMI was taken into consideration. Internationally, most studies indicate higher energy intakes in women with PCOS, with excessive saturated fat and inadequate fiber consumption. However, there appears to be no significant differences in self-reported physical activity between women with and without PCOS. The use of objective tools may be the next step to determine energy expenditure in this population. Moving forward, we recommend that researchers incorporate life stage and clinical phenotypes into their analysis when examining dietary intake and physical activity in the PCOS population. Larger sample sizes with sufficient power to discern the impact of BMI and clinical phenotype will also serve to strengthen future studies.

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Supplementary Table S1.1. Summary of cross-sectional study characteristics used in narrative review[1]

Characteristics	Summary
Mean Age Range	22.7 to 46.7 years
Mean BMI Range	23.0 to 35.2 kg/m^2
Race Distribution	White: 83 to 97% Black: 10 to 13% Other: 3 to 13%
Countries (N, number of studies)	Australia (N = 1) Brazil (N = 2) Iran (N = 1) Italy (N = 1) Spain (N = 1) Taiwan (N = 1) United Kingdom (N =1) United States (N = 2)
PCOS Definitions (N, number of studies)	NIH (N=4) Rotterdam (N=4) Other/Unknown (N= 2)
PCOS Sample Size Range	22 to 409 participants
Diet Assessments (N, number of studies)	Food frequency questionnaire (N = 4) Food records (N = 4) 24-hour recall (N = 2)
Number of Studies Compared with Government Recommended Guidelines	3 studies (no US studies)
Physical Activity Assessments	Physical activity questionnaire (N =2) Interviews (N = 1) Records (N =1) Pedometer (N = 1)
Limitations	Older population Objective instruments not used to measure physical activity Not many studies compared with government recommended guidelines

[1] Not all studies included information about these characteristics, summary results are based on available data.

Abbreviations: BMI, Body Mass Index

CHAPTER 2: USUAL DIETARY INTAKE AND PHYSICAL ACTIVITY LEVELS OF WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS) IN THE CARDIA WOMEN'S STUDY (CWS)

Working Manuscript

Plan to Submit: October 31, 2017 to Journal of Nutrition

ABSTRACT

Background: Current evidence supports adoption of healthy diet and physical activity (PA) behaviors in PCOS patients, given positive effects on their physical and emotional well-being. However, an improved understanding of the associations between dietary and PA behaviors with PCOS is needed to develop tailored interventions for this population.

Objective: This study investigated the cross-sectional associations between diet and PA behaviors with PCOS. Associations between these behaviors and isolated PCOS features, as well as any modifying effect of race, were also examined.

Methods: Of the 748 women who participated in the Coronary Artery Risk Development in Young Adults (CARDIA) Women's Health Study, 40 were classified as having PCOS, 104 had isolated hyperandrogenism (IH) and 75 had isolated oligomenorrhea (IO). The remaining 529 participants comprised the reference group. Diet quality was computed using the Alternative Healthy Eating Index 2010 (AHEI-2010) and self-reported PA was measured using a validated interviewer-administered questionnaire. Multinomial logistic regression analyses examined the associations between diet and PA (exposure variables) and the PCOS, IH, and IO outcomes, adjusting for age, race, total energy intake, and education. The threshold for statistical

significance was set at P<0.10 because of the low number of outcomes available for analysis.

Results: The mean age was 25.4 (SD 3.6) years and 46.8% of participants were black. In considering dietary quality using the AHEI total score and subscores, there was little to no association of total score with odds of the outcomes. For the subscores, a lower intake of red and processed meat was associated with lower odds of PCOS (OR = 0.90; 90% confidence interval, 0.81-0.99). In analyses of vegetable consumption, there was evidence for effect modification by race; a higher vegetable intake score was associated with lower odds of PCOS in black women only [β=-0.33 (SE 0.19); $P_{interaction}$=0.08]. In contrast, a higher score on whole grain consumption was positively associated with odds of PCOS [β=0.29 (SE 0.15); $P_{interaction}$=0.08] and IO [β=0.21 (SE 0.12); $P_{interaction}$=0.07] in black women, but little to no association was found in white women. There was little to no association of macro- or micronutrients, or of PA, with PCOS, IH or IO.

Conclusions: Food groups, but not nutrient composition or PA, were associated with PCOS, and findings varied by race. Longitudinal studies evaluating the preventive impact of better diet quality are needed to establish the temporal direction of diet and PA behaviors on the development and progression of PCOS, and our findings suggest there may be differences by race.

INTRODUCTION

Little is understood about the role of diet and physical activity (PA) in the development of polycystic ovary syndrome (PCOS), a complex disorder characterized by oligomenorrhea, hyperandrogenism and/or polycystic ovaries (1). Anovulatory infertility is a common consequence of PCOS (2), yet represents only one of many health concerns that can impact PCOS patients across the lifespan (3,4). In particular, PCOS is closely associated with metabolic complications (such as hyperinsulinemia and abdominal obesity), which are hypothesized to propagate androgen production and impair ovarian function (5). Observational studies have linked poorer diet composition and lower PA levels to features of PCOS (higher antral follicle count and biochemical androgens) and surrogate markers of infertility (lower progesterone concentrations, self-reported infertility) (6–16). These findings are consistent with about 5 studies that reported differences in total energy (17–21) and fat (17,18,21–23) intake between women with and without PCOS. Of the six studies that investigated PA, one study found women with PCOS reported longer sitting intervals than the comparison group (19). The other studies, with smaller sample sizes, reported no associations between diet and PA with PCOS (24), leaving this an area of current controversy.

Mixed evidence for the association of diet and PA with PCOS may be partly attributed to the differences in the diagnostic criteria for PCOS between studies. PCOS defined by the combined presence of oligomenorrhea and androgen excess defines the most severe manifestation of the syndrome [National Institutes of Health (NIH) criteria; (25)]. Though women with isolated features of oligomenorrhea and hyperandrogenism do not meet NIH PCOS diagnostic criteria, these women are considered to be at risk for

the development of PCOS, particularly if they later experience common physiological stressors (for example, weight gain) (4,26). Thus, understanding how diet and PA associate with both PCOS and the isolated features of PCOS (IH and IO) may generate further hypotheses about the role of diet and PA in the development of PCOS.

Race and ethnicity influence the likelihood of adverse metabolic outcomes associated with PCOS (27–32). Studies of U.S. women with PCOS reported a higher odds and/or prevalence of abnormal fasting glucose concentrations (28,31), obesity, and hypertension (29,30) in black women with PCOS compared to white women with PCOS. A recent consensus statement from the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) pointed out these racial differences and emphasized the importance of investigating the best management practices for PCOS across races and ethnicities (3). The majority of studies reporting the associations of diet and physical activity with PCOS do not investigate whether associations vary by race, highlighting an important research gap.

General dietary modifications for weight loss are currently recommended to treat or prevent adverse reproductive and metabolic outcomes in overweight and obese women with PCOS (5,33,34). Despite the unique metabolic and reproductive complications associated with PCOS, there are no specific dietary or PA recommendations for PCOS patients (35). A demonstration of specific differences in health-related behaviors between women with and without the isolated features of PCOS would help inform potential treatment recommendations. The primary objective of this study was to investigate associations between dietary and PA behaviors with

PCOS, to consider whether these associations were similar in black and white women, and to examine the consistency of association when the outcome is an isolated feature of PCOS (i.e., either hyperandrogenism alone or oligomenorrhea alone).

METHODS

Study Design and Sample

The research questions were addressed in the Coronary Artery Risk Development in Young Adults (CARDIA) multi-center longitudinal prospective cohort study. From 1985 to 1986, CARDIA investigators enrolled 5115 men and women, ages 18 to 30 years of age residing in one of four cities: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Participants visited research centers at years 2, 5, 7, 10, 15 and 20 after the initial examination (year 0), with a 72% retention rate at year 20. Anthropometry (e.g., height, weight) and venipuncture were performed at each examination. Details about additional CARDIA procedures are described elsewhere (36). At year 16 (2002-2003), a subset of women were enrolled in an ancillary study (CARDIA Women's Study; CWS) that investigated associations among androgens, polycystic ovaries and cardiovascular risk factors. Women were eligible if they had participated in the year 15 examination, had at least one ovary and were not pregnant. Eighty-six percent (n = 1163) of eligible women in the CARDIA cohort enrolled in the CWS (ages 34 – 46 years). As part of CWS, participants completed questionnaires about their reproductive health history and the occurrence of unwanted hair growth when they were between the ages of 20 and 39 years, an age range that coincided with years 0 and 2 of the CARDIA study. Exclusion criteria for this current study included missing data on PCOS features (n = 294), pregnancy and/or breastfeeding at year 2 (n=103), and

implausible total energy (kcal) intake (defined as <600 and >6000 kcal) (n=18). The sample for the cross-sectional study reported herein comprised 748 women (64%) from the CWS cohort who had dietary and PA data collected at year 0 of the CARDIA study. The Institutional Review Board at each CARDIA research site approved the study protocol and all participants provided written informed consent.

Group Definitions

Participants were classified into four mutually exclusive groups: 1) PCOS; 2) isolated hyperandrogenism (IH); 3) isolated oligomenorrhea (IO); and 4) reference (i.e., participants in the CARDIA CWS study with neither PCOS, IH, nor IO). National Institutes of Health (NIH) criteria [both oligomenorrhea (irregular menstrual cycles) and hyperandrogenism (clinical and/or biochemical)] were used to identify women with PCOS. Women were considered to have oligomenorrhea if they reported menstrual cycle lengths ≥ 34 days during their 20s and 30s on the year 16 reproductive history questionnaire. Women were considered to have hyperandrogenism if they reported unwanted hair growth at two or more regions of the body (with the exception of the lower leg and/or underarm) during their 20s and 30s on the year 16 reproductive history questionnaire, or, if there was evidence of biochemical hyperandrogenemia in serum samples taken at year 2. Biochemical hyperandrogenemia was defined as total testosterone (T) ≥ 76 ng/dL and/or free T ≥ 0.69 ng/dL; cut points were defined by the 95th percentile of androgen concentrations in CWS women with regular menstrual cycles (20 to 30 days) and no symptoms of unwanted hair growth during their 20s or 30s (N=415). Androgens and sex hormone binding globulin were assayed by the OB/GYN Research and Diagnostic Laboratory at the University of Alabama,

Birmingham as previously described (37). Women who had only one of the two PCOS criteria were classified as either IH or IO. Women with regular menstrual cycles and no evidence of hyperandrogenism comprised the reference group.

Data Collection

Diet and physical activity measurements

Year 0 dietary data, collected using the interviewer-administered CARDIA Diet History, were studied given the close proximity to the year 2 androgen concentrations (38). Participants reported their dietary intake in the past 28 days, including the frequency and amount of food consumption and methods of food preparation. Forty-six food and beverage subgroups were defined by the Nutrient Data Software for Research (NDSR; University of Minnesota, Minneapolis, MN). The intake of each food or beverage intake subgroup was calculated by summing the number of daily servings of items included in the subgroup.

Diet quality was scored using the Alternate Healthy Eating Index 2010 (AHEI-2010). The AHEI-2010 includes 11 dietary components (seven food groups, four nutrient groups) that have been linked to multiple adverse health outcomes, including cardiovascular disease and diabetes (39). Each dietary component score ranged from zero to ten, with a higher score representing a healthier diet. The total AHEI-2010 score was calculated as the sum of all 11 components and ranged from 0 to 110 (higher score represents more optimal quality diet). The 46 NDSR food and beverage subgroups were sorted into the seven AHEI-2010 food groups (Supplemental Figure S2.1). Higher intakes of vegetables, fruits, whole grains, nuts/legumes, long chain omega 3 fatty acids (eicosapentaenoic and docosahexaenoic acids; EPA+DHA), polyunsaturated fatty acids

(PUFAs without EPA+DHA) were assigned higher scores. Sugar-sweetened beverages and fruit juices, red and processed meats, *trans*-fats and sodium were assigned scores on a reverse scale due to their association with adverse health outcomes (thus, higher scores indicate lower consumption). Given the complex relation of alcohol to health outcomes, women who consumed 0.5 to 1.5 drinks/day were assigned the highest score (score of 10), women who consumed >1.5 drinks/day were assigned the lowest scores, and non-drinkers were assigned a score of 2.5.

Self-reported PA data were collected during year 0 with the CARDIA Physical Activity History questionnaire, which asked about the frequency of 13 types of moderate and vigorous intensity activities in the past year (40,41). This questionnaire was adapted and simplified from the Minnesota Leisure Time Physical Activity Questionnaire. The PA score of each category was calculated by multiplying the frequency and intensity of each activity in that category and then computing the sum across all included activities. Activity scores were expressed as 'exercise units' (EU) since the questionnaire did not contain separate questions on the duration of each activity. However, a score of approximately 100 EU is equivalent to a vigorous exercise class that meets two to three hours a week for half a year (42).

Sociodemographic and clinical measurements

Sociodemographic data (age, race, education) were collected at year 0 using interviewer-administered questionnaires. Participants changed into light clothing and removed their shoes prior to anthropometric measurements taken by trained research staff. Weight was obtained using a digital scale (Detecto model 439; Webb City, MO) and measured to the nearest 0.2 pounds. Height was collected using a vertical mounted

ruler and measured to the nearest 0.5 centimeters. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters, squared.

Statistical Analyses

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary NC). The statistical significance threshold was set at $P < 0.05$ for the bivariate analyses. The t-test was used to test the difference in the means of continuous variables across groups, and $\chi 2$ tests were used to test categorical variable differences by group. Fully adjusted multinomial logistic regression models estimated the association of dietary and PA (continuous) variables with the odds of PCOS, IH and IO after adjusting for age and BMI (continuous), and race (categorical). To investigate whether associations between health-related behaviors with combined and isolated features of PCOS varied by race, regression models were extended to include interaction terms between race and the dietary and PA variables. The significance level threshold for logistic regression models was set at $P < 0.10$ due to the small sample size in the PCOS group (43). A focus on effect sizes and confidence intervals (CI) to address the precision of the estimates is supported by the American Psychological Association (44). Sensitivity analyses omitted women on oral contraceptives from the reference group.

RESULTS

Participant Characteristics

Among the 748 participants included in this analysis, 40 (5.3%) women were classified as PCOS, 104 (13.9%) as IH, 75 (10.0%) as IO, and 529 comprised the reference group. Mean age and BMI were similar across the four groups (Table 2.1 and Supplemental Table S2.1). Compared to the reference group, there were lower proportions of black

women in the PCOS and IO groups, and a higher proportion of women with advanced degrees in the PCOS group ($P < 0.05$).

Association of Dietary Intake and PA with PCOS

Multinomial logistic regression models identified one food group that was statistically significantly associated with PCOS (Table 2.2). A higher AHEI-2010 red and processed meat intake score was associated with a lower odds of PCOS in the partially adjusted model [OR 0.90 (90% CI: 0.81, 0.99); P = 0.05]. A one-unit increase in AHEI-2010 red and processed meat scores is equivalent to a decrease of one serving per week, thus lower red and processed meat intake was associated with a lower odds of PCOS. Although the coefficient for red and processed meat intake did not reach the statistical significance threshold in the fully adjusted model [OR 0.92 (90% CI: 0.83, 1.01); P = 0.15], the effect size was similar between models. There were no significant associations of individual macro- or micronutrients, or PA with the odds of PCOS (Supplemental Table S2.2).

The consideration of whether the association of food group variables with PCOS differed by race (Table 2.3) was tested next. We found that a higher AHEI-2010 vegetable score was associated with a lower odds of PCOS, but only in black women [β=-0.33 (SE 0.19); $P_{interaction}$=0.08]. A one-unit increase in AHEI-2010 vegetable score is consistent with an increase of one serving of vegetables per day, and was associated with 27% lower odds of PCOS in black participants. Differential associations by race were found for AHEI-2010 whole grain scores [$\beta_{interaction}$=0.29 (SE 0.15); $P_{interaction}$=0.05] such that half a serving of whole grains per day was associated higher

Table 2.1. Characteristics of participants in the CARDIA Women's Study cohort by group[1]

Variable	PCOS (n = 40)	IH (n = 104)	IO (n = 75)	Reference (n = 529)
Age, years	24.7 ± 3.6	25.6 ± 3.8	25.4 ± 3.8	25.4 ± 3.6
Black, n (%)	11 (27.5)[2]	57 (54.8)	26 (34.7)[2]	256 (48.4)
Center, n (%)				
Birmingham, Alabama	8 (20.0)	22 (21.6)	14 (18.7)	125 (23.9)
Chicago, Illinois	5 (12.5)	27 (26.5)	18 (24.0)	117 (22.4)
Minneapolis, Minnesota	10 (25.0)	28 (27.5)	15 (20.0)	125 (23.9)
Oakland, California	17 (42.5)	25 (24.5)	28 (37.3)	156 (29.8)
Education, n (%)				
High School or Lower	8 (20.0)[2]	40 (38.5)	29 (38.7)	177 (33.5)
College	21 (52.5)	55 (52.9)	39 (52.0)	312 (59.0)
Advanced Degree	11 (27.5)	9 (8.7)	7 (9.3)	40 (7.6)
BMI (kg/m^2)	25.5 ± 5.9	26.3 ± 6.8[2]	25.0 ± 5.8	24.6 ± 5.7
Unwanted Hair, n (%)	33 (82.5)[2]	60 (57.7)[2]	0 (0.0)	0 (0.0)
Menstrual Cycle ≥ 34 Days, n (%)	40 (100.0)[2]	0 (0.0)	75 (100.0)[2]	0 (0.0)
Total Testosterone, ng/dL	78.4 ± 65.3[2]	79.9 ± 101.9[2]	35.9 ± 17.5	34.1 ± 17.7
Free Testosterone, ng/dL	0.7 ± 0.6[2]	0.7 ± 1.2[2]	0.3 ± 0.2	0.2 ± 0.2
TBG, ng/dL	26.8 ± 12.4[2]	26.9 ± 14.8[2]	32.8 ± 15.8	33.7 ± 15.4

[1]Groups are defined according to reproductive variables as PCOS, IH, IO or none of the three (reference group); data are expressed as mean (SD) or N (% within each group). Statistical Test: Independent T-Tests or Chi Square

[2]$P < 0.05$ (each group vs. reference group)

Abbreviations: BMI, Body Mass Index; IH, Isolated Hyperandrogenism (elevated testosterone and/or hirsutism at 2 sites or more); IO, Isolated Oligomenorrhea (≥34 days in menstrual cycle); PCOS, Polycystic Ovary Syndrome (hyperandrogenism and oligomenorrhea); Reference (neither PCOS nor hyperandrogenism nor oligomenorrhea); TBG, Total Binding Globulin

Table 2.2. Multinomial logistic regression models estimating the associations of AHEI-2010 scores with odds of PCOS, IH or IO for women in the CARDIA Women's Study cohort

AHEI-2010 Subcomponent Scores	Partial Model[1]		Full Model[2]	
	Odds Ratio	**90% CI**	**Odds Ratio**	**90% CI**
Vegetables				
PCOS	0.94	0.84, 1.06	0.95	0.85, 1.07
IH	1.01	0.94, 1.09	1.02	0.94, 1.09
IO	1.03	0.95, 1.12	1.03	0.95, 1.12
Fruits				
PCOS	0.96	0.85, 1.08	0.97	0.87, 1.09
IH	1.04	0.97, 1.12	1.05	0.98, 1.13
IO	1.00	0.92, 1.09	1.01	0.92, 1.09
Whole Grains				
PCOS	0.98	0.86, 1.11	0.99	0.87, 1.13
IH	0.93	0.86, 1.02	0.94	0.86, 1.03
IO	0.94	0.85, 1.04	0.95	0.86, 1.05
SSB, Fruit Juice				
PCOS	1.04	0.95, 1.14	1.05	0.96, 1.16
IH	1.03	0.96, 1.10	1.03	0.96, 1.10
IO	1.01	0.93, 1.08	1.01	0.94, 1.09
Nuts and Legumes				
PCOS	1.00	0.92, 1.09	1.00	0.92, 1.10
IH	0.98	0.93, 1.04	0.98	0.92, 1.04
IO	0.95	0.89, 1.02	0.95	0.89, 1.02
Red, Processed Meats				
PCOS	0.90[3]	0.81, 0.99	0.92	0.83, 1.02
IH	1.00	0.93, 1.07	1.01	0.94, 1.08
IO	0.99	0.91, 1.06	1.00	0.92, 1.08
trans-Fat				
PCOS	0.91	0.70, 1.18	0.88	0.68, 1.15
IH	1.00	0.85, 1.18	0.98	0.83, 1.16
IO	0.93	0.77, 1.13	0.92	0.76, 1.11
Long Chain Omega 3 Fats				
PCOS	1.00	0.89, 1.11	1.01	0.91, 1.13
IH	1.05	0.98, 1.12	1.06	0.99, 1.13
IO	1.05	0.97, 1.13	1.05	0.97, 1.14

Table 2.2. Multinomial logistic regression models estimating the associations of AHEI-2010 scores with odds of PCOS, IH or IO for women in the CARDIA Women's Study cohort

AHEI-2010 Subcomponent Scores	Partial Model[1]		Full Model[2]	
	Odds Ratio	**90% CI**	**Odds Ratio**	**90% CI**
PUFA				
PCOS	0.99	0.86, 1.13	1.00	0.87, 1.14
IH	1.07	0.98, 1.16	1.07	0.98, 1.17
IO	1.05	0.95, 1.17	1.05	0.95, 1.17
Sodium				
PCOS	0.94	0.79, 1.12	0.95	0.80, 1.13
IH	0.99	0.89, 1.10	0.99	0.89, 1.11
IO	0.97	0.86, 1.10	0.98	0.86, 1.11
Alcohol				
PCOS	1.03	0.93, 1.13	1.05	0.95, 1.15
IH	1.06	1.00, 1.13	1.07[3]	1.01, 1.14
IO	0.98	0.91, 1.05	0.98	0.91, 1.05
Total AHEI-2010 Score				
PCOS	0.99	0.96, 1.02	1.00	0.97, 1.02
IH	1.01	0.99, 1.03	1.01	1.00, 1.03
IO	1.00	0.98, 1.02	1.00	0.98, 1.02

[1]Partially adjusted model adjusted for covariates: age, race, total energy intake, education
[2]Fully adjusted model adjusted for covariates in partial model plus BMI
[3]$P < 0.10$ (each group vs. reference group)

Abbreviations: AHEI, Alternative Healthy Eating Index; IH, Isolated Hyperandrogenism (elevated testosterone and/or hirsutism at 2 sites or more); IO, Isolated Oligomenorrhea (≥34 days in menstrual cycle); PCOS, Polycystic Ovary Syndrome (hyperandrogenism and oligomenorrhea); PUFA, Polyunsaturated Fatty Acid; SSB, Sugar-sweetened Beverages

Table 2.3. Summary of statistically significant race-diet interactions in multinomial logistic regression models estimating the associations of AHEI-2010 food groups with PCOS

Variables	**All women**[1]		**Black**[2]		**White**[3]	
	$\beta_{interaction}$ ***(SE)***	$P_{interaction}$	**Odds Ratio**	**90% CI**	**Odds Ratio**	**90% CI**
AHEI-2010 subcomponent score:						
Vegetables						
PCOS	-0.33 (0.19)	0.08	0.73	0.54, 0.98	1.37	1.02, 1.84
Whole Grains						
PCOS	0.29 (0.15)	0.05	1.31	1.05, 1.65	0.76	0.61, 0.96
IO	0.21 (0.12)	0.07	1.21	1.02, 1.43	0.83	0.70, 0.99
SSB, Fruit Juice						
IO	0.16 (0.09)	0.08	1.14	1.01, 1.29	0.88	0.77, 0.99

[1]Adjusted for independent effect of race. Baseline group = White.
[2]Black sample sizes: PCOS N = 11, IO N = 26, Reference N = 256
[3]White sample sizes: PCOS N = 29, IO N = 49, Reference N = 273

Abbreviations: AHEI, Alternative Healthy Eating Index; IO, Isolated Oligomenorrhea (≥34 days in menstrual cycle); PCOS, Polycystic Ovary Syndrome (hyperandrogenism and oligomenorrhea); SSB, Sugar-sweetened Beverages

odds of PCOS in black women [OR 1.21 (90% CI: 1.00, 1.47)], but a lower odds of PCOS in white women [OR 0.90 (90% CI: 0.77, 1.05)]. Sensitivity analyses in which women with PCOS were compared to non-OC users in the reference group (thus omitting all women in the reference group who were using oral contraceptives) confirmed results from the primary analyses, with the exception of the caffeine intake—PCOS association (Supplementary Table S2.3). A significant interaction of caffeine intake and race was found in sensitivity analyses, but the effect size was considered trivial [$\beta_{interaction}$=0.00 (SE 0.00); $P_{interaction}$=0.08].

Association of Dietary Intake and PA with Isolated IH and/or Isolated IO

A 1-unit higher AHEI-2010 alcohol intake score was associated with a 7% greater odds of IH in fully adjusted models (OR=1.07, 90% CI: 1.01, 1.14; P = 0.07; Table 2.2). However, a continuous variable for alcohol intake (grams/day) had little to no association with IH [OR = 1.03, (90% CI: 0.99, 1.02); P = 0.74], suggesting that the association demonstrated by the AHEI score may be reflecting a nonlinear association. Magnesium intake was associated with the odds of IH, but the estimated effect sizes were trivial in both the partially and fully adjusted models [OR = 1.00, (90% CI: 1.00, 1.00); P < 0.10]. No other statistically significant diet and/or PA associations with IO and/or IH were detected (Supplemental Table S2.2).

Race modified the association of dietary quality with the odds of IO (Table 2.3). Similar to the findings for the PCOS outcome, an increase in half serving of whole grain intake was associated with a higher odds of IO in black women, but a lower odds of IO in white women [$\beta_{interaction}$=0.21 (SE 0.12); $P_{interaction}$=0.07]. A healthier AHEI-2010 sugar-sweetened beverage and fruit juice score (one serving decrease per week) was

associated with higher odds of IO in black women only [$\beta_{interaction}$=0.16 (SE 0.09); $P_{interaction}$=0.08], but the interaction was not confirmed in the sensitivity analysis [$\beta_{interaction}$=0.04 (SE 0.13); $P_{interaction}$=0.15]. Significant race interactions with vitamin C, zinc, and caffeine were identified in the sensitivity analyses for IH, but the interaction effect sizes were considered trivial (Supplementary Table S2.3).

DISCUSSION

This study investigated whether diet and/or PA were associated with PCOS, a topic that is timely given the growing emphasis on using health-related behavioral modifications to treat and prevent PCOS (5). The identification of specific dietary and PA factors that differ between women with and without PCOS would lead to targets for tailored interventions. Cross-sectional analyses in the large biracial CARDIA cohort study revealed that a higher intake of red and processed meat was associated with higher risk of PCOS. Further, diet patterns showed differential associations with PCOS by race with black women demonstrating lower odds of PCOS with higher vegetable and with lower whole grain intake. Our analyses of total daily energy, macro- and micronutrient intake, and PA between women with and without PCOS did not find differences between women with and without PCOS. Collectively, our study supports the conclusion that food groups, but not nutrient composition or PA, were associated with PCOS.

Food groups were associated with the odds of PCOS. A one-unit increase in AHEI-2010 red and processed meat scores, which is consistent with a decrease of one serving per week, was associated with a 10% lower risk of PCOS in the partially adjusted model. Although there was no significant association between PCOS and red

and processed meat intake in the fully adjusted model, the addition of BMI as a covariate may have resulted in overadjustment. A potential mechanism by which red meat consumption may increase the risk of PCOS includes the adverse effects of consuming nitrosamines and advanced glycation end products, two substrates shown to destroy pancreatic insulin-secreting beta cells and contribute to insulin resistance (45,46). Red and processed meat consumption has been shown to be associated with higher fasting glucose and/or insulin concentrations in several animal and human trials (47–49). In particular, nitrosamine-induced insulin resistance and compensatory hyperinsulinemia are posited to contribute to the pathogenesis of androgen excess and disordered folliculogenesis in PCOS (49). Despite systemic resistance to the metabolic effects of insulin, the ovaries remain sensitive to insulin whose actions include augmenting androgen biosynthesis (50) and increasing bioavailable androgens. Further, insulin appears to inhibit follicular maturation in PCOS by inhibiting granulosa cell proliferation and interfering with estrogen and progesterone production at later stages of folliculogenesis (50). Future longitudinal studies should examine changes in red and processed meat intake and the subsequent risk of PCOS.

To our knowledge, no other studies have examined the modifying effect of race in the context of health-related behaviors in PCOS. We observed that associations between aspects of diet quality with PCOS and isolated PCOS features differed between black and white women. An improved understanding of how race impacts the pathogenesis of PCOS is important, given that there are racial differences in the risk of glucoregulatory and cardiometabolic conditions in black versus white PCOS patients (28–31) – impairments that can be modified by healthy dietary and PA behaviors. Two

of our findings were paradoxical: a higher whole grain intake and a lower sugar-sweetened beverage and fruit juice intake were associated with a higher odds of PCOS and/or IO for black women. Given that these two dietary patterns are typically associated with better health outcomes (51), our findings stratified by race might have been caused by differences in how black and white participants interpreted items on the CARDIA dietary history. This hypothesis explanation is consistent with results from a validation study, where the nutrient correlations between the questionnaire and mean nutrient values from seven 24 hour recalls were lower in black than white CARDIA participants (38).

This study did not identify any differences in macro- and micronutrient intake between women with and without PCOS. These findings are consistent with previous US (22,52) and international studies (23,53,54) that reported no differences in total energy and/or macro- or micronutrient intake between women with and without PCOS. The similarity of our finding to other US studies may reflect our common use of the NIH diagnostic criteria to define the presence of PCOS; with other studies outside the U.S. often using a different definition of PCOS (18,20,21,23) thus identifying a case group that is inherently different to the one studied herein. Our study of relatively younger women taken together with other US studies of older women (22) suggests that there are no differences in total daily energy intake between women with and without PCOS during the reproductive and peri-menopausal years. The results from our study conflict with three previous studies that identified higher carbohydrate intake (ranging from 31 to 43 grams) in women with PCOS than the comparison groups (17,18,22). The conflicting evidence may be explained by differences in the outcome definition, data

collection methods, sample characteristics, and statistical approaches. Additionally, the CARDIA cohort was purposively sampled by race, allowing us to test interactions of diet and PA with race, in contrast to prior studies that either combined races into one group and/or were less diverse.

In addition to investigating whether the diet—PCOS and/or the PA—PCOS associations vary by race, we evaluated the associations between diet and PA with clinical and/or biochemical markers of androgen excess to understand whether syndrome features were associated with diet and/or PA. Our findings for the OA outcome are at odds with two longitudinal cohort studies that reported a greater intake of carbohydrate and folic acid were associated with a reduced risk of anovulatory infertility (9,10). In contrast, our study agrees with findings of a longitudinal cohort study of B vitamins as predictors of self-reported anovulatory infertility, which reported no significant associations (10). Furthermore, the association of diet and PA with PCOS and its isolated features were not consistent, which may be due to heterogeneity in the IH and IO groups (55). For example, cycle irregularity can manifest secondary to stress and nutrient deficiency (56), and not only as an indicator of PCOS risk.

There was little to no association of PA behaviors with PCOS, which is consistent with previous studies that noted no differences in self-reported moderate and vigorous intensity PA between women with and without PCOS (24). Consistent with previous studies that investigated PA in adult women with PCOS (19–22,53), our findings do not support the hypothesis that women with PCOS engage in less moderate and vigorous PA (57). Other researchers reported differences in PA patterns in women with PCOS (i.e. longer sitting intervals), which have been associated with increased risk

of all-cause mortality (58). The CARDIA measurement of PA did not capture patterns of exercise types across time, and further research using objective PA data are needed to provide more unbiased estimates of the association between PA behaviors and the development of PCOS.

Strengths of this study include the use of a biracial cohort, which enabled us to examine how health-related behaviors and PCOS associations differed by race. Reverse causality as an explanation of the findings is unlikely because diet and PA data were collected prior to widespread recognition of PCOS with the establishment of formal NIH (1990) criteria for PCOS. However, our study was limited by the use of self-reported menstrual cycle history and clinical signs of androgen excess that were not confirmed with clinical assessments. The generalizability of our results may also be restricted to the classic and most severe clinical phenotype of PCOS (defined as hyperandrogenism and irregular menses) since ovarian data were not available to determine the presence of polycystic ovarian morphology, which would have enabled the detection of subtler variants of PCOS.

Previous studies have identified potential nutrient predictors for anovulatory infertility (9,10), but associations between food groups and PA with PCOS remained largely unexplored. Though macro- and micronutrients are important components of the diet, evaluation of diet quality provides further knowledge about the potential targets for intervention since alterations in foods and/or dietary patterns, rather than nutrients, may be easier for patients to follow in their diet. Overall, results from this study revealed that lower red and processed meat intake was associated with a lower odds of PCOS. This study also found preliminary evidence that associations between food groups and

PCOS may differ by race. Findings from this study are formative and provide the basis for new hypotheses regarding the role of dietary behaviors on the development of PCOS to inform targeted interventions for PCOS patients.

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Supplemental Figure S2.1. Food groups from the NDSR (Nutrient Data Software for Research) that were collapsed into AHEI-2010 food groups, after ensuring the approach was consistent with the Willet food frequency questionnaire (FFQ).

Supplementary Table S2.1. Diet and physical activity for all women in the CARDIA Women's Study cohort by group[1]

Variable	PCOS (n = 40)	IH (n = 104)	IO (n = 75)	Ref (n = 529)
Nutrient				
Energy (kcal /d)	2229.3 ± 879.4	2312.6 ± 981.1	2170.3 ± 925.7	2246.7 ± 912.3
Total Carbohydrate (g/d)	260.0 ± 108.2	270.7 ± 122.6	258.5 ± 114.9	262.5 ± 111.0
Fiber (g/d)	4.9 ± 2.3	5.2 ± 3.0	5.1 ± 3.3	5.0 ± 2.8
Total Protein (g/d)	83.3 ± 29.7	84.7 ± 36.8	78.1 ± 32.4	82.7 ± 35.8
Total Fat (g/d)	93.3 ± 43.2	97.1 ± 46.7	90.4 ± 45.9	94.2 ± 44.7
Cholesterol (mg/d)	357.2 ± 178.8	357.7 ± 165.7	325.2 ± 159.2	354.2 ± 207.4
Total SFA (g/d)	35.3 ± 18.0	35.5 ± 17.0	33.6 ± 18.3	35.4 ± 17.7
Total MUFA (g/d)	34.6 ± 16.8	35.8 ± 18.7	32.6 ± 16.9	34.5 ± 17.3
Total PUFA (g/d)	16.6 ± 7.3	18.8 ± 10.3	17.8 ± 12.1	17.5 ± 9.0
Omega 3 (mg/day)	77.3 ± 93.2	96.3 ± 125.1	77.9 ± 78.3	83.4 ± 129.4
Vitamin A (IU/d)	10450.2 ± 8330.0	10453.8 ± 8623.8	11464.6 ± 12917.5	10612.7 ± 11420.3
Vitamin C (mg/d)	231.6 ± 373.2	292.8 ± 386.7	273.7 ± 452.9	249.1 ± 445.1
Vitamin D (mcg /d)	7.0 ± 4.1	8.5 ± 6.9	7.0 ± 4.9	7.4 ± 6.7
Alpha Tocopherol Equivalents (mg/d)	21.1 ± 62.3	21.0 ± 55.2	11.6 ± 9.2	16.6 ± 44.1
Sodium (mg/d)	3412.6 ± 1561.3	3383.1 ± 1472.6	3265.2 ± 1518.3	3298.8 ± 1530.7
Calcium (mg/d)	1098.3 ± 520.0	1151.1 ± 830.3	1030.4 ± 509.8	1084.4 ± 673.1
Phosphorus (mg/d)	1454.2 ± 500.8	1474.2 ± 637.9	1403.3 ± 584.5	1459.7 ± 629.7
Thiamin (mg/d)	2.0 ± 0.9	2.7 ± 2.8	2.0 ± 0.9	2.4 ± 2.4
Potassium (mg/d)	3075.7 ± 1148.9	3195.1 ± 1577.9	3048.2 ± 1276.9	3120.1 ± 1361.8
Riboflavin (mg/d)	2.5 ± 1.0	3.1 ± 2.9	2.4 ± 1.1	2.8 ± 2.5
Niacin (mg/d)	24.5 ± 8.9	31.2 ± 24.2	24.2 ± 11.0	27.7 ± 23.5
Iron (mg/d)	20.0 ± 9.2	21.8 ± 16.6	19.0 ± 10.0	21.7 ± 33.0
Copper (mg/d)	2.5 ± 1.4	3.0 ± 2.0	2.8 ± 1.8	2.7 ± 1.9
Magnesium (mg/d)	332.2 ± 168.9	356.5 ± 260.8	308.8 ± 126.3	324.2 ± 149.8
Zinc (mg/d)	14.5 ± 6.3	18.2 ± 12.7	16.4 ± 8.9	16.2 ± 11.7
Folic Acid (mcg/d)	565.9 ± 1248.4	507.9 ± 773.2	385.6 ± 275.9	470.7 ± 1922.4
Caffeine (mg/d)	263.1 ± 289.4	279.2 ± 452.2	231.9 ± 320.6	268.2 ± 585.1

Supplementary Table S2.1. Diet and physical activity for all women in the CARDIA Women's Study cohort by group[1]

Variable	PCOS (n = 40)	IH (n = 104)	IO (n = 75)	Ref (n = 529)
AHEI-2010[2]				
Vegetables Score	5.0 ± 2.7	5.0 ± 2.7	5.2 ± 2.8	5.0 ± 2.8
Fruits Score	3.5 ± 2.2	3.7 ± 2.9	3.5 ± 2.7	3.5 ± 2.5
Whole Grains Score	3.3 ± 2.0	2.8 ± 2.1	2.9 ± 2.1	3.1 ± 2.3
SSB, Fruit Juice Score	2.3 ± 3.1	1.7 ± 2.9	1.9 ± 2.9	1.7 ± 2.9
Nuts and Legumes Score	4.7 ± 3.4	4.5 ± 3.5	4.1 ± 3.3	4.6 ± 3.5
Red, Processed Meats Score	4.6 ± 3.1	4.7 ± 3.4	5.2 ± 3.3	5.0 ± 3.1
trans-Fat Score	3.8 ± 0.9	3.8 ± 1.0	3.8 ± 1.2	3.9 ± 1.1
Long Chain Omega 3 Fats Score	3.0 ± 2.6	3.5 ± 3.0	3.2 ± 2.9	3.1 ± 2.6
PUFA Score	5.8 ± 1.6	6.2 ± 2.1	6.1 ± 2.2	5.9 ± 2.1
Sodium Score	5.6 ± 3.0	5.6 ± 3.0	5.9 ± 3.1	5.8 ± 3.0
Alcohol Score	6.3 ± 2.9	6.2 ± 2.7	5.7 ± 2.8	5.8 ± 3.0
Total AHEI-2010 Score	47.3 ± 11.6	47.8 ± 12.0	47.5 ± 11.7	47.2 ± 11.6
Physical Activity				
Moderate Exercise Units	137.8 ± 101.9	126.2 ± 100.9	124.9 ± 99.5	126.3 ± 98.5
Heavy Exercise Units	243.6 ± 175.2	233.8 ± 198.8	252.9 ± 262.6	218.2 ± 191.3
Total Exercise Units	381.4 ± 217.4	360.0 ± 267.2	377.8 ± 324.8	344.5 ± 257.0

Abbreviations: IH, Isolated Hyperandrogenism (elevated testosterone and/or hirsutism at 2 sites or more); IO, Isolated Oligomenorrhea (≥34 days in menstrual cycle); IU, International Units; MUFA, Monounsaturated Fatty Acids; PCOS, Polycystic Ovary Syndrome (hyperandrogenism and oligomenorrhea); PUFA, Polyunsaturated Fatty Acids; SFA, Saturated Fat; SSB, Sugar-sweetened Beverages

Supplemental Table S2.2. Multinomial logistic regression models estimating the associations of macro- and micronutrients with odds of PCOS, IH or IO for women in the CARDIA Women's Study cohort

Variables	Partial Model[1]		Full Model[2]	
	Odds Ratio	**90% CI**	**Odds Ratio**	**90% CI**
Total Carbohydrate (g/d)				
PCOS	1.00	0.99, 1.01	1.00	0.99, 1.01
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.01	1.00	1.00, 1.01
Fiber (g/d)				
PCOS	0.92	0.81, 1.05	0.94	0.82, 1.07
IH	1.04	0.96, 1.12	1.04	0.97, 1.13
IO	1.03	0.95, 1.13	1.04	0.95, 1.13
Total Protein (g/d)				
PCOS	1.00	0.98, 1.02	1.00	0.98, 1.02
IH	1.00	0.99, 1.01	1.00	0.99, 1.01
IO	0.99	0.98, 1.00	0.99	0.97, 1.00
Total Fat (g/d)				
PCOS	1.01	0.99, 1.02	1.01	0.99, 1.03
IH	1.00	0.99, 1.01	1.00	0.99, 1.01
IO	1.00	0.99, 1.01	1.00	0.99, 1.02
Cholesterol (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Total SFA (g/d)				
PCOS	1.01	0.97, 1.04	1.01	0.97, 1.05
IH	0.98	0.96, 1.00	0.98	0.96, 1.01
IO	0.99	0.97, 1.02	0.99	0.97, 1.02
Total MUFA (g/d)				
PCOS	1.03	0.99, 1.07	1.03	0.99, 1.07
IH	1.00	0.98, 1.03	1.00	0.98, 1.03
IO	1.00	0.97, 1.03	1.00	0.97, 1.03
Total PUFA (g/d)				
PCOS	0.98	0.93, 1.04	0.98	0.93, 1.04
IH	1.02	0.99, 1.05	1.02	0.99, 1.05
IO	1.03	1.00, 1.06	1.03	0.99, 1.06
Omega 3 (mg/day)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Vitamin A (IU/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00

Supplemental Table S2.2. Multinomial logistic regression models estimating the associations of macro- and micronutrients with odds of PCOS, IH or IO for women in the CARDIA Women's Study cohort

Variables	Partial Model[1]		Full Model[2]	
	Odds Ratio	**90% CI**	**Odds Ratio**	**90% CI**
Vitamin C (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Vitamin D (mcg /d)				
PCOS	0.97	0.92, 1.03	0.98	0.92, 1.03
IH	1.02	1.00, 1.05	1.03	1.00, 1.05
IO	0.98	0.94, 1.02	0.98	0.95, 1.02
Alpha Tocopherol Eq (mg/d)				
PCOS	1.00	1.00, 1.01	1.00	1.00, 1.01
IH	1.00	1.00, 1.01	1.00	1.00, 1.01
IO	0.99	0.98, 1.01	0.99	0.98, 1.01
Sodium (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Calcium (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00,1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Phosphorus (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Thiamin (mg/d)				
PCOS	0.82	0.63, 1.08	0.83	0.64, 1.09
IH	1.06	0.99, 1.12	1.06	1.00, 1.13
IO	0.86	0.73, 1.03	0.87	0.73, 1.03
Potassium (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Riboflavin (mg/d)				
PCOS	0.87	0.70, 1.07	0.88	0.71, 1.08
IH	1.05	0.98, 1.11	1.05	0.99, 1.12
IO	0.87	0.74, 1.01	0.87	0.75, 1.02
Niacin (mg/d)				
PCOS	0.98	0.96, 1.01	0.98	0.96, 1.01
IH	1.01	1.00, 1.01	1.00	1.00, 1.01
IO	0.99	0.97, 1.00	0.99	0.97, 1.01

Supplemental Table S2.2. Multinomial logistic regression models estimating the associations of macro- and micronutrients with odds of PCOS, IH or IO for women in the CARDIA Women's Study cohort

Variables	Partial Model[1]		Full Model[2]	
	Odds Ratio	**90% CI**	**Odds Ratio**	**90% CI**
Iron (mg/d)				
PCOS	0.99	0.98, 1.01	1.00	0.98, 1.01
IH	1.00	0.99, 1.01	1.00	0.99, 1.01
IO	0.99	0.98, 1.01	0.99	0.98, 1.01
Copper (mg/d)				
PCOS	0.85	0.67, 1.08	0.86	0.67, 1.10
IH	1.07	0.97, 1.18	1.08	0.98, 1.19
IO	1.04	0.93, 1.18	1.05	0.93, 1.18
Magnesium (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00[3]	1.00, 1.00	1.00[3]	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Zinc (mg/d)				
PCOS	0.96	0.92, 1.01	0.96	0.92, 1.01
IH	1.01	1.00, 1.03	1.02	1.00, 1.03
IO	1.00	0.98, 1.02	1.00	0.98, 1.02
Folic Acid (mcg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00
Caffeine (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	1.00	1.00, 1.00	1.00	1.00, 1.00
IO	1.00	1.00, 1.00	1.00	1.00, 1.00

[1]Partially adjusted model adjusted for covariates: age, race, total energy intake, education
[2]Fully adjusted model adjusted for covariates: age, race, total energy intake, education, and BMI
[3]Overall significance level $P < 0.10$ (each group vs. reference group)

Abbreviations: Eq, Equivalent; IH, Isolated Hyperandrogenism (elevated testosterone and/or hirsutism at 2 sites or more); IO, Isolated Oligomenorrhea (≥34 days in menstrual cycle); IU, International Units; MUFA, Monounsaturated Fatty Acid; PCOS, Polycystic Ovary Syndrome (hyperandrogenism and oligomenorrhea); PUFA, Polyunsaturated Fatty Acid; SFA, Saturated Fatty Acid

Supplementary Table S2.3. Significant race-specific multinomial logistic regression models estimating the associations of diet with reproductive status reported in the sensitivity analysis[1]

Variables	Overall[2]		Black[3]		White[4]	
	β (SE)	***$P_{interaction}$***	**Odds Ratio**	**90% CI**	**Odds Ratio**	**90% CI**
AHEI-2010						
Vegetables Score						
PCOS	-0.44 (0.26)	0.09	0.79	0.61, 1.01	1.27	0.99, 1.64
Whole Grains Score						
PCOS	0.51 (0.20)	0.06	1.29	1.04, 1.60	0.78	0.63, 0.96
IO	0.26 (0.16)	0.08	1.18	1.01, 1.39	0.85	0.72, 0.99
SSB, Fruit Juice Score						
IO	0.04 (0.13)	0.15	1.11	0.99, 1.24	0.90	0.80, 1.01
Nutrients						
Vitamin C (mg)						
IH	0.00 (0.00)	0.08	1.00	1.00, 1.00	1.00	1.00, 1.00
Zinc (mg)						
IH	0.02 (0.03)	0.09	0.98	0.97, 1.00	1.02	1.00, 1.03
Caffeine (mg)						
PCOS	0.00 (0.00)	0.08	1.00	1.00, 1.00	1.00	1.00, 1.00
IH	0.00 (0.00)	0.05	1.00	1.00, 1.00	1.00	1.00, 1.00

[1] Sensitivity analysis in which women on oral contraceptives were excluded from the reference group

[2]Adjusted for independent effect of race. Baseline group = White. Sensitivity analysis: removed participants on OCP from the reference group

[3]Black sample sizes: PCOS N = 11, IO N = 26, Reference N = 112

[4] White sample sizes: PCOS N = 29, IO N = 49, Reference N = 129

Abbreviations: IH, Isolated Hyperandrogenism (elevated testosterone and/or hirsutism at 2 sites or more); IO, Isolated Oligomenorrhea (≥34 days in menstrual cycle); PCOS, Polycystic Ovary Syndrome (hyperandrogenism and oligomenorrhea); SSB, Sugar-sweetened Beverages

CHAPTER 3: COMPARISON OF DIET AND PHYSICAL ACTIVITY BEHAVIORS BETWEEN WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME (PCOS)

Working Manuscript

ABSTRACT

Background: There is conflicting evidence about whether diet and physical activity (PA) behaviors differ between women with and without polycystic ovary syndrome (PCOS). Specific differences in health-related behavior could explain the propensity for obesity and serve as targets to design tailored interventions in PCOS.

Objective: To investigate the cross-sectional associations between diet and PA with PCOS.

Methods: A semi-structured interview was conducted with 89 participants (PCOS, n=50 and non-PCOS reference n=39) to collect sociodemographic and reproductive health history data, in conjunction with the following assessments: 1) a fasting blood draw to measure reproductive hormones; 2) a transvaginal ultrasound scan to evaluate ovarian morphology; 3) hirsutism scoring and anthropometry; 4) an on-line food frequency questionnaire and dietary interview to assess dietary intake, 5) accelerometry to capture PA over a minimum of four days. Diet quality was evaluated using the Healthy Eating Index 2010. Binomial logistic regression analyses (adjusting for age, total calories, and/or BMI) were performed to estimate associations between diet and PA with PCOS. The statistical significance threshold was set at $P < 0.10$ to detect significant associations in a small sample size.

Results: Higher HEI-2010 empty calories scores were positively associated with odds of PCOS after adjusting for age, total energy intake, and BMI [OR = 1.07 (90% CI: 1.01, 1.12); P =0.04]. A higher intake of niacin, vitamin B6, vitamin B12, zinc, and iron were also associated with odds of PCOS. No differences in macronutrient intake nor PA were noted between women with and without PCOS.

Conclusions: A healthier diet, as defined by a higher intake of B vitamins and lower intake of empty calories, was positively associated with PCOS. Whether consumption of better quality diets in women with PCOS results from advice after receiving a PCOS diagnosis should be determined.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a broad-spectrum endocrine disorder that is diagnosed by a combination of oligo/amenorrhea, hyperandrogenism, and/or polycystic ovaries (1). PCOS affects approximately 7 to 18% of reproductive-aged women globally (2–4) and represents a severe healthcare-related economic burden in the United States (US) (5). Obesity is known to worsen reproductive and metabolic profiles in PCOS (6), which is particularly concerning since up to 80% of PCOS patients are considered to be overweight or obese (7,8). While preliminary evidence support that women with PCOS are more susceptible to weight gain (9), controversy exists on whether obesity and/or dietary and physical activity (PA) behaviors contribute to the development of PCOS (8,10). Poor dietary intake has been associated with PCOS features, such as hyperandrogenemia and polycystic ovaries (11–14), as well as self-reported infertility (15–19). However, evidence on whether PCOS patients consume poorer diets and/or participate in shorter intervals of PA activities than women without PCOS remains mixed (20).

The inconsistent evidence about whether diets and PA differ in women with and without PCOS may be dependent on the diagnostic criteria used to define PCOS (20). Studies in the US that have examined dietary and PA behaviors in PCOS have used the National Institutes of Health (NIH) criteria, which does not consider polycystic ovarian morphology as a diagnostic criterion (21). This approach omits other distinct PCOS phenotypes commonly seen in clinical settings and limits the generalizability of the study results (21). Additionally, different measurement approaches may contribute to the conflicting data. Studies have used a variety of instruments to collect dietary (e.g.,

food records, recalls, questionnaires) and PA data (e.g., questionnaires, interview). Overall, PA data have been based on self-report and can be biased by the recall period or social desirability (22). Objective tools to measure PA (e.g., accelerometers) have rarely been implemented in the area of PCOS (23,24), which could help to address controversy in this area (20).

General dietary and PA modifications are recommended as the first-line therapy to treat overweight and obese women with PCOS (25,26). However, studies have reported lower participation with self-help programs in this patient population (27). To successfully influence behavior change, studies outside of PCOS have shown that incorporation of health strategies into existing practices could improve compliance (28,29). Current evidence from other countries suggests that PCOS patients exceed government recommendations for fat intake, while not meeting fiber, potassium and vitamin E dietary guidelines (30–32). However, comparisons between current health-related behaviors of PCOS patients and government recommendations have not been examined in the US. To that end, we investigated the current diet and PA level of PCOS patients in the US and compared these behaviors with those without PCOS to identify factors that could serve as potential targets for tailored PCOS intervention.

METHODS

This case-comparison study included data that were collected as part of three separate protocols between January 2013 and April 2017 (ClinicalTrials.gov Identifiers: NCT01859663, NCT01927432, NCT01785719). Institutional Review Boards (IRB) approved the study protocols. All participants provided written informed consent. Participants were recruited to these protocols from the general population using paper

and electronic advertising in Tompkins, Monroe, New York and Bronx counties, NY. Women were eligible to participate if they were of reproductive age (defined as 18 to 45 years) and had clear visualization of their ovaries on ultrasonography. Exclusion criteria included use of insulin-sensitizing medications and/or statins within three months of study participation; presence of medical conditions known to interfere with reproductive or metabolic function (such as hyperprolactinemia, diabetes, untreated thyroid dysfunction and premature ovarian failure); absence of both diet and PA data; evidence of implausible energy intake (defined as <600 and >6000 calories/day); and inability to determine reproductive status due to missing data.

Study Procedures

Participants were screened for eligibility during a semi-structured interview in which they estimated their average menstrual cycle length (MCL) in the past year, and underwent a transvaginal ultrasound scan of the ovaries to ascertain visibility of the ovaries and stage of cycle. If eligible, women were invited to return to the participating clinical research center either during the early follicular phase (i.e. between days 2 and 7 of menses) if they had a regular MCL or at their convenience if they had unpredictable cycles. Clinical assessments at the follow-up visit included a fasting blood draw to measure reproductive hormones; a transvaginal ultrasound scan to evaluate ovarian morphology; a physical exam to assess degree of hirsutism, vitals and anthropometry; and dietary and physical activity assessments to quantify health-related behaviors.

Participants wore light clothing and removed their shoes prior to anthropometric assessments. Height was measured using a standard stadiometer to the nearest 0.5 cm and weight was taken using a calibrated digital scale to the nearest 0.1 kg. Body mass

index was calculated as weight in kilograms divided by height in meters squared. Participants were asked to confirm hirsutism scores suggested by investigators using the modified Ferriman-Gallwey scoring system (33), as previously described (34). Blood was processed for serum, and stored at -80ºC until the time of analyses. Serum was sent to the Brigham Research Assay Core (Boston, MA), as part of the Centers for Disease Control and Prevention Hormone Standardization Program, and assayed for total testosterone using liquid chromatography-tandem mass spectrometry (CV ± 6.4%).

Ovaries were scanned from the inner to outer margins in the longitudinal plane by experienced ultrasonographers. De-identified cineloops throughout each ovary were exported and analyzed offline using Santesoft DICOM Editor (Emmanouil Kannellopoulus, Athens, Greece). Reliable estimates of follicle number per ovary (FNPO), follicle number in the largest cross-sectional plane of the ovary (FNPS), and ovarian volume (OV) were obtained using the grid system approach as previously described (35). Mean FNPO, FNPS and OV values were calculated by averaging values of the left and right ovary. Follicle numbers were rounded to the nearest whole number and OV to the nearest decimal place. FNPS was used to phenotype four participants (4.5%) due to missing FNPO and OV data.

Nutrient and diet quality data were collected using VioScreen™ (VioCare, Inc., Princeton, NJ), a validated web-based food frequency questionnaire (FFQ) that assesses habitual diet over the past three months (36). The Nutrition Data System for Research software (V42; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) was used to calculate nutrient and food intake. Diet quality was assessed with the Healthy Eating Index 2010 (HEI-2010) (37). The HEI-2010 comprised of 12 dietary

components that were associated with health promotion (total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids) and adverse health outcomes (refined grains, sodium, and empty calories as defined by energy from solid fats, alcohol and added sugars). Higher scores reflect more optimal diet quality within each dietary component in accordance to the 2010 US Dietary Guidelines for Americans. Total HEI-2010 scores were computed by aggregating the scores across dietary components; total scores ranged from 0 to 100 (higher score represents adherence to government dietary recommendations). Semi-structured diet interviews were conducted by a registered dietitian who asked participants to describe changes in dietary practice and weight trajectories over time. To collect objective PA data, participants were asked to wear Actigraph triaxial accelerometers GT3X (27 g; 3.8 cm x 3.7 cm x 1.8 cm) and wGT3X+ (19g; 4.6 cm x 3.3 cm x 1.5 cm) at the left hip with a maximum acceleration sampling rate of 50 Hertz and without a low frequency extension (Actigraph LLC, Pensacola, FL) for seven days. Physical activity data were included if the participant wore the accelerometer for at least four days – where an entire day was defined as wear for at least 10 hours. Raw data from accelerometers were processed to generate wear minutes from vector magnitude counts using the Sasaki algorithm with the internally developed AutocalcMET Excel model (38). Minutes spent within moderate and vigorous activities were reported due to their known health benefits (39).

Group definitions

The Rotterdam consensus criteria (having at least two of three PCOS features) was used to classify patients with PCOS (40). Oligo/amenorrhea was defined as self-

reported unpredictable MCL that averaged ≥36 days in the year prior to study enrollment. Women were considered to have hyperandrogenism if they were hirsute (defined as modified Ferriman-Gallwey score ≥7) (33) and/or if they had elevated fasting serum total testosterone (TT) concentrations (defined as ≥65.4 ng/dL). These thresholds were generated by the investigators based on the 95th percentile of women with predictable MCL that were enrolled across our studies. Polycystic ovarian morphology was characterized by mean FNPO ≥25 per ovary (41) or mean FNPS ≥9 (42). The remaining participants were placed in the comparison group.

Statistical Analyses

Statistical analyses were performed using SPSS 23.0 (IBM, Armonk, NY). Results for bivariate analyses were considered significant at $P<0.05$. Clinical and health-related behavioral data were compared between the PCOS and comparison groups using independent t-tests and χ^2 analyses. Binomial logistic regression models reported as odds ratios (OR) were used to explore associations between diet and PA (continuous) variables with PCOS status (categorical). For each exposure variable, Model 1 adjusted for age, total energy intake (continuous variables), while Model 2 was extended to include BMI (continuous variable). Significance level threshold for the logistic regression analyses were set at $P <0.10$ due to the small sample size (43). Effect sizes and confidence intervals (CI) were also reported to provide information on the precision of estimates according to American Psychological Association recommendations (44).

RESULTS

Demographics and clinical characteristics

Eighty-nine participants were included in the study, and comprised of 50 (56.2%) women classified as PCOS and 39 (43.8%) as reference (Figure 3.1). The majority of the study sample was Caucasian and was categorized as overweight or obese [n=60 (69.8%)]. A small proportion of women in the entire sample used oral contraceptive pills (OCPs) [n=7 (7.9%)]. Relative to the comparison group, women with PCOS were significantly younger and had higher BMIs (Table 3.1). The PCOS group had longer mean MCL, greater degrees of hyperandrogenism, and ovarian dysmorphology, compared to women without PCOS ($P \leq 0.006$). In this study, 54% of women in the PCOS group self-reported a previous diagnoses of PCOS by a healthcare professional in contrast to 13% of women in the comparison group.

Dietary intake and diet quality

The PCOS group exceeded Acceptable Macronutrient Distribution Range total fat recommendations as established by US guidelines (>35% of daily total energy). Women with PCOS also consumed greater amounts of sodium than the US Dietary Reference Intake (>2,300 mg/day), and did not meet fiber (<25 g/day) and potassium (<4,700 mg/day) recommendations, similar to the reference group. Women with and without PCOS had similar macro-and micronutrient intake in their diets, while the PCOS group scored higher in the HEI-2010 empty calories component. There were no differences in total energy intake between women with and without PCOS. Mean (SD) data for nutrient composition, diet quality and PA levels are presented in Table 3.2.

When adjusting for age, total calories and/or BMI, HEI-2010 empty calories scores continued to be positively associated with risk of PCOS (Table 3.3). Binomial logistic regression analyses also reported select B vitamins and minerals were positively

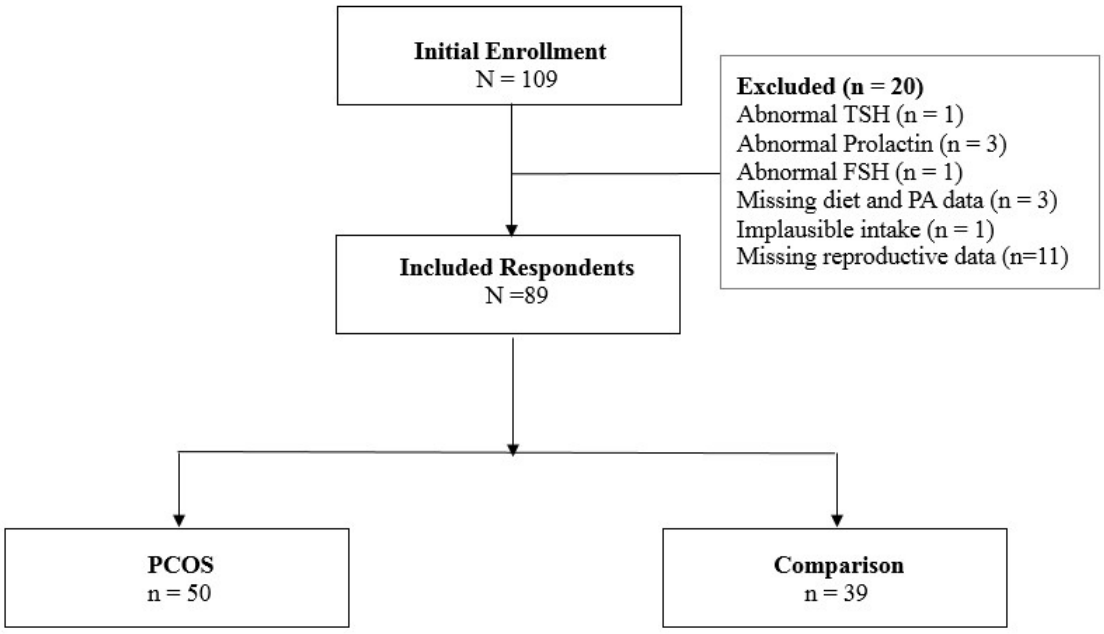

Figure 3.1. Participant flowchart. Flow diagram of the process through which participants were classified into PCOS and comparison groups.

Abbreviations: *FSH, follicle stimulating hormone; PA, physical activity TSH, thyroid stimulating hormone; PCOS, polycystic ovary syndrome*

Table 3.1. Characteristics for all women in the study[1]

Variable	Overall (n = 89)	Study Groups		*P*
		PCOS (n = 50)	Comparison (n = 39)	
Age, years	27.4 ± 6.0	26.0 ± 5.4	29.2 ± 6.3	0.01
Hispanic, n (%)	12 (14.3)	5 (10.6)	7 (18.9)	0.45
Race, n (%)				
Black	12 (14.0)	6 (12.2)	6 (16.2)	0.67
White	60 (69.8)	36 (73.5)	24 (64.9)	
Other	14 (16.3)	7 (14.3)	7 (18.9)	
BMI, kg/m^2	29.8 ± 7.6	31.6 ± 8.5	27.5 ± 5.7	<0.01
BMI, n (%)				
Healthy	29 (32.6)	13 (26.0)	16 (41.0)	0.17
Overweight	18 (20.2)	9 (18.0)	9 (23.1)	
Obese	42 (47.2)	28 (56.0)	14 (35.9)	
Highest Completed Education, n (%)				
High School or Lower	15 (27.8)	7 (35.0)	8 (23.5)	0.13
College	25 (46.3)	11 (55.0)	14 (41.2)	
Advanced Degree	14 (25.9)	2 (10.0)	12 (35.3)	
Reproductive History				
On OCP (Yes), n (%)	7 (7.9)	3 (6.0)	4 (10.3)	0.36
Mean Menstrual Cycle Length (days)	64.4 ± 75.9	95.3 ± 96.8	32.7 ± 12.8	<0.01
Mean Ovarian Volume (mL)	10.5 ± 5.7	12.3 ± 5.7	8.1 ± 4.7	<0.01
Mean FNPO (2 to 9 mm)	33.6 ± 22.4	44.5 ± 23.8	20.5 ± 10.5	<0.01
Total AFC	69.8 ± 44.3	88.8 ± 47.0	43.5 ± 20.9	<0.01
Total Testosterone (ng/dL)	51.9 ± 45.8	62.8 ± 58.3	38.3 ± 12.4	<0.01
Total Hirsutism Score	6.1 ± 4.9	7.5 ± 5.3	4.2 ± 3.6	<0.01

[1]Data are expressed as mean ± SD or n (% of those with data in each group). Statistical Test: Independent T-Tests or Chi Square. Comparison group (remaining women not classified as PCOS)
[2]Overall significance level $P < 0.05$

Abbreviations: AFC, Antral Follicle Count; BMI, body mass index; OCP, Oral contraceptive pill; PCOS, Polycystic Ovary Syndrome (Rotterdam Criteria); FNPO, Follicle Number Per Ovary

Table 3.2. Nutrient intake, diet quality, and physical activity for all women in the study[1]

Variable	Overall (n = 89)	DRI	Study Groups		
			PCOS (n = 50)	Comparison (n = 39)	*P*
Energy (kcal /d)	2098.1 ± 901.5	-	2107.9 ± 887.7	2085.5 ± 930.2	0.91
Total Carbohydrate (g/d)	254.6 ± 116.0	RDA: 130	253.6 ± 110.8	255.9 ± 123.7	0.93
Glycemic Index	514.6 ± 243.1		520.9 ± 240.6	506.5 ± 249.2	0.78
Glycemic Load	132.5 ± 69.2		134.3 ± 67.2	130.3 ± 72.3	0.79
Total sugars (g/d)	116.4 ± 65.9		115.9 ± 63.1	117.0 ± 70.2	0.94
Fiber (g/d)	22.9 ± 9.3	RDA: 25	22.4 ± 9.0	23.5 ± 9.8	0.58
Total Protein (g/d)	80.5 ± 34.2	RDA: 46	81.7 ± 33.6	79.0 ± 35.3	0.72
Total Fat (g/d)	83.6 ± 38.4	-	85.2 ± 40.3	81.4 ± 36.2	0.65
Cholesterol (mg/d)	279.4 ± 157.4	-	291.6 ± 165.2	263.8 ± 147.6	0.41
Total SFA (g/d)	27.2 ± 14.8	-	27.4 ± 15.3	27.0 ± 14.3	0.90
Total MUFA (g/d)	32.3 ± 14.6	-	33.1 ± 15.9	31.2 ± 13.0	0.54
Total PUFA (g/d)	17.1 ± 7.9	-	17.6 ± 8.2	16.5 ± 7.7	0.51
Omega 3 (mg/day)	1.8 ± 0.9	-	1.9 ± 0.9	1.8 ± 0.9	0.86
Trans-fat (g/d)	2.8 ± 2.2		3.0 ± 2.5	2.5 ± 1.6	0.31
Vitamin A (IU/d)	14298.6 ± 11056.8	UL: 10,000	13977.9 ± 11566.0	14709.7 ± 10502.7	0.76
Thiamin (mg/d)	1.7 ± 0.7	EAR: 0.9	1.8 ± 0.7	1.6 ± 0.7	0.30
Riboflavin (mg/d)	2.2 ± 0.9	EAR: 0.9	2.3 ± 0.8	2.1 ± 1.0	0.39
Niacin (mg/d)	22.4 ± 9.0	EAR: 11	23.8 ± 8.6	20.6 ± 9.1	0.09
Vitamin B6 (mg/d)	2.0 ± 0.7	AI: 1.2-1.3	2.1 ± 0.7	1.9 ± 0.7	0.10
Vitamin B12	5.3 ± 2.9	AI: 2.4	5.7 ± 2.9	4.7 ± 2.7	0.08
Vitamin C (mg/d)	126.3 ± 72.4	EAR: 60	127.4 ± 76.7	124.9 ± 67.4	0.87
Vitamin D (mcg /d)	5.3 ± 3.2	EAR: 10	5.4 ± 3.2	5.1 ± 3.3	0.70
Alpha Tocopherol Eq (mg/d)	19.6 ± 8.4	EAR: 12	20.7 ± 8.7	18.2 ± 7.9	0.15

Table 3.2. Nutrient intake, diet quality, and physical activity for all women in the study[1]

			Study Groups		
Variable	**Overall (n = 89)**	**DRI**	**PCOS (n = 50)**	**Comparison (n = 39)**	***P***
Sodium (mg/d)	3748.4 ± 1703.0	RDA: 1500	3792.8 ± 1694.2	3691.5 ± 1734.8	0.78
Calcium (mg/d)	1050.4 ± 468.2	EAR: 800	1035.9 ± 421.4	1069.0 ± 527.2	0.74
Phosphorus (mg/d)	1349.7 ± 542.5	EAR: 580	1339.2 ± 518.3	1363.1 ± 578.7	0.84
Potassium (mg/d)	3007.8 ± 1103.7	RDA: 4700	2992.3 ± 1080.1	3027.8 ± 1147.3	0.88
Iron (mg/d)	15.6 ± 6.4	EAR: 8.1	16.5 ± 6.1	14.4 ± 6.7	0.13
Copper (mg/d)	1.5 ± 0.5	EAR: 0.7	1.5 ± 0.5	1.4 ± 0.6	0.87
Magnesium (mg/d)	342.5 ± 120.4	EAR: 255-265	334.5 ± 110.1	352.9 ± 133.3	0.48
Zinc (mg/d)	12.4 ± 5.1	EAR: 6.8	13.2 ± 5.1	11.4 ± 5.0	0.11
Folic Acid (mcg/d)	562.9 ± 228.1	-	597.1 ± 218.5	519.2 ± 235.5	0.11
Caffeine (mg/d)	162.6 ± 145.0	-	153.0 ± 140.6	174.9 ± 151.4	0.48
HEI-2010 Scores[2]		**Max Score**			
Fruit	3.5 ± 1.6	5	3.5 ± 1.7	3.6 ± 1.5	0.66
Whole Fruit	3.8 ± 1.6	5	3.9 ± 1.6	3.7 ± 1.6	0.67
Vegetables	4.1 ± 1.1	5	4.1 ± 1.2	4.1 ± 1.1	0.87
Green Beans	3.5 ± 1.7	5	3.5 ± 1.8	3.6 ± 1.7	0.88
Whole Grains	4.9 ± 3.0	10	4.7 ± 3.1	5.2 ± 3.0	0.47
Dairy	6.2 ± 2.6	10	6.1 ± 2.5	6.4 ± 2.8	0.58
Protein Foods	4.5 ± 0.8	5	4.5 ± 0.8	4.5 ± 0.8	0.82
Seafood and Plant Proteins	3.9 ± 1.5	5	3.8 ± 1.6	4.0 ± 1.5	0.65
Fatty Acids	5.2 ± 3.1	10	5.5 ± 3.2	4.9 ± 2.9	0.33
Refined Grains	8.3 ± 2.3	10	8.2 ± 2.4	8.6 ± 2.1	0.44
Sodium	2.9 ± 2.5	10	2.8 ± 2.4	3.0 ± 2.6	0.67

Table 3.2. Nutrient intake, diet quality, and physical activity for all women in the study[1]

			Study Groups		
Variable	**Overall (n = 89)**	**DRI**	**PCOS (n = 50)**	**Comparison (n = 39)**	***P***
Empty Calories	7.3 ± 8.1	20	9.4 ± 8.0[3]	4.8 ± 7.6	<0.01
Total HEI-2010 Score	58.3 ± 14.1	100	59.9 ± 14.6	56.3 ± 13.4	0.24
Physical Activity					
Moderate Exercise (min/day)	55.2 ± 23.8	-	55.5 ± 24.2	55.0 ± 23.9	0.93
Vigorous Exercise (min/day)	7.5 ± 9.3	-	8.2 ± 8.5	6.9 ± 10.0	0.59
Total Moderate and Vigorous Exercise (min/day)	62.7 ± 27.9	-	63.8 ± 27.0	61.9 ± 29.0	0.80

[1]Data are expressed as mean (SD). Statistical Test: Independent T-Tests. Comparison group (remaining women not classified as PCOS)
[2] Higher score represents better quality for all components
[3]Overall significance level P < 0.05

Abbreviations: DRI, Dietary Reference Intake; EAR, Estimated Average Requirement; Eq, Equivalent; HEI, Healthy Eating Index; IU, International Units; MUFA, Monounsaturated Fatty Acid; PCOS, Polycystic Ovary Syndrome (Rotterdam Criteria); PUFA, Polyunsaturated Fatty Acid; RDA, Recommended Daily Allowance; SFA, Saturated Fatty Acid; UL, Upper Limit

Table 3.3. Multinomial logistic regression models estimating the association of diet and physical activity with PCOS[1]

Variables	Model 1: Age, Total Kcal		Model 2: Age, Total Kcal, BMI	
	Odds Ratio	**95% CI**	**Odds Ratio**	**95% CI**
Energy (kcal/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
Total Carbohydrate (g/d)				
PCOS	0.99	0.98, 1.01	1.00	0.98, 1.01
Glycemic Index				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
Glycemic Load				
PCOS	1.00	0.99, 1.02	1.00	0.98, 1.02
Total Sugar				
PCOS	1.00	0.99, 1.01	1.00	0.99, 1.01
Fiber (g/d)				
PCOS	0.98	0.93, 1.02	1.00	0.95, 1.05
Total Protein (g/d)				
PCOS	1.01	0.98, 1.04	1.01	0.98, 1.03
Total Fat (g/d)				
PCOS	1.02	0.99, 1.05	1.02	0.99, 1.05
Cholesterol (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
Total SFA (g/d)				
PCOS	1.03	0.96, 1.10	1.01	0.94, 1.09
Total MUFA (g/d)				
PCOS	1.03	0.98, 1.08	1.04	0.98, 1.09
Total PUFA (g/d)				
PCOS	1.05	0.96, 1.16	1.06	0.96, 1.17
Omega 3 (mg/day)				
PCOS	0.95	0.47, 1.92	1.20	0.58, 2.49
Trans-fat (g/day)				
PCOS	1.47	1.00, 2.17	1.30	0.88, 1.92
Vitamin A (IU/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
Thiamin (mg/d)				
PCOS	2.62	0.94, 7.33	2.25	0.76, 6.64
Riboflavin (mg/d)				
PCOS	1.81	0.94, 3.48	1.43	0.72, 2.88
Niacin (mg/d)				
PCOS	1.12[1]	1.04, 1.22	1.11[1]	1.02, 1.20
Vitamin B6 (mg/d)				
PCOS	2.30*	1.06, 5.00	2.47[1]	1.09, 5.58
Vitamin B12 (mg/d)				
PCOS	1.25[1]	1.04, 1.51	1.20	0.99, 1.45

Table 3.3. Multinomial logistic regression models estimating the association of diet and physical activity with PCOS[1]

Variables	Model 1: Age, Total Kcal		Model 2: Age, Total Kcal, BMI	
	Odds Ratio	**95% CI**	**Odds Ratio**	**95% CI**
Vitamin C (mg/d)				
PCOS	1.00	0.99, 1.01	1.00	1.00, 1.01
Vitamin D (mcg /d)				
PCOS	1.03	0.90, 1.18	1.02	0.88, 1.18
Alpha Tocopherol Eq (mg/d)				
PCOS	1.03	0.98, 1.09	1.05	0.99, 1.11
Sodium (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
Calcium (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
Phosphorus (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
Potassium (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
Iron (mg/d)				
PCOS	1.10[1]	1.01, 1.20	1.09	0.99,1.20
Copper (mg/d)				
PCOS	0.86	0.27, 2.71	1.45	0.42, 4.94
Magnesium (mg/d)				
PCOS	1.00	0.99, 1.00	1.00	0.99, 1.00
Zinc (mg/d)				
PCOS	1.18[1]	1.04, 1.34	1.15[1]	1.01, 1.31
Folic Acid (mcg/d)				
PCOS	1.00[1]	1.00, 1.00	1.00	1.00, 1.00
Caffeine (mg/d)				
PCOS	1.00	1.00, 1.00	1.00	1.00, 1.00
HEI-2010 Scores				
Fruit				
PCOS	0.90	0.70, 1.15	1.02	0.78, 1.34
Whole Fruit				
PCOS	1.06	0.83, 1.36	1.21	0.92, 1.60
Vegetables				
PCOS	1.02	0.72, 1.43	1.31	0.89, 1.93
Green Beans				
PCOS	0.96	0.76, 1.21	1.11	0.85, 1.44
Whole Grains				
PCOS	0.94	0.83, 1.06	0.97	0.85, 1.10
Dairy				
PCOS	0.98	0.85, 1.12	0.91	0.77, 1.06

Table 3.3. Multinomial logistic regression models estimating the association of diet and physical activity with PCOS[1]

Variables	Model 1: Age, Total Kcal		Model 2: Age, Total Kcal, BMI	
	Odds Ratio	**95% CI**	**Odds Ratio**	**95% CI**
Protein Foods				
PCOS	0.89	0.57, 1.39	0.99	0.63, 1.57
Seafood and Plant Proteins				
PCOS	0.87	0.68, 1.11	0.95	0.73, 1.23
Fatty Acids				
PCOS	1.05	0.92, 1.20	1.11	0.96, 1.28
Refined Grains				
PCOS	0.94	0.80, 1.11	0.95	0.80, 1.13
Sodium				
PCOS	0.97	0.84, 1.13	0.97	0.83, 1.14
Empty Calories				
PCOS	1.07[1]	1.02, 1.12	1.07[1]	1.01, 1.12
Total HEI-2010 Scores				
PCOS	1.01	0.99, 1.04	1.03	0.99, 1.06
Physical Activity				
Moderate Exercise				
PCOS	1.00	0.98, 1.02	1.00	0.98, 1.02
Vigorous Exercise				
PCOS	1.01	0.96, 1.06	1.02	0.96, 1.07
Total Moderate and Vigorous Exercise				
PCOS	1.00	0.98, 1.02	1.00	0.98, 1.02

[1]Overall significance level $P < 0.10$ due to exploratory analysis (vs. Comparison)

Abbreviations: Eq, Equivalent; HEI, Healthy Eating Index; IU, International Unit; MUFA, Monounsaturated Fatty Acid; PCOS, Polycystic Ovary Syndrome (hyperandrogenism and oligomenorrhea); PUFA, Polyunsaturated Fatty Acid; SFA, Saturated Fatty Acid

associated with PCOS. Higher intake of niacin (vitamin B3), vitamin B6, and zinc were associated with greater odds of PCOS in Models 1 and 2 ($P \leq 0.08$). In Model 1, an increase of 1 mg/day in vitamin B12 or iron intake was associated with 10 to 25% greater odds of having PCOS ($P \leq 0.08$). The main effects of vitamin B12 and iron were comparable between Models 1 and 2, yet results from Model 2 did not reach statistical significance. No other food groups and macro- or micronutrients were associated with PCOS.

Results from dietary interviews in a subset of participants confirmed findings that women with PCOS altered their eating behaviors. A higher proportion of participants in the PCOS group (21 of 33 interviews; 64%) reported attempting to increase intake of fiber and whole grains and/or limit refined sugar and fat than the reference group (10 of 23 interviews; 43%). Additionally, participants with PCOS described that they altered their diet due to health markers related to PCOS (e.g., weight gain, elevated triglycerides and glucose concentrations) (data not shown).

Physical activity

Women with and without PCOS met the 2008 PA guidelines for performing 150 minutes of moderate and/or 75 minutes of vigorous activity over 4 to 7 days (Table 3.2). No significant differences were observed in the duration spent in moderate and/or vigorous activities between the PCOS and comparison groups. There were also no significant associations detected between markers of PA and PCOS after adjusting for age, total calories and/or BMI (Table 3.3).

DISCUSSION

The objectives of this study were to understand the current diet and PA behavior of women with PCOS, and contrast these results with women without PCOS. By understanding the current dietary and PA behaviors in PCOS patients, potential targets for PCOS-specific interventions could be identified and integrated into existing practices. Our cross-sectional analyses revealed that women with PCOS did not meet US dietary recommendations for fat (% total energy/day), fiber (g/day), and potassium (mg/day). These findings agreed with two prior studies conducted outside the US that noted PCOS patients exceeded US and United Kingdom government recommendations on fat intake (30,32) and/or did not meet fiber (30,32) and potassium guidelines (32). High fat and low fiber and potassium intake have been linked to increased risk of cardiovascular disease (45) – an adverse outcome that is more likely to develop in women with PCOS than the general population (46). Despite these findings, we observed no association between total energy intake and PCOS, a finding that was consistent with two other studies conducted in the US (47,48). While the mounting cross-sectional evidence suggests that higher total energy intake is not associated with PCOS, we are unable to conclude whether this pattern is present for participants during their earlier reproductive years.

The current study confirmed that women with PCOS had healthier diets compared to women without PCOS. Our study revealed that a 1.6% decrease in total energy intake from sugar, fat, and alcohol was associated with a 7.0% increase in odds of PCOS. Higher intake of niacin, vitamin B6, and zinc were positively associated with PCOS in Models 1 and 2, while significant associations between vitamin B12 and iron

with PCOS were only observed in the Model 1. However, estimates of vitamin B12 and iron with PCOS were similar between the Models 1 and 2, suggesting that the addition of BMI as a covariate may lead to overadjustment in the regression analyses. Our findings paralleled results reported by Moran et al. (2013), in which the PCOS group reported better diet quality scores than a non-PCOS group (31). We hypothesize that our findings may be attributed to a greater proportion of women with PCOS changing their health-related behaviors, which was corroborated by our review of data from the diet interviews. Fewer empty calories and higher intake of B vitamins, iron, and zinc were significantly associated with PCOS, suggesting that patients with PCOS may have adopted specific dietary recommendations provided by either physicians and/or social media. Clinicians often provide government dietary recommendations, such as reducing healthy snacks, to encourage weight loss in overweight and obese PCOS patients (26,49,50). This may explain why the PCOS group in our study consumed fewer calories from solid fat, alcohol, and added sugars. The benefits of B vitamins, iron and zinc have also been encouraged in recent years on popular patient websites due to associations with markers of cardiovascular disease and diabetes (51), which is a preferred source of information for women with PCOS (52–55). Notably, an emphasis has been placed on consuming greater amounts of B vitamins to reduce homocysteine concentrations (an amino acid linked with cardiovascular disease) (56,57).

Outside of dietary recommendations, increasing PA is another fundamental strategy to achieve weight loss and treat PCOS symptoms (50). Our study found that women in the PCOS group met the recommended national PA guidelines, though we noted no significant associations between minutes spent in moderate and vigorous PA

with PCOS. These findings were consistent with five studies that detected no differences in self-reported moderate and vigorous PA between women with and without PCOS (31,32,47,58,59). A single study that measured PA using accelerometers also noted no significant differences in sedentary levels of obese adolescents with and without PCOS (24), suggesting that physical activity levels may not differ between women with and without PCOS across the reproductive life course. That said, we are aware of one study that reported longer sitting intervals in women with PCOS compared to the reference group (31). Differences in the patterns and types of PA and sedentary behaviors may exist between women with and without PCOS. However, future research involving assessments of PA patterns is ultimately needed to corroborate the relevance of these findings.

This study had several strengths. This was the first US study to use Rotterdam diagnostic criteria and new morphological criteria for PCOS when examining dietary and PA behaviors of the PCOS population, an approach recommended by the National Institutes of Health Evidence-based Methodology steering committee for clinical and research settings (21). Through this approach, we were able to capture the health-related behavior of women across all variants of PCOS, thereby improving the clinical applicability of our results. Our study was also among the first to use US government recommended benchmarks (60,61) to assess whether PCOS patients met nutrition needs and physical activity guidelines. This evaluation was particularly informative since these recommendations were created to reduce risk of chronic disease and are often indicators of healthy behaviors (39,60). However, our study was limited by the small sample size of women in the control group and by its cross-sectional design. Though

we identified potential associations between dietary and PA behaviors with PCOS, the temporal relationship has yet to be established. We also excluded women who were previously diagnosed with other chronic diseases due to institutional regulations, thus restricting the generalizability of our results to a healthier sample of PCOS patients.

Our findings build upon previous evidence to confirm a relationship between dietary intake and PCOS. Overall, women with PCOS met US dietary and PA guidelines, while higher intake of B vitamins, zinc, and iron, and fewer empty calories were associated with PCOS. These results suggest that women with PCOS may adopt certain healthy dietary and PA behaviors after receiving a PCOS diagnosis. However, these results also highlight a need for future longitudinal cohort studies to assess dietary and PA exposures to PCOS-related outcomes at earlier stages of the reproductive life course, particularly during adolescence. The early identification of dietary and PA factors that may promote or hasten progression to PCOS are needed to develop tailored preventative strategies for this chronic disorder.

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PART TWO PREFACE

The narrative review in **Part One** also identified the importance of understanding the psychosocial influences on lifestyle behaviors of PCOS patients. To encourage behavior change, health-related knowledge, personal beliefs and environmental influences are often incorporated in interventions at research and clinical settings. Data were collected on health-related knowledge status, beliefs about health, and perceptions directed toward healthcare providers for the following specific aims:

AIM 1: To compare health-related knowledge, beliefs, and self-efficacy between women with and without PCOS.

*This aim was addressed in **Chapter 4**.*

AIM 2: To compare perceptions of trust and social support from healthcare providers (medical experiences) between women with and without PCOS.

*This aim was addressed in **Chapter 5**.*

AIM 3: To examine whether trust towards physicians varied between general and PCOS health concerns in PCOS patients.

*This aim was addressed in **Chapter 5**.*

Both instruments were internally developed and validated using a nationwide US sample. Details on the reliability and validation analyses, as well as the final drafts of both instruments, are presented in **Appendices B and C.** This chapter yielded two primary research manuscripts.

CHAPTER 4: HEALTH-RELATED KNOWLEDGE, BELIEFS, AND SELF-EFFICACY IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

Submitted, with Decision to Revise, Resubmit: August 2017 by Human Reproduction

* Lin AW, Dollahite JS, Sobal, Lujan ME. Health-related knowledge, beliefs, and self-efficacy in women with polycystic ovary syndrome.

ABSTRACT

Study question: Do health-related knowledge, beliefs, and self-efficacy differ between women with and without polycystic ovary syndrome (PCOS)?

Summary answer: Women with PCOS felt at greater risk for adverse health outcomes, yet believed diet and PA behaviors were less beneficial to prevent weight gain relative to a comparison group.

What is known already: Dietary and physical activity interventions are often used to treat PCOS, but there are high attrition rates and less engagement in self-help methods. It is unclear whether there are unique psychosocial considerations in PCOS that should be incorporated into these interventions.

Study design, size, duration: This cross-sectional study enrolled 475 women with and without PCOS who were recruited through flyers and online advertisements across the United States.

Participants/materials, setting, methods: Participants were females who lived in the United States (mean age: 28.1 ± 5.4 years). Participants were considered to have PCOS if they responded affirmatively about whether they were previously diagnosed with PCOS by a healthcare provider. The remaining women were placed in the comparison

group. A reliable and valid online instrument about health-related knowledge, beliefs, and self-efficacy was administered to these participants.

Main results and the role of chance: Most women with PCOS had a basic understanding of nutrition (96%), but had misconceptions about diagnostic criteria for PCOS (≤86%). PCOS was associated with greater perceived susceptibility for disease and weight gain and poorer perceived control over these health outcomes (all $P \leq 0.05$), in relation to the comparison group. Women with PCOS also perceived fewer benefits of healthy behaviors on weight gain ($P=0.03$) with less than half of the PCOS group attempting to follow government diet recommendations (47%). There were no differences in the self-efficacy of dietary behaviors between groups.

Limitations, reasons for caution: It is likely that participant self-selection occurred due to the nature of recruitment in this study. Additionally, most of the sample identified as having European ancestry**,** which reduces the generalizability of the results.

Wider implications of the findings: These findings provide evidence that behavioral interventions should incorporate the unique psychosocial considerations associated with PCOS to encourage patient participation in health interventions.

Study funding/competing interest(s): This manuscript was partially supported by Cornell University Human Ecology Alumni Association and College of Agriculture and Life Sciences Alumni Association. The authors have no competing interests.

Trial registration number: NCT01859663

Keywords: Health Behaviors, PCOS, Psychosocial, Counseling

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder whose symptoms and co-morbidities have far-reaching implications for the health of women across the lifespan (Fauser *et al.*, 2012). Rotterdam criteria for PCOS define the condition by the presence of at least two of three features: 1) oligo- or amenorrhea; 2) hyperandrogenism; and 3) polycystic ovarian morphology (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Using these criteria, PCOS affects up to 10% of reproductive-aged women globally (Bozdag *et al.*, 2016) and is established as an independent risk factor for cardiovascular disease, diabetes, infertility, endometrial cancer, and obesity (Fauser *et al.*, 2012). Consequently, diet and physical activity (PA) modifications are recommended to treat PCOS symptoms and/or prevent the development of these adverse health outcomes (Harrison *et al.*, 2011; Moran *et al.*, 2009; Fauser *et al.*, 2012). Women with PCOS are frequently provided general behavioral advice, such as reducing high caloric and/or fat foods, and incorporating more PA (Humphreys and Costarelli, 2008; Jeanes *et al.*, 2009). Prior research has revealed that women with PCOS perceive these general diet and PA recommendations to be useful, but simultaneously vague and insufficient (Humphreys and Costarelli, 2008; Gibson-Helm *et al.*, 2014). Dissatisfaction with current recommendations suggest more targeted multidisciplinary interventions are needed to address barriers to adopting healthy practices in women with PCOS.

Studies in obese populations have established that effective interventions integrate a multidisciplinary approach (Ross *et al.*, 2010; Montesi *et al.*, 2016). A major component of this approach is the use of theories to understand the patient's health-

related knowledge, beliefs and self-efficacy (Ross *et al.*, 2010). Social Cognitive Theory (SCT) and the Health Belief Model (HBM) are two theories used in clinical and research settings to encourage behavior change (Bandura, 2004; Anderson *et al.*, 2007; Deshpande *et al.*, 2009). Social Cognitive Theory examines the interaction between personal, environmental, and behavioral factors, emphasizing self-efficacy (Bandura, 2004). The Health Belief Model can be implemented in conjunction with SCT to examine beliefs toward a disease and/or a behavior (Janz and Becker, 1984). Both theories maintain the assumption that cognitive (e.g., health-related knowledge) and affective (e.g., health-related beliefs, self-efficacy) factors are prerequisites for behavior change (Janz and Becker, 1984; Bandura, 2004). This assumption is supported by several studies involving women without PCOS wherein knowledge, beliefs, and self-efficacy (psychosocial constructs) were shown to influence adoption of behavioral modifications (Bunting and Boivin, 2007; Lo *et al.*, 2015; Stacey *et al.*, 2015; Teixeira *et al.*, 2015).

It remains unclear whether experiences related to PCOS impart additional psychosocial considerations when designing behavioral interventions. Unique concerns associated with PCOS may explain the high attrition rates in intervention studies (Sorensen *et al.*, 2012; Mutsaerts *et al.*, 2013) and less engagement in self-help methods (Jeanes *et al.*, 2009; Kozica *et al.*, 2013). Currently, there is limited understanding about the actual health-related knowledge, beliefs and self-efficacy of women with PCOS, and whether PCOS is associated with poor perceptions of health behaviors. The few studies published to date report conflicting evidence about whether women with PCOS have different health-related beliefs relative to women without PCOS, despite experiencing

poorer overall health and greater impairment from adverse health outcomes (Moran *et al.*, 2010; Kozica *et al.*, 2013). To address this knowledge gap, we compared health-related knowledge, beliefs, and self-efficacy between women with PCOS and a comparison group.

MATERIALS AND METHODS

Ethics Approval

The study was approved by the Institutional Review Board at Cornell University and all participants provided informed consent.

Participants

This project was an ancillary study of a larger observational investigation of the differences in diet and physical activity in women with and without PCOS (ClinicalTrials.gov Identifier: NCT01859663). Women were initially recruited through flyers posted in clinics throughout Tompkins County, New York, and through online local advertisements. Subsequently, recruitment was extended more broadly using several electronic platforms nationwide (Twitter, Facebook, Reddit, ResearchMatch).

Inclusion criteria were female, 18 to 38 years of age, US residents, and self-reported history of predictable menstrual cycles or self-reported physician diagnosis of PCOS. Exclusion criteria included incomplete surveys (defined as less than half of the instrument completed), implausible (defined as <16 kg/m^2 or >80 kg/m^2) or missing body mass index (BMI) values, diagnosis of major chronic disease (such as diabetes, kidney disease, and/or thyroid conditions), and/or a history of isolated oligo-amenorrhea (defined as unpredictable menstrual cycles and/or menstrual cycle length <20 or >35 days without a PCOS diagnosis). A participant was considered to have PCOS if she

responded ‘yes’ to the item: “Have you been diagnosed with PCOS by a medical professional?” Participants who responded ‘no’ and reported predictable menstrual cycles between 20 and 35 days were included in the comparison group. As such, PCOS status was based on self-report and not confirmed with clinical and/or biochemical data. This approach has been used in other studies (Kozica *et al.*, 2013; Gibson-Helm *et al.*, 2016) with the understanding that self-report may lead to random misclassification and an underestimate of true effect sizes. The large sample size employed in this study, and the validity of self-reported PCOS status as described by others (Teede *et al.*, 2013), were expected to reduce random misclassification bias.

Procedure

The Instrument for PCOS: Knowledge, Health-Related Beliefs, and Self-Efficacy (I-PCOSK) was developed as an online instrument (Qualtrics©, Provo, UT, USA) over a 21-month period (June 2014 to March 2016). The final instrument was comprised of 77 items designed using SCT and HBM constructs to assess 1) reproduction-, nutrition-, and PCOS-related knowledge, 2) beliefs about health outcomes and confidence in dietary and PA behaviors, and 3) self-evaluation of current behaviors (Supplemental Table S4.1). The majority of items were formatted as multiple choice questions or five-point rating scales. Items related to beliefs about the severity and inevitability of adverse health outcomes and evaluation of dietary and PA behaviors were assessed on a continuous scale (1=‘disagree’ to 5=‘agree’). For items about perceived susceptibility to adverse health outcomes, a value of 1 indicated ‘much lower than average’ and 5 indicated ‘much higher than average.’ Higher values on items assessing health-related worries denoted greater occurrences of worrying about adverse health outcomes

(1='never' to 5='almost all the time'). For self-efficacy, higher values indicated greater confidence to perform a given dietary behavior (1='cannot do' to 5='certainly can do'). Additional details about the development and validation of the I-PCOSK are presented in the Appendix B.

Statistical Analyses

Statistical analyses were performed using SPSS 23.0 (IBM, Armonk, NY, USA), with the significance level threshold set at $P<0.05$. Differences in demographics, self-reported anthropometrics, and health-related knowledge between women in the PCOS and comparison groups were analyzed with independent t-tests and/or Fisher's exact tests. Linear regression methods estimated the associations between PCOS status (exposure) with health-related beliefs and self-efficacy (outcomes). Each valid item in the I-PCOSK was analyzed as a separate regression model. Multiple linear regression models were adjusted for potential confounders: age (continuous), BMI (categorical), and highest completed education level (categorical). Unadjusted and adjusted model estimates were compared to confirm the presence of covariates. Due to the potentially high interrelatedness of the items, a correction for multiple comparisons across models was not used (Rothman, 1990).

RESULTS

Women across the US (n=786) responded to electronic advertisements for the self-administered I-PCOSK and 475 (69%) were eligible to participate in the study (Figure 4.1). The study sample was comprised of female adults who were primarily white, with at least a high school education (Table 4.1). The sample size exceeded the target recruitment goal (N = 150), which was calculated to provide 86% power to detect a 1-

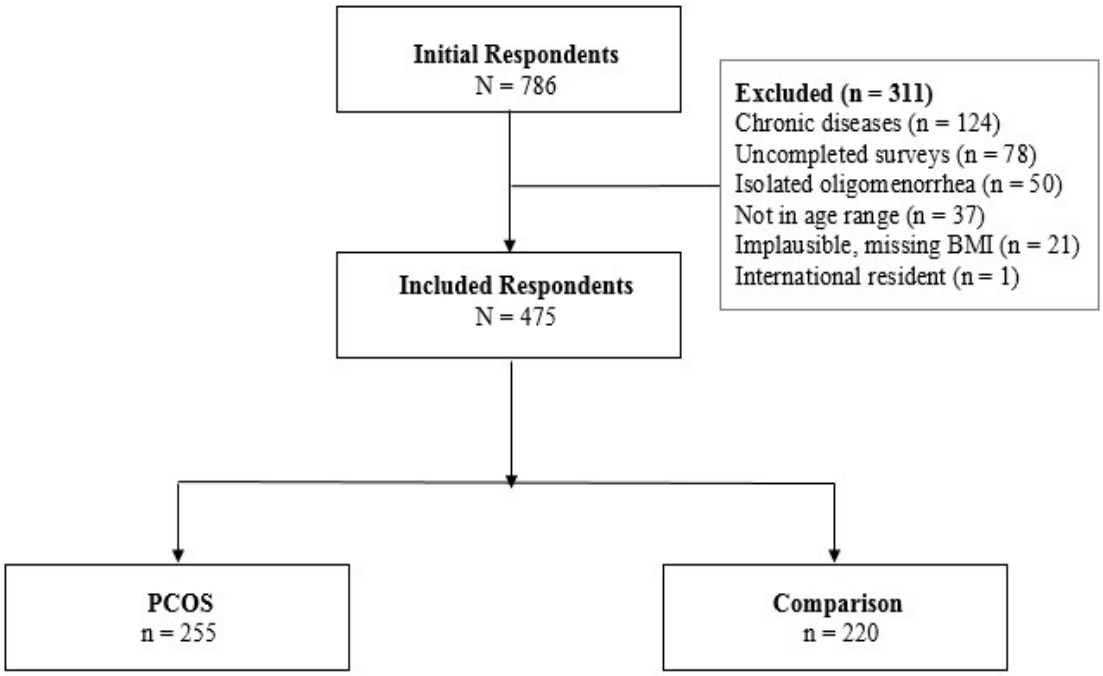

Figure 4.1. Participant flowchart. Flow diagram of the process through which participants were classified into PCOS and comparison groups.

Table 4.1. Characteristics of I-PCOSK participants

Characteristics	**PCOS[a] (n = 255)**	**Comparison (n = 220)**	***P***
Age (years)	29.3 ± 4.7	26.7 ± 5.7	<0.01
Race (%)			
Asian	11 (4.3)	13 (5.9)	
Black	18 (7.1)	14 (6.4)	
White	200 (78.5)	169 (77.2)	0.65
Latina	14 (5.5)	8 (3.7)	
Other	12 (4.7)	15 (6.8)	
Highest Education (%)			
≤ High School Degree	71 (27.8)	74 (33.6)	
Associate's Degree	30 (11.8)	26 (11.8)	0.01
College Graduate	91 (35.7)	92 (41.8)	
Advanced Degree	63 (24.7)	28 (12.7)	
BMI Categories (%)			
Underweight (< 18.5 kg/m^2)	4 (1.6)	8 (3.6)	
Normal (18.5- < 25 kg/m^2)	47 (18.4)	122 (55.5)	<0.01
Overweight (25- < 30 kg/m^2)	51 (20.0)	51 (23.1)	
Obese (≥ 30 kg/m^2)	153 (60.0)	39 (17.7)	

Data are expressed as mean ± SD, n (%). Significance level $P < 0.05$ between PCOS and comparison groups. *Abbreviations: PCOS, Polycystic ovary syndrome.*

[a] Prompt used to determine PCOS status: "Have you been diagnosed with PCOS by a medical professional?"

unit difference in measures of knowledge, beliefs and self-efficacy (scale). Women with PCOS (n=255) were older, more likely to be obese and to have an advanced degree relative to the comparison group (n=220, P <0.01). Those excluded from the analysis (n=311) were ineligible due to having a major chronic disease (n =124), submitting incomplete surveys (n=78), reporting a history of oligo-amenorrhea without a PCOS diagnosis (n=50), being ≤ 18 and ≥ 38 years old (n = 37), and/or meeting other exclusion criteria (n=22).

Health-related Knowledge in PCOS and Relation to the Comparison Group

A majority of women with PCOS (>76%) correctly answered knowledge items related to ovarian physiology and function (Figure 4.2). Most of the participants with PCOS (96%) also accurately identified at least one food group containing fiber and one national nutrition recommendation. When responding to items about PCOS, participants correctly answered items about evidence-based adverse health outcomes and treatments (Figure 4.3), but did not consistently identify components of established diagnostic criteria for PCOS. Features that were incorrectly identified as diagnostic criteria included sudden weight gain (64%), insulin resistance (81%) and trouble losing weight (86%). Relative to the comparison group, a greater percentage of the PCOS group correctly answered items related to knowledge of female reproductive hormones (Figure 4.2). By contrast, there were no differences in nutrition-related knowledge between the two groups.

Health-Related Beliefs in PCOS and Relation to the Comparison Group

The PCOS group reported high scores for perceived severity of cardiovascular disease, diabetes, and endometrial cancer, indicating that these outcomes were considered to

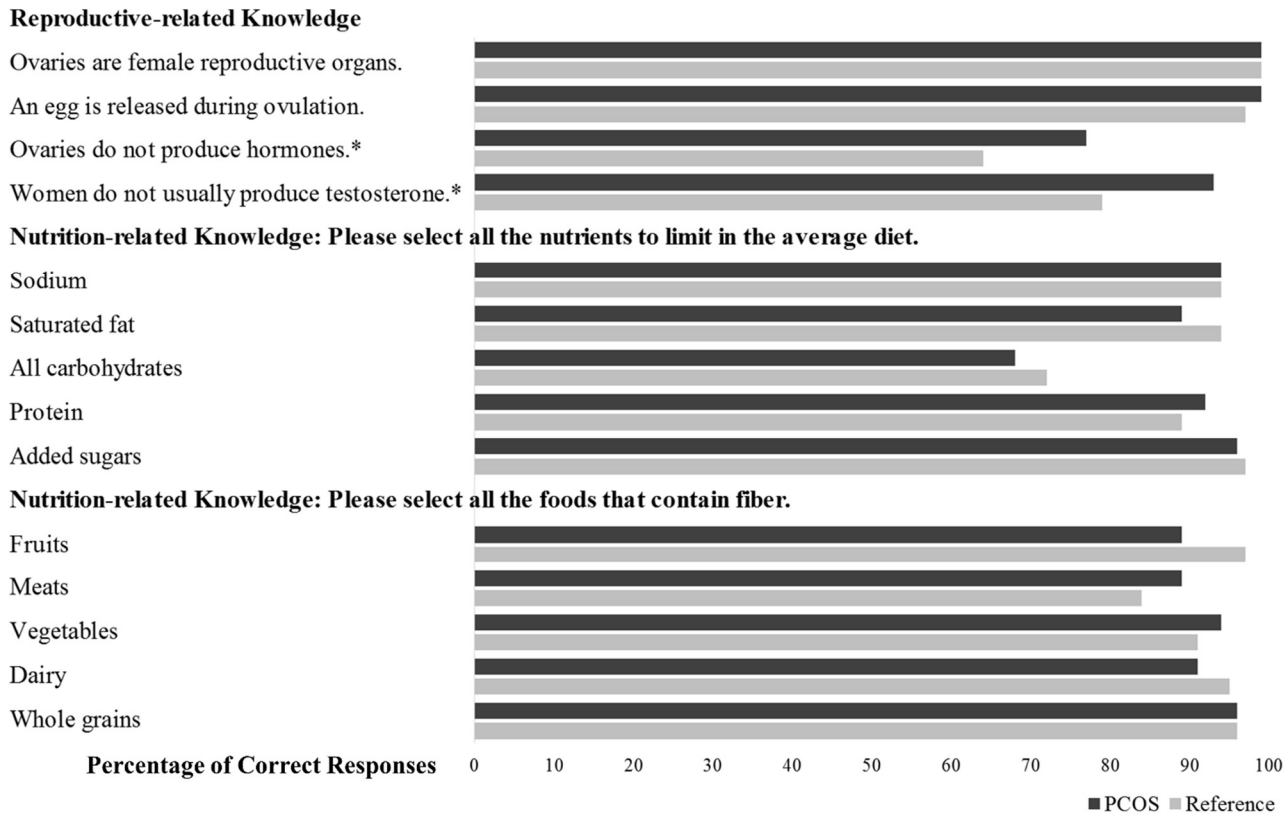

Figure 4.2. Correct responses on reproductive- and nutrition-related knowledge. Percentage of correct responses on reproductive- and nutrition-related knowledge in the PCOS and comparison groups (PCOS n = 255; Comparison n = 250). Asterisks represent significantly different responses between groups ($P \leq 0.01$).

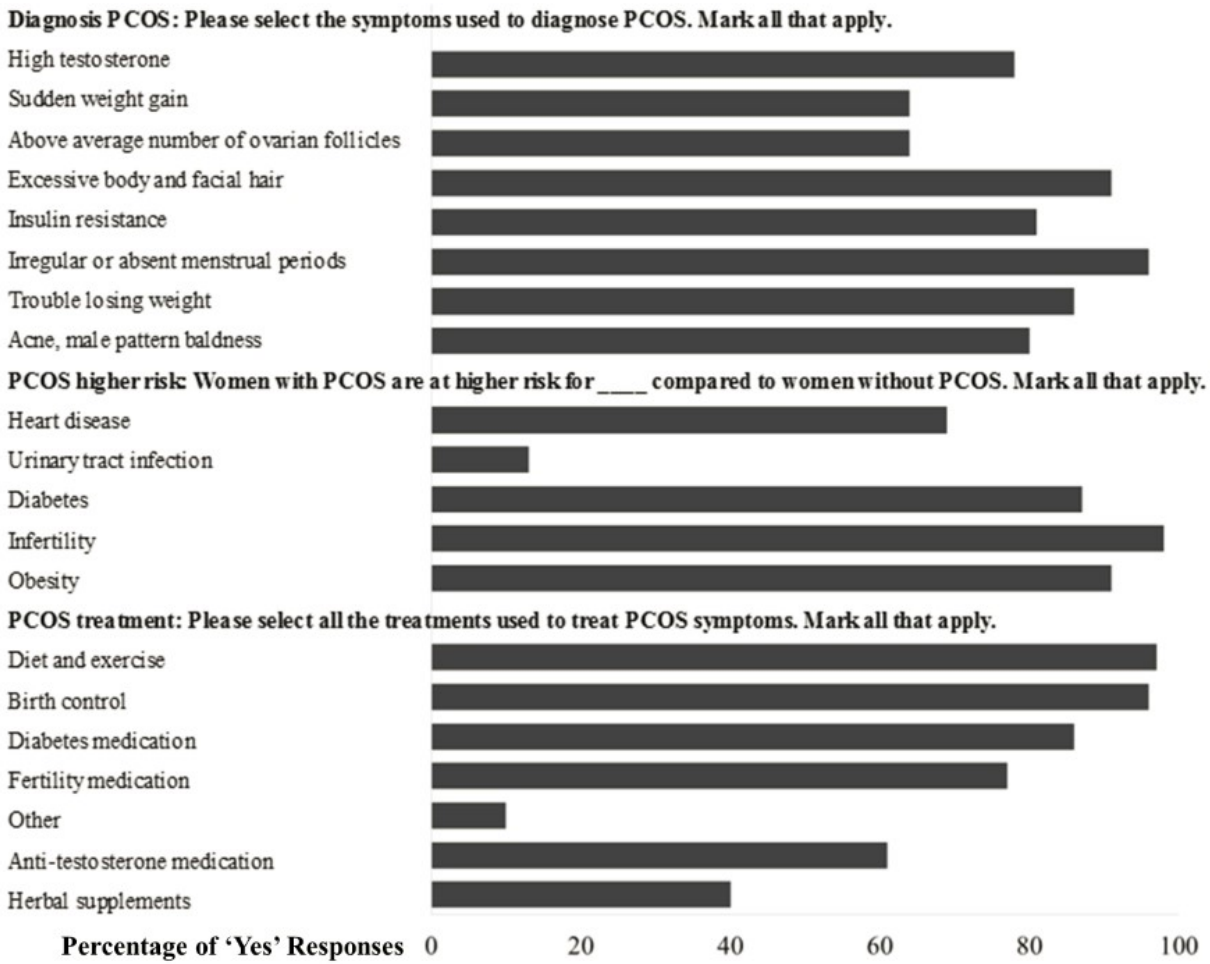

Figure 4.3. Responses on PCOS-related Knowledge. Percentage of "yes" responses on PCOS-related knowledge in the PCOS group (n = 255).

be serious health issues for this group (Table 4.2). Women with PCOS also reported they were at higher risk of developing adverse health outcomes. However, overall scores on the occurrence of worrying about cardiovascular disease and diabetes for this group fell between "hardly ever" and "usually" [2.55 (SD 1.19) and 3.21 (SD 1.13), respectively]. Women with PCOS were likely to believe that cardiovascular disease, diabetes, and weight gain were preventable (mean scores ≥3.90), but not endometrial cancer and infertility (mean scores ≤2.60). These beliefs were further corroborated by their responses that a healthy diet and/or physical activity would reduce their risk for adverse health outcomes, except for endometrial cancer and infertility (Table 4.2). Nevertheless, the PCOS group was ambivalent about the importance of meeting diet and physical activity government recommendations. Sixty-four percent reported they searched for the MyPlate guidelines on the Internet and fewer (47%) attempted to follow these recommendations, which was consistent with how the PCOS group rated the overall quality of their diet and lifestyle [3.12 (SD 1.00) and 2.86 (SD 1.04), respectively.

The PCOS group perceived greater severity of and susceptibility to endometrial cancer relative to the comparison group in both the unadjusted and adjusted regression models (Table 4.3). The addition of age, BMI, and education to the adjusted model did not appreciably alter estimates from the unadjusted model. Women with PCOS felt more susceptible to adverse health outcomes and were more concerned about developing cardiovascular disease and diabetes relative to the comparison group (P<0.01). Although the PCOS group reported poorer perceived control over cardiovascular disease and weight gain, this pattern was not observed for endometrial cancer and

Table 4.2. Health-related beliefs and self-efficacy scores in the PCOS group from the nationwide distribution (n = 255)

Item Prompt	PCOS	*Range of Scales (1 to 5)*
Health-Related Beliefs		
_____ is a very serious problem.		
Heart disease*	5.00 ± 0.00	*1 (disagree) to 5 (agree)*
Diabetes*	5.00 ± 0.00	
Endometrial cancer*	5.00 ± 0.00	
Compared to most people your age and weight in the United States, what would you say your chances are of getting:		
Heart disease	3.61 ± 1.11	*1 (much lower than average) to 5 (much higher than average)*
Diabetes	4.01 ± 1.05	
Endometrial cancer	3.50 ± 1.11	
Weight gain	4.29 ± 0.95	
During the past year, how often have you thought about your chances of getting:		
Heart disease	2.55 ± 1.19	*1 (never) to 5 (almost all the time)*
Diabetes	3.21 ± 1.13	
There is a lot I can do to prevent getting:		
Heart disease*	4.00 ± 1.00	*1 (disagree) to 5 (agree)*
Diabetes*	4.00 ± 1.00	
Endometrial cancer	2.61 ± 1.14	
Weight gain*	4.00 ± 2.00	

Table 4.2. Health-related beliefs and self-efficacy scores in the PCOS group from the nationwide distribution (n = 255)

Item Prompt	**PCOS**	***Range of Scales (1 to 5)***
Infertility	2.47 ± 1.15	
It is important for me to meet government _____ recommendations.		
Diet	3.11 ± 1.26	*(1 disagree) to 5 (agree)*
Physical activity	3.71 ± 1.28	
_____ will reduce my risk of _____.		
Healthy diet: Heart disease*	5.00 ± 1.00	*1 (disagree) to 5 (agree)*
Healthy diet: Diabetes*	5.00 ± 1.00	
Healthy diet: Endometrial cancer	2.77 ± 1.22	
Healthy diet: Weight gain*	5.00 ± 1.00	
Healthy diet: Infertility	2.73 ± 1.24	
Physical activity: Heart disease*	5.00 ± 1.00	
Physical activity: Diabetes*	5.00 ± 1.00	
Physical activity: Endometrial cancer	2.73 ± 1.27	
Physical activity: Weight gain*	5.00 ± 1.00	
Physical activity: Infertility	2.80 ± 1.28	
In general, how healthy is your overall _____?		
Diet	3.12 ± 1.00	*1 (poor) to 5 (excellent)*
Lifestyle	2.86 ± 1.04	

Table 4.2. Health-related beliefs and self-efficacy scores in the PCOS group from the nationwide distribution (n = 255)

Item Prompt	**PCOS**	***Range of Scales (1 to 5)***
Self-Efficacy: Please select how confident you are in your ability to do the following things FOR THE NEXT MONTH.		
Incorporate low fat foods into my diet.*	4.00 ± 2.00	*1 (cannot do) to 5 (certainly can do)*
Incorporate low salt foods into my diet.*	4.00 ± 2.00	
Decrease the amount of refined sugar in my diet.*	4.00 ± 2.00	
Eat more high fiber foods.*	5.00 ± 1.00	
Eat smaller portions at dinner.*	4.00 ± 2.00	
Control my eating on weekends.	3.84 ± 1.07	
Resist eating too much when there are many different kinds of food available.	3.72 ± 1.05	
Resist eating when I am at a party.	3.37 ± 1.23	
Resist eating when I am anxious or nervous.	3.58 ± 1.13	
Resist eating when I am depressed or feel down.	3.41 ± 1.18	
Resist eating when I am angry or irritable.	3.73 ± 1.11	
Resist eating when I experience failure.	3.66 ± 1.11	

Data are expressed as mean ± SD or median ± IQR (*). *Abbreviations: PCOS, Polycystic ovary syndrome*

Table 4.3. Differences in health-related beliefs and self-efficacy scores of the PCOS group (n = 255) in relation to the comparison group (n = 250) from the nationwide distribution

Item: Abbreviated Prompts	Unadjusted β (SE)	$P_{\text{Unadjusted}}$	Adjusted β (SE)[a]	P_{Adjusted}
Health-Related Beliefs				
_____ is a very serious problem.				
Heart disease	0.01 (0.05)	0.78	0.03 (0.05)	0.63
Diabetes	0.03 (0.05)	0.54	-0.01 (0.05)	0.80
Endometrial cancer	0.14 (0.06)	0.02	0.16 (0.07)	0.02
Compared to most people your age and weight in the United States, what would you say your chances are of getting:				
Heart disease	1.16 (0.10)	<0.01	0.83 (0.11)	<0.01
Diabetes	1.59 (0.10)	<0.01	1.25 (0.11)	<0.01
Endometrial cancer	1.02 (0.10)	<0.01	0.89 (0.11)	<0.01
Weight gain	1.60 (0.09)	<0.01	1.05 (0.09)	<0.01
During the past year, how often have you thought about your chances of getting:				
Heart disease	0.71 (0.10)	<0.01	0.47 (0.11)	<0.01
Diabetes	1.25 (0.10)	<0.01	0.93 (0.11)	<0.01
There is a lot I can do to prevent getting:				
Heart disease	-0.21 (0.08)	0.01	-0.19 (0.09)	0.04
Diabetes	-0.16 (0.08)	0.05	-0.19 (0.09)	0.05
Endometrial cancer	0.10 (0.10)	0.34	0.09 (0.12)	0.43
Weight gain	-0.52 (0.09)	<0.01	-0.44 (0.10)	<0.01
Infertility	0.28 (0.11)	0.08	0.20 (0.12)	0.10
It is important for me to meet government _____ recommendations.				

Table 4.3. Differences in health-related beliefs and self-efficacy scores of the PCOS group (n = 255) in relation to the comparison group (n = 250) from the nationwide distribution

Item: Abbreviated Prompts	**Unadjusted β (SE)**	***P*** **Unadjusted**	**Adjusted β (SE)[a]**	***P*** **Adjusted**
Diet	0.07 (0.12)	0.56	0.20 (0.13)	0.13
Physical activity	0.15 (0.12)	0.21	0.38 (0.13)	<0.01
_____ will reduce my risk of _____.				
Healthy diet: Heart disease	-0.12 (0.07)	0.08	-0.06 (0.08)	0.43
Healthy diet: Diabetes	-0.10 (0.07)	0.13	-0.10 (0.08)	0.22
Healthy diet: Endometrial cancer	-0.16 (0.11)	0.15	-0.12 (0.13)	0.34
Healthy diet: Weight gain	-0.27 (0.08)	<0.01	-0.19 (0.09)	0.03
Healthy diet: Infertility	0.11 (0.11)	0.32	0.15 (0.13)	0.25
Physical activity: Heart disease	-0.05 (0.07)	0.48	-0.03 (0.08)	0.72
Physical activity: Diabetes	-0.02 (0.07)	0.79	-0.05 (0.08)	0.53
Physical activity: Endometrial cancer	-0.13 (0.12)	0.26	-0.09 (0.13)	0.48
Physical activity: Weight gain	-0.24 (0.07)	<0.01	-0.18 (0.08)	0.03
Physical activity: Infertility	0.13 (0.12)	0.26	0.08 (0.13)	0.54
In general, how healthy is your overall _____?				
Diet	-0.15 (0.09)	0.10	0.04 (0.10)	0.72
Lifestyle	-0.32 (0.09)	<0.01	-0.11 (0.10)	0.27
Self-efficacy: Please select how confident you are in your ability to do the following things FOR THE NEXT MONTH.				
Incorporate low fat foods into my diet.	0.14 (0.10)	0.89	0.13 (0.11)	0.24
Incorporate low salt foods into my diet.	0.07 (0.10)	0.51	0.10 (0.12)	0.40
Decrease the amount of refined sugar in my diet.	0.14 (0.09)	0.14	0.20 (0.10)	0.06

Table 4.3. Differences in health-related beliefs and self-efficacy scores of the PCOS group (n = 255) in relation to the comparison group (n = 250) from the nationwide distribution

Item: Abbreviated Prompts	Unadjusted β (SE)	$P_{\text{Unadjusted}}$	Adjusted β (SE)[a]	P_{Adjusted}
Eat more high fiber foods.	0.09 (0.08)	0.25	0.14 (0.09)	0.14
Eat smaller portions at dinner.	0.17 (0.10)	0.08	0.17 (0.11)	0.13
Control my eating on weekends.	-0.06 (0.10)	0.57	0.05 (0.11)	0.62
Resist eating too much when there are many different kinds of food available.	0.09 (0.10)	0.35	0.19 (0.11)	0.09
Resist eating when I am at a party.	-0.06 (0.11)	0.61	-0.04 (0.12)	0.73
Resist eating when I am anxious or nervous.	-0.04 (0.11)	0.70	0.09 (0.12)	0.44
Resist eating when I am depressed or feel down.	-0.07 (0.11)	0.51	0.06 (0.12)	0.61
Resist eating when I am angry or irritable.	-0.20 (0.10)	0.05	-0.06 (0.11)	0.60
Resist eating when I experience failure.	-0.09 (0.10)	0.38	0.06 (0.11)	0.62

Significance level $P < 0.05$. *Abbreviations: PCOS, Polycystic ovary syndrome*

[a] Adjusted model: Independent variable: PCOS status (Reference category: comparison group); Dependent variable: I-PCOSK item; Covariates: age, BMI, education.

infertility as evidenced by the regression models. Women with PCOS were less likely to agree that a healthy diet or physical activity could reduce risk of weight gain relative to the comparison group (both P = 0.03), though the PCOS group placed greater importance in meeting national physical activity recommendations [adjusted model, β=0.38 (SE 0.13), P<0.01]. No differences were observed in how both groups rated their diet when accounting for age, BMI, and education level.

Health-Related Self-efficacy in PCOS and Relation to the Comparison Group

Women with PCOS were confident in their ability to incorporate low-fat, low-sodium and high-fiber food products, restrict refined sugar in the diet and eat smaller portions of food (Table 4.2). Although women with PCOS did not score as confidently on items related to resisting cues to eating compared to confidence to change one's diet, mean scores fell between "possibly can do" and "certainly can do." No significant differences were observed in self-efficacy scores on items related to diet modification and resistance to eating cues between the PCOS and comparison groups in either the unadjusted or adjusted models (Table 4.3).

DISCUSSION

Objectives of this study were to investigate health-related knowledge, beliefs and self-efficacy in women with PCOS. The PCOS group demonstrated basic understanding of female reproduction, current national diet recommendations and PCOS-related health risks and treatments. However, a majority of the women with PCOS did not correctly identify established PCOS diagnostic criteria. Overall, women with PCOS had significantly less optimal health-related beliefs relative to the comparison group but did not differ in their health-related self-efficacy.

Our study provides evidence that women with PCOS have some misconceptions surrounding criteria used to diagnose this condition. The high percentage of women who identified unestablished criteria as diagnostic may reflect current disagreements and/or confusion related to the actual clinical spectrum of PCOS among clinicians and researchers (Azziz, 2006; Teede *et al.*, 2014). In a recent publication documenting the PCOS diagnosis experience, a significant proportion of patients reported formal assessments by three or more health professionals occurring over several years prior to obtaining a formal diagnosis (Gibson-Helm *et al.*, 2016). The relatively long time to diagnosis and interaction with multiple specialists would be expected to engender some degree of confusion among patients related to how their diagnosis was ultimately established.

In particular, features related to body weight were selected as a diagnostic for PCOS by many women in this study, which may explain why the PCOS population was less likely to engage in self-help methods (Jeanes *et al.*, 2009; Kozica *et al.*, 2013). In a recent qualitative study with obese participants, those who expected failure with weight loss experienced more unsuccessful attempts (Hollywood and Ogden, 2016). Similarly, we hypothesize that women with PCOS may become less motivated to adopt healthy behaviors if they feel they are predisposed to have weight issues. Our findings suggest that despite believing that healthy behaviors decreases risk of weight gain, the PCOS group felt they had significantly poorer control over their weight relative to the comparison group and did not follow a self-described 'good' quality diet. Focusing on the known success of weight loss interventions in women with PCOS and providing strong encouragement about health-related issues from healthcare providers may

represent important targets for intervention when counseling women with PCOS about the benefits of behavior changes.

Although informed about their elevated risk for adverse health outcomes, women with PCOS are provided with government diet recommendations for the general population (e.g., avoid high-fat meals, reduce intake of unhealthy snacks) that they perceive as inadequate (Cussons *et al.*, 2005; Humphreys and Costarelli, 2008; Jeanes *et al.*, 2009). Our study showed that the PCOS group was ambivalent about meeting government diet recommendations. Fewer than half of the PCOS group attempted to follow these recommendations, despite being more concerned about developing adverse health outcomes relative to the comparison group.

Our findings also point to potential incongruences between attitudes toward government recommendations and self-efficacy of behavior performance in PCOS. Namely, participants with PCOS reported higher scores on self-efficacy items related to general diet recommendations in contrast to other dietary behaviors, though they did not usually adopt these behaviors. Further investigation is needed to explore whether attitudes toward diet recommendations may explain why women with PCOS are not practicing these dietary behaviors despite having confidence that they could successfully adopt the recommendations.

Endometrial cancer has emerged as a health concern for which women with PCOS may require further education. The PCOS group reported that they were more susceptible to endometrial cancer, but felt limited in their ability to prevent this condition. Despite consensus in the field that PCOS patients are at greater risk for endometrial cancer, very few clinicians reported this disease as their most important

concern compared to other adverse health outcomes for PCOS (Fauser *et al.*, 2012; Conway *et al.*, 2014). This finding is reflected in interviews with patients with PCOS who expressed receiving inadequate care for health outcomes outside of infertility (Weiss and Bulmer, 2011; Humphreys and Costarelli, 2008). Factors recognized to reduce risk of endometrial cancer (behavioral modifications, hormonal contraception) are prescribed to women with PCOS to treat their reproductive and metabolic complications (Cussons *et al.*, 2005; Ding *et al.*, 2016). However, our study suggests that women with PCOS may be unaware of the additional health benefits of these treatments.

Strengths of this study include the multiple recruitment methods used to administer the questionnaire, allowing opportunities to reach a variety of potential respondents. We also employed statistical models that accounted for significant sociodemographic differences between groups enabling us to address the main effect of PCOS on psychosocial constructs. Our emphasis on "PCOS identity" is also an important strength. Previous studies outside of PCOS support the idea that identity influences health-related psychosocial factors and behaviors (Hooker *et al.*, 2012; Grabowski, 2013). The participants involved in this study self-identify as having PCOS based on diagnosis made by a medical professional and would be expected to consider a professional medical opinion as a valid basis for their PCOS diagnosis.

Limitations include the study relying on participant self–selection particularly those with access to internet and interest in study participation, which can contribute to bias. Though the age and BMI distribution of our study sample was similar with an unselected US population of women with PCOS (Lo *et al*., 2006), most of the

participants also identified as non-Hispanic whites in contrast to a lower percentage of white women reported by Lo et al. (2006) (n=34%). This may reduce the generalizability of our results to other racial and ethnic groups. There is some evidence that the prevalence of PCOS and metabolic outcomes vary by race and ethnicity, which may create race-ethnic differences in health-related knowledge, beliefs, and self-efficacy in PCOS (Williamson *et al.*, 2001; Hillman *et al.*, 2014). Generalizability of the results may also be limited due to the convenience sampling approach employed in this study. However, to our knowledge, there is currently no evidence that health-related beliefs associated with PCOS differ across geographical locations within the US.

CONCLUSION

Despite these limitations, findings from this cross-sectional study provide groundwork for further research in this area. A future longitudinal cohort study would provide additional evidence about the temporal order between PCOS diagnosis and health-related beliefs. Few studies to date have identified potential psychosocial targets to improve attrition when designing weight loss interventions for PCOS. Our analyses support the conclusion that women with PCOS perceived themselves to be susceptible to adverse health outcomes and weight issues despite the adoption of healthy behaviors. A major theme emerging from this study is the importance of targeted diet and PA interventions for the PCOS population which addresses these unique perceptions. By directing multidisciplinary interventions to PCOS-specific issues, the high attrition in intervention studies and less engagement in self-help methods by patients may be addressed. Future studies are needed to examine how these psychosocial constructs can be successfully incorporated into targeted PCOS interventions with a multidisciplinary

healthcare team. Additionally, the interaction between obesity and PCOS should be further examined to determine whether there are different psychosocial considerations across the adiposity spectrum in women with PCOS.

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Supplemental Table S4.1. Constructs in the I-PCOSK

Constructs	Definition	Preliminary No. of Items	Retained No. of Items
Knowledge Constructs			
Reproduction	Knowledge of facts about reproduction	4	4
Nutrition	Knowledge of facts about nutrition	10	10
PCOS[b]	Knowledge of facts about PCOS	20	20
Belief Constructs			
Perceived severity of health outcome	Belief about the seriousness of a disease or condition	5	3
Perceived inevitability of health outcome	a) Perceived control over disease or condition; b) Belief that diet and/or physical activity can prevent a disease or condition	15	15
Perceived susceptibility of health outcome	Belief about risk of developing a disease or condition	5	4
Worry about health outcome	Concerns about developing a disease or condition	5	2
Evaluation of health behaviors	a) Actions taken to improve physical health; b) Evaluation of importance of meeting health guidelines	7	5
Self-efficacy Construct			
Self-efficacy for dietary behaviors	Confidence about successfully performing a dietary behavior	19	13
	Total No. of Items	91	77

Abbreviations: No., Number; I-PCOSK, Instrument for Polycystic Ovary Syndrome: Knowledge, Health-Related Beliefs, and Self-Efficacy.
[a] Total knowledge scores were only used in test-retest reliability analyses.
[b] Only administered in participants with PCOS.

CHAPTER 5: PERCEPTIONS OF TRUST AND SOCIAL SUPPORT TOWARD HEALTHCARE PROVIDERS DIFFER BETWEEN WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME

Plan to Submit: August 31, 2017

* Lin AW, Bergomi EJ, Dollahite JS, Sobal J, Hoeger KM, Lujan ME. Perceptions of trust and social support toward healthcare providers differ between women with and without polycystic ovary syndrome.

ABSTRACT

BACKGROUND: Women with polycystic ovary syndrome (PCOS) have reported dissatisfaction with their early medical care, which may foster poor relationships between patients and their healthcare providers. Positive perceptions of trust and social support toward healthcare providers are associated with a strong patient-provider relationship, but have not been measured in a larger-scale study of patients with PCOS.

OBJECTIVE: The objective of the study was to investigate whether perceptions of trust and social support toward physicians [primary care physicians (PCPs) and specialists] and/or other healthcare providers varied between women with and without PCOS.

STUDY DESIGN: A reliable and valid online instrument surveying aspects of trust and social support toward healthcare providers was advertised through paper and electronic adverts across the United States. Women, between 18 and 38 years old, used five point rating scales to rate trust and social support toward healthcare providers within the last three years. Participants who responded that they had a previous diagnosis with PCOS were placed in the PCOS group, while the remaining women were included in the comparison group. Linear regression models accounting for age, BMI, and income were

used 1) to compare trust and social support between PCOS (N=134) and comparison groups (N=198) and 2) to ascertain associations between type of health concern with perceptions of trust and social support in the PCOS group.

RESULTS: PCOS was associated with greater distrust in the PCP's opinion [β=0.38 (SE 0.15); *P*<0.01], but also greater confidence about the PCP's prioritization of general health concerns [β=0.31 (SE 0.13); *P*=0.04] relative to the comparison group. Patients with PCOS felt that the PCP spent less effort in treating PCOS health concerns [β=0.79 (SE 0.19); *P*<0.001] and were less qualified to treat PCOS symptoms [β=-0.75 (SE 0.17); *P*<0.001], in contrast to general health concerns. No significant associations were observed between having PCOS and trust in specialists. When examining social support, women with PCOS felt their healthcare providers argued with them more often relative to the comparison group [β=0.30 (SE 0.13); *P*=0.02].

CONCLUSION: Patient perceptions of trust and social support toward healthcare professionals differed between women with and without PCOS. Our findings support a need for improving trust and social support, particularly between patients with PCOS and PCPs. Future studies should confirm whether patients with PCOS view their medical experiences differently depending on the sub-specialty of the provider. Identifying areas for improvement in the patient-provider relationship may help to ensure continuity of care for patients with PCOS who require life-long surveillance to reduce reproductive and metabolic health risks.

Keywords: healthcare, physicians, polycystic ovary syndrome, social support, specialization, trust

INTRODUCTION

Patient perceptions of medical care have long been used to evaluate healthcare quality and inform clinical practice guidelines (Williams, 1994; Sitzia and Wood, 1997). The emphasis on understanding patient perception toward healthcare providers (such as beliefs on trust and social support) is attributed to its link with treatment adherence (Thom *et al.*, 2004; Reblin and Uchino, 2008) – an important consideration when treating polycystic ovary syndrome (PCOS). PCOS is characterized by the presence of at least two of the following features: androgen excess, irregular menstrual cycles and/or polycystic ovarian morphology (Carmina, 2004), and its effects extend well beyond impaired reproductive function. Several metabolic abnormalities (such as obesity, increased prevalence of risk factors for cardiovascular disease and diabetes) are closely associated with PCOS and lifelong medical care is required to manage PCOS symptoms and mitigate long-term health complications (Fauser *et al.*, 2012). As such, patients with PCOS are encouraged to engage in healthy dietary and physical activity (PA) behaviors, which improve the cardinal symptoms and metabolic status of PCOS. (Cussons *et al.*, 2005; Moran *et al.*, 2009; Jarrett and Lujan, 2016). However, women with PCOS may face unique barriers that impede the adoption of these health-related behaviors due to their previous medical experiences (Sills *et al.*, 2001; Gibson-Helm *et al.*, 2016). The degree to which beliefs about trust and social support in healthcare providers contribute to these barriers is uncertain.

There are few data evaluating the patient-provider relationship in PCOS (Gibson-Helm *et al.*, 2016; Tomlinson *et al.*, 2017). A substantial proportion of patients with PCOS across several countries reported feeling frustrated with their early medical

experiences (Gibson-Helm *et al.*, 2016), resulting in negative feelings toward healthcare providers (Crete and Adamshick, 2011; Tomlinson *et al.*, 2017). Further, patients' perceptions of the quality of medical care appeared to vary between primary care physicians (PCPs) and specialists (Crete and Adamshick, 2011; Weiss and Bulmer, 2011; Tomlinson *et al.*, 2017). This observation is particularly relevant in the United States (US), where a gatekeeping approach involving PCPs operates within the healthcare system for access to specialist referrals (Forrest, 2003; Shi, 2012). Women with PCOS will likely require care from multiple healthcare providers across the life course, due to the evolution of their endocrine and metabolic symptoms with aging and/or changes to treatment goals at different life stages (Goodman *et al.*, 2015; Gibson-Helm *et al.*, 2016).

It is also unclear whether medical experiences related to PCOS influence patient perceptions during treatment for general medical concerns. Previous studies reported about patients' perceptions of limited informational support provided about specific PCOS issues, but did not investigate other health concerns that are addressed during patient-provider interactions (Humphreys and Costarelli, 2008; Crete and Adamshick, 2011; Gibson-Helm *et al.*, 2016). Themes of emotional support have been only briefly discussed these studies, leaving this concept largely unexplored in this patient population. To that end, our primary objective was to examine whether there were differences in perceptions of trust and social support between women with and without PCOS with types of physicians (i.e., PCP, specialists) and/or other healthcare providers (i.e., nurse practitioners, physician assistants). Our secondary objective was to examine whether perceptions of trust in physicians varied between the types of health concerns

(i.e., general vs. PCOS-related). This study provides context about the current perceptions of medical care in women with PCOS with the goal of identifying factors which could be targeted to improve patients' overall medical experiences.

MATERIALS AND METHODS

This project was registered as part of a larger observational study comparing health-related behaviors (i.e., diet, physical activity) in women with and without PCOS (ClinicalTrials.gov Identifier: NCT01859663). Flyers and online advertisements (i.e., Twitter, Facebook, Reddit, ResearchMatch) were used to recruit locally around Tompkins County, NY, and broadly across the United States (US). Participants met inclusion criteria if they reported that they were between 18-38 years of age, and either a history of predictable menstrual cycles (i.e., between 20 and 35 days) or an existing PCOS diagnosis. A participant was placed in the PCOS group if they responded affirmatively to the item, "Have you been diagnosed with PCOS by a medical professional?" Those who never received a PCOS diagnosis and reported predictable menstrual cycle lengths (i.e., 20 and 35 days) were placed in the comparison group. Participants were excluded if they had 1) incomplete surveys (less than half of the instrument), or reported 2) implausible or missing BMI (defined as < 16 kg/m^2 or > 80 kg/m^2), 3) a major chronic disease, 4) a self-reported history of isolated oligomenorrhea (defined as unpredictable menstrual cycles and/or menstrual cycle length <20 or >35 days without a PCOS diagnosis), and/or 5) non-US resident status. The Institutional Review Board approved the study protocol and all participants provided informed consent.

I-PCOSM Instrument

The I-PCOSM (Instrument for Polycystic Ovary Syndrome: Medical Experiences) was distributed as a web-based instrument (Qualtrics, Provo, UT, USA) over a 2-year interval (August 2014 to August 2016). Details about the development and validation of the I-PCOSM are described in the Appendix C. After evaluating the validity and reliability of the I-PCOSM, the final instrument contained 28 items that assessed the recent medical experiences of women with PCOS within the last three years (Supplemental Table S5.1). Items related to trust in physicians were consistently worded across types of physicians (PCP or specialist) and health concerns (general or PCOS-related). The PCOS group was presented with items on both types of health concerns, while the comparison group was only asked about general health issues. Responses to each I-PCOSM item were formatted as five-point rating scales. Response options on trust in physicians ranged from 'strongly disagree' to 'strongly agree', while the scales on social support ranged from 'never' to 'always.'

Statistical Analysis

Data were analyzed with SPSS 23.0 (IBM, Armonk, NY, USA) and a $P < 0.05$ was considered statistically significant. Demographic and anthropometric data were compared between PCOS and comparison groups using independent t-tests and Chi-square analyses. To address the primary objective, multiple linear regression was used to examine associations between PCOS status (exposure) with trust and social support outcomes. Mixed-effects regression models were used to investigate whether trust towards physicians differed between types of health concerns. Given that each participant in the PCOS group had two observations for this secondary objective, participants were treated as a random effect in the mixed model. All regression models

were adjusted for age (continuous), BMI (categorical), and income (categorical). As a result of the high correlation between trust items, multiple comparison correction methods were not used in the analyses (Thom *et al.*, 1999).

RESULTS

Of the 755 women that completed the I-PCOSM in the nationwide sample (Figure 5.1), 332 (44%) met eligibility criteria for the PCOS (n=134) and the comparison groups (n=198) (Table 5.1). Excluded participants (n=423) were ineligible based on incomplete surveys (n=312), report of oligo-amenorrhea without a PCOS diagnosis (n=80), non-US resident status (n=30), and/or implausible or missing BMI values (n=1). The eligible study sample included 262 (78.9%) white participants and 188 (56.6%) participants with a college degree. Most women were New York State residents (62.2%), with the remaining participants residing at different areas in the United States. Groups did not differ by age, race, education or BMI. By contrast, the PCOS group reported higher yearly household incomes relative to the comparison group ($P < 0.001$).

Women with PCOS felt their physicians (both PCPs and specialists) were well qualified to treat general health concerns and were able to place patients' medical needs above other considerations (Table 5.2). Overall, the PCOS group had positive beliefs regarding the physicians' efforts to treat their general health concerns. While women with PCOS disagreed with the statement, "I sometimes distrust the recent specialized doctor's opinions and would like a second one" [2.47 (SD 1.16)], they had more neutral attitudes towards the PCP [3.05 (SD 1.16)]. These findings were confirmed with results from the multiple linear regression models (Table 5.3). Relative to the comparison

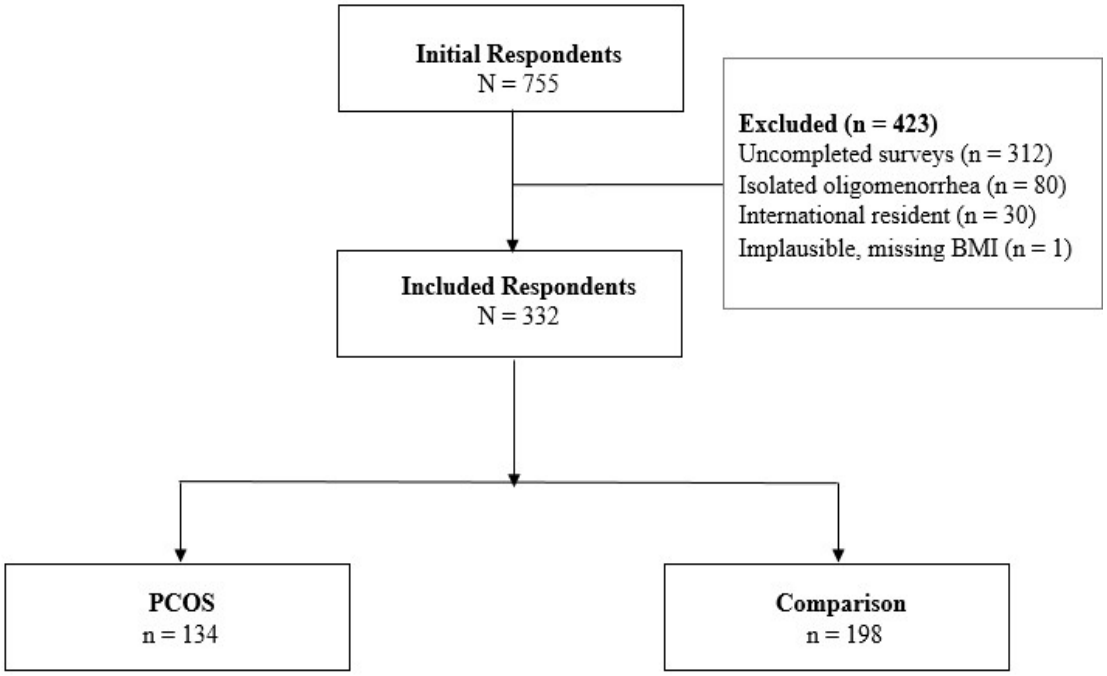

Figure 5.1. Participant flowchart. Flow diagram of the process through which participants were classified into PCOS and comparison groups.

Table 5.1. Characteristics of I-PCOSM participants

Characteristics	**PCOS[a] (n = 134)**	**Comparison (n = 198)**	***P***
Age (years)	28.2 ± 4.7	27.5 ± 5.5	0.22
Race (%)			
Asian	4 (3.0)	15 (7.6)	0.39
Black	8 (6.0)	15 (7.6)	
White	112 (83.6)	150 (75.8)	
Latina	2 (1.5)	3 (1.5)	
Other	8 (6.0)	15 (7.6)	
Highest Education (%)			
≤ High School Degree	34 (25.4)	61 (30.8)	0.19
Associate's Degree	16 (11.9)	33 (16.7)	
College Graduate	54 (40.3)	75 (37.9)	
Advanced Degree	30 (22.4)	29 (14.6)	
Household Yearly Income (%)			
≤ $19,999	19 (14.2)	57 (28.8)	<0.001
$20,000 - $39,999	29 (21.6)	60 (30.3)	
$40,000 - $59,999	16 (11.9)	30 (15.2)	
$60,000 - $79,999	18 (13.4)	17 (8.6)	
$80,000 - $99,999	35 (26.1)	16 (8.1)	

Table 5.1. Characteristics of I-PCOSM participants

Characteristics	**PCOS[a] (n = 134)**	**Comparison (n = 198)**	***P***
≥ $100,000	17 (12.7)	18 (9.1)	
BMI Categories (%)			
Underweight (< 18.5 kg/m^2)	2 (1.5)	2 (1.0)	0.34
Normal (18.5-< 25 kg/m^2)	46 (34.3)	74 (37.4)	
Overweight (25-29.9 kg/m^2)	23 (17.2)	46 (23.2)	
Obese (≥ 30 kg/m^2)	63 (47.0)	76 (38.4)	
Medical Visits in Past 3 Years: General Health Concerns			
Seen by Primary Care Physician	112 (83.6)	164 (82.8)	0.88
Seen by Specialist	70 (52.2)	129 (65.2)	0.02
Medical Visits in Past 3 Years: PCOS Health Concerns			
Seen by Primary Care Physician	62 (46.3)	NA	NA
Seen by Specialist	81 (60.4)	NA	NA

Data are expressed as mean ± SD or n (%). Significance level P < 0.05 between PCOS and comparison groups.
[a] Prompt used to determine PCOS status: "Have you been diagnosed with PCOS by a medical professional?"

Abbreviations: *I-PCOSM, Instrument for Polycystic Ovary Syndrome: Medical Experiences; NA, Not applicable; PCOS, Polycystic ovary syndrome.*

Table 5.2. Trust and social support scores in the polycystic ovary syndrome group (n = 134)

Trust in Physicians	**General Concerns**	**PCOS Concerns**	**Scoring Range**
Primary Care Physicians			
I feel the recent Primary Doctor does not do everything he/she should about my medical care.	2.67 ± 1.16	3.44 ± 1.38	*1 = Strongly disagree* *2 = Disagree* *3 = Neutral* *4 = Agree* *5 = Strongly agree*
I sometimes distrust the recent Primary Doctor's opinions and would like a second one.	3.05 ± 1.16	3.19 ± 1.22	
I trust the recent Primary Doctor to put my medical needs above all other considerations when treating my medical problems.	3.85 ± 1.00	3.78 ± 1.10	
The recent Primary Doctor is well qualified to treat medical problems that I experience.	4.08 ± 0.89	3.39 ± 1.43	
Specialists[a]			
I feel the recent Specialized Doctor does not do everything he/she should about my medical care.	2.26 ± 1.02	2.52 ± 1.16	*1 = Strongly disagree* *2 = Disagree* *3 = Neutral* *4 = Agree* *5 = Strongly agree*
I sometimes distrust the recent Specialized Doctor's opinions and would like a second one.	2.47 ± 1.16	2.50 ± 1.16	
I trust the recent Specialized Doctor to put my medical needs above all other considerations when treating my medical problems.	3.74 ± 0.94	3.83 ± 0.99	
The recent Specialized Doctor is well qualified to treat medical problems that I experience.	4.13 ± 0.85	4.02 ± 0.92	
Social Support from Healthcare Providers[b]	**General and/or PCOS Concerns**		**Scoring Range**
How often...			
Do they give you advice or information about health (whether you want it or not)?	4.18 ± 0.78		*1 = Never*

Table 5.2. Trust and social support scores in the polycystic ovary syndrome group (n = 134)

Do they give you advice or information about nutrition (whether you want it or not)?	3.41 ± 1.17	*2 = Rarely* *3 = Sometimes* *4 = Usually* *5 = Always*
Do they give you advice or information about PCOS (whether you want it or not)?	3.25 ± 1.11	
Do they give you reassurance, encouragement and emotional support (affection) concerning your health?	2.84 ± 1.23	
Do they listen to and try to understand your worries about your health?	3.42 ± 1.08	
Can you relax and be yourself around them?	3.05 ± 1.15	
Can you open up to them if you need to talk about your worries about your health?	3.34 ± 1.17	
How…		
Satisfied are you with the emotional support provided?	3.04 ± 1.17	*1 = Never* *2 = Rarely* *3 = Sometimes* *4 = Usually* *5 = Always*
Often do they argue with you relating to your health?	1.67 ± 0.98	
Often do they criticize you relating to your health?	1.81 ± 1.01	
Often do they let you down when you are counting on them?	2.01 ± 1.08	
Often do they withdraw from discussions or try to change the topic away from your health?	1.46 ± 0.86	

Data are expressed as mean ± SD

[a] Examples include gynecologists, endocrinologists, dermatologists.

[b] Includes physicians, nurse practitioners, physician assistants

Abbreviations*: PCOS, Polycystic ovary syndrome*

Table 5.3. Differences in trust and social support scores between PCOS (n = 134) and comparison groups (n = 198)

Trust in Physicians				
Primary Care Physicians (PCOS vs Comparison Group)[a]	**Unadjusted β (SE)**	$P_{\text{Unadjusted}}$	**Fully Adjusted β (SE)**	P_{Adjusted}
I sometimes distrust the recent Primary Doctor's opinions and would like a second one.	0.34 (0.14)	0.02	0.38 (0.15)	<0.01
I trust the recent Primary Doctor to put my medical needs above all other considerations when treating my medical problems.	0.35 (0.12)	0.01	0.31(0.13)	0.04
The recent Primary Doctor is well qualified to treat medical problems that I experience.	0.24 (0.11)	0.03	0.22 (0.11)	0.05
Primary Care Physicians (General vs. PCOS Concerns)[b]	**Partial Adjusted β (SE)**	P_{Partial}	**Fully Adjusted β (SE)**	P_{Adjusted}
I feel the recent Primary Doctor does not do everything he/she should about my medical care.	0.81 (0.20)	< 0.001	0.79 (0.19)	< 0.001
The recent Primary Doctor is well qualified to treat medical problems that I experience.	-0.75 (0.17)	< 0.001	-0.75 (0.17)	< 0.001
Social Support from Healthcare Providers[ac]	**Unadjusted β (SE)**	$P_{\text{Unadjusted}}$	**Fully Adjusted β (SE)**	P_{Adjusted}
How often do they argue with you relating to your health?	0.30 (0.12)	0.02	0.30 (0.13)	0.02

Significance level $P < 0.05$.

[a] Adjusted models: Independent variable: PCOS (Reference category: comparison group); Dependent variable: I-PCOSM item; Covariates: age, BMI, income.

[b] Adjusted mixed model: Independent variable: PCOS (Reference category: general health issues); Dependent variable: I-PCOSM item; Covariates: participant (partial and fully adjusted), age, BMI, income (fully adjusted)

[c] Includes physicians, nurse practitioners, physician assistants

***Abbreviations**: PCOS, Polycystic ovary syndrome*

group, women with PCOS experienced greater distrust in the opinions offered by the PCP but reported greater confidence in the PCP's prioritization of their general health concerns. PCOS was also positively associated with patient's trust in the PCP's qualifications to treat general health concerns ($P<0.02$), albeit this association became non-significant after adjusting for covariates. No significant associations were observed between PCOS status and trust in specialists.

Women with PCOS provided favorable scores when asked about their trust in specialists regarding PCOS-related concerns (Table 5.2). Similar to perceptions about general health concerns, women with PCOS agreed that the PCPs were able to prioritize PCOS medical needs [3.78 (SD 1.10)] but had neutral feelings about their PCP's qualifications to treat PCOS [3.39 (SD 1.43)]. The PCOS group's responses to items relating to the PCPs efforts to treat and advise on PCOS concerns suggested they were not completely satisfied with their interactions with the PCP [3.44 (SD 1.38) and 3.19 (SD 1.22)]. Results from the mixed model confirmed that the PCOS group felt their PCP placed less effort in treating PCOS issues compared to general health concerns (Table 5.3). Moreover, women with PCOS were less likely to believe that their PCP was well qualified to treat PCOS concerns relative to general health concerns ($P<0.001$). The adjustment for potential covariates did not appreciably alter the estimates of these associations.

The PCOS group reported that they usually received general health advice (informational support) from healthcare providers, but did not usually receive specific information about nutrition and PCOS (Table 5.2). Women with PCOS reported that they rarely had negative encounters with their healthcare providers, yet were only

sometimes satisfied with the emotional support provided during their medical care. The limited satisfaction may be attributed to the patients' inability to usually relax and discuss their health concerns with their healthcare providers [3.05 ± 1.15 and 3.34 ± 1.17], as well as the patients' perception that healthcare providers only sometimes comprehended their health concerns [3.42 ± 1.08]. When examining differences in perceptions of social support by mixed models, the PCOS group reported that their healthcare providers were more inclined to argue about health-related issues relative to the comparison group (Table 5.3).

DISCUSSION

To our knowledge, this was the first study to directly investigate the perceptions of trust and social support with healthcare providers in a sample of women with PCOS. Our data support the conclusion that women with PCOS believe that their PCPs are well qualified to treat general health concerns, but are less qualified to address issues related to PCOS. Accordingly, PCOS was associated with greater distrust of the PCP's opinions to treat PCOS concerns, but this association was not observed with specialists. Women with PCOS were only somewhat satisfied with the provision of emotional support experienced during medical visits and felt they had more arguments with their healthcare providers about their health concerns compared to the comparison group.

Differences in trust between study groups emerged only when medical experiences with PCPs were evaluated, suggesting that patient perceptions may differ between PCP and specialists. We hypothesize that PCPs face greater feelings of distrust because they are at the front-line of healthcare delivery (Forrest, 2003) and generally provide referrals when encountering medical conditions outside their usual scope of

practice (Mehrotra *et al.*, 2011). However, the absence of significant associations between PCOS and trust items related to specialists should not be interpreted to mean that all types of specialized care are associated with better perceptions of trust. The I-PCOSM did not distinguish patient experiences by physician sub-specialty, leaving this as an important area of future research. The need for more research in this area was emphasized by recent findings of varying levels of knowledge between reproductive endocrinologists and gynecologists (Dokras *et al.*, 2017) and the substantial lag period between PCOS symptom onset and diagnosis by multiple healthcare providers (Gibson-Helm *et al.*, 2016).

This study showed that women with PCOS only sometimes received information about PCOS, per se, and the beneficial dietary and PA behaviors, which is consistent with previous findings that patients with PCOS are provided with limited information from their healthcare providers (Humphreys and Costarelli, 2008; Crete and Adamshick, 2011; Gibson-Helm *et al.*, 2016; Tomlinson *et al.*, 2017). Further, we also noted that women with PCOS were only sometimes satisfied with the emotional support provided by their healthcare providers, which was closely linked to poor perceptions of receiving encouragement about their health. Among the few qualitative studies that have examined the concept of emotional support, interviews revealed that women with PCOS perceived a lack of empathy and experienced greater frequency of arguments with their physicians (Weiss and Bulmer, 2011; Tomlinson *et al.*, 2017). Tomlinson et al. (Tomlinson *et al.*, 2017) identified conflicts stemming from disagreements about whether PCOS symptoms would alleviate with age and on the necessity of specialist referrals. Our demonstration that PCOS was associated with greater arguments about

health-related issues relative to the comparison group support these earlier findings. Collectively, results across studies reveal the healthcare provider should address different aspects of social support (informational and emotional) to improve the PCOS patient-provider relationship.

Strengths of this study include the systematic approach used to develop and ensure the validity and reliability of the I-PCOSM in a large study sample. Further, the main effect of PCOS on trust and social support toward healthcare providers was investigated after adjusting for several potential covariates to better reflect an approximation of the actual effect sizes between exposure and outcome variables. Also, this study relied on self-reported PCOS diagnosis – an approach that was shown to be reproducible in previous PCOS studies (Moran *et al.*, 2013; Gibson-Helm *et al.*, 2016). We did not collect specific information about androgenic symptoms to corroborate the self-reported diagnoses in our cohort. Rather, our approach relied on the concept of "self-identity" to address perceptions associated with having a medical condition – a factor known to influence health-related behaviors (Grabowski, 2013). We acknowledge that this study was limited by the possibility of self-selection bias particularly by those with Internet access and interest in study participation.

Previous research has shown that patients who were most satisfied with their medical care were often the first to respond to surveys, but that evaluations became less affirmative through repeated prompting of initial non-responders (Barron *et al.*, 2014). The I-PCOSM did not employ repeated prompts to ensure participants completed the survey, so it is possible that our survey primarily captured responses from individuals with more positive outlooks about their medical care. Compared to a study with an

unselected population (Lo *et al.*, 2006), a greater percentage of women with PCOS in our study identified as white. This suggests that we may not have captured a representative sample of US women with PCOS and reduces the generalizability of the results to other racial and ethnic groups. There is some evidence that black women are less trusting of physicians than whites and more concerned about potential for harm in hospital-settings (Boulware, 2003). For these reasons, future research would benefit from evaluating perceptions across a more diverse spectrum of patients with PCOS.

This study examined the current perceptions of medical care in the PCOS patient population and identified potential areas of improvement to enhance the patient-provider relationships. Though delays in the diagnosis can be partly attributed to controversies with the PCOS diagnosis (Azziz, 2006), negative medical experiences can ultimately lead to feelings of greater dissatisfaction with healthcare providers (Gibson-Helm *et al.*, 2016). Providing strong informational and emotional support may help reduce feelings of distrust between patients and physicians. We also recommend the importance of strengthening the specialty-referral process and identifying patient cues for when a referral may be the optimal approach when diagnosing and/or treating women at risk for PCOS (Mehrotra *et al.*, 2011; Gibson-Helm *et al.*, 2016). Future studies should investigate and establish recommendations to improve the medical experiences of women with PCOS. Efforts to directly compare medical experiences by sub-specialty and how the PCOS diagnosis experience influences impressions of general medical care are needed. By investigating these questions, the far-reaching implications of PCOS medical experiences could be further understood with the goal of

ensuring quality and continuity of care for patients who require life-long surveillance to curb health risks related to chronic reproductive and metabolic dysfunction.

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Supplementary Table S5.1. Constructs in the initial and final versions of the I-PCOSM

Domains	Preliminary No. of Items	Retained No. of Items
Trust in Physicians: Seen within the past three years[a]		
Primary Care Physicians	18	8
Specialists[b]	18	8
Social Support		
Healthcare Providers[c]	12	12
Total No. of Items	48	28

[a] PCOS group was asked about general and/or PCOS health concerns; Comparison group was asked about general health concerns. Reverse scoring for items with negative statements.
[b] Examples include gynecologists, endocrinologists, dermatologists.
[c] Includes physicians, nurse practitioners, physician assistants

Abbreviations: *No., Number; I-PCOSM, Instrument for Polycystic Ovary Syndrome: Medical Experiences*

AFTERWORD

Though health-related behaviors and PCOS are closely linked with obesity, it is unclear whether certain dietary and PA behaviors predict risk of PCOS. Additionally, current health-related behaviors and psychosocial perspectives of PCOS patients have not been widely studied. We addressed these knowledge gaps by developing and conducting cross-sectional studies on dietary and PA behaviors and psychosocial beliefs in women with PCOS. The major findings and implications of this research are summarized below.

Part 1: Associations between lifestyle behaviors with PCOS

- Both studies observed that food groups, rather than total daily energy intake nor PA, were significantly associated with PCOS (as defined by both NIH and Rotterdam criteria). The CARDIA study **(Chapter 2)** determined that red meat and processed meat intake was positively associated with PCOS, while the case-comparison study **(Chapter 3)** observed that better diets (as determined by higher B vitamins and lower empty calories) were associated with PCOS. Results from **Chapter 3** suggest that women with PCOS may have altered their behaviors after their diagnosis. However, reverse causality was less likely to occur in the CARDIA study **(Chapter 2)** since data were collected prior to the establishment of the first formal diagnostic criteria for PCOS. Thus, we believe that it is more probable that health-related behavior results from **Chapter 2** address the etiology of PCOS compared to other cross-sectional studies that have examined health-related behaviors in PCOS to this point.

- Use of different approaches in scoring diet quality in **Chapters 2** and **3** were used given the differences in the instruments used to collect dietary intake data. AHEI-2010 diet quality scores could not be implemented in **Chapter 3** due to unavailable food subgroup data generated by the Vioscreen questionnaire. There are strengths and limitations to each approach. The AHEI-2010 scoring system is closely linked to adverse health outcomes associated with PCOS and there is less overlap between food groups. However, the AHEI-2010 does not consider dairy consumption and is not as widely used as the HEI-2010, an approach based on the 2010 US Dietary Guidelines. Despite the widespread use of the HEI-2010, certain food products can be counted twice among different food groups, thereby biasing the total score. Nevertheless, both are accepted approaches to assess diet quality.

- Associations between food groups and PCOS varied across race, highlighting the need for future studies to further delineate race-specific associations between lifestyle behavior and PCOS. We recommend that future studies examine the external validity of our results using data outside of CARDIA given that race-specific differences were observed with the validity of the CARDIA Diet History questionnaire.

The focus on diet quality in this dissertation provides clinicians with the opportunity to directly translate study results into clinical practice by addressing food groups and interactions among food choices. It is possible that patient counseling on reducing red and processed meat intake may improve features of PCOS. However,

our studies were not designed to establish the temporal order of the relationship between diet and PCOS. Future longitudinal studies that recruit adolescents prior to the development of PCOS are needed in order to confirm whether lower red meat and processed meat can prevent or curb progression to PCOS.

Part 2: Associations between health-related knowledge and beliefs with PCOS status.

- The majority of PCOS patients incorrectly believed that weight gain, insulin resistance, and difficulty with losing weight were established criteria for diagnosing PCOS.
- Though women with PCOS agreed that a healthy lifestyle would help reduce risk for heart disease, diabetes, and weight gain, they felt more susceptible to adverse health outcomes and perceived fewer health benefits of implementing lifestyle changes.
- Less than half of the PCOS group attempted to follow US government diet recommendations. There were no differences in the self-efficacy of diet behaviors between PCOS and comparison groups.
- PCOS patients felt that their primary care physicians (PCP) spent less effort and were less qualified to treat PCOS symptoms than general health concerns.
- There was greater distrust of the PCP's opinion to treat general health concerns in the PCOS group than the reference group, which may have contributed to more frequent arguments between PCOS patients and healthcare providers.

Results from **Chapters 3 and 4** build upon previous literature that suggest there are potential psychosocial targets for tailored interventions in PCOS. We hypothesize that

greater misconceptions about diagnosis and poorer health-related beliefs by the PCOS group (compared to the comparison group) suggest that clinicians should provide stronger informational and emotional support about PCOS. By improving patient-provider communication about PCOS issues, a greater level of trust directed towards the PCPs' opinions may also develop in the PCOS population. Additionally, trust between the patient and provider can be strengthened by clinicians tailoring their recommendations to PCOS-specific health issues (e.g., endometrial cancer, infertility) to demonstrate their understanding about PCOS concerns while encouraging performance of these health-related behaviors. Future longitudinal cohort or experimental study designs are needed to substantiate these findings.

APPENDIX A

IMPACT OF ACCELEROMETER DATA REDUCTION ALGORITHM SELECTION IN REPRODUCTIVE-AGED WOMEN*

Submitted: April 15, 2017 to Journal of Science and Medicine in Sport

*Lin AW, Larsen D, Hsu AC, Luna S, Chin SM, Parry SA, Hoeger KM, Lujan ME. Impact of accelerometer data reduction algorithm selection in reproductive-aged women.

ABSTRACT

Objectives: Physical activity (PA) estimates obtained from recent accelerometer data reduction algorithms have not been compared in reproductive-aged women. We investigated whether the accelerometer counts from the Crouter, Sasaki and Santos-Lozano algorithms: 1) reported significantly different PA estimates; 2) interacted with weight and age to modify PA estimates; and 3) provided different prevalence of adults meeting PA guidelines and/or associations between PA and clinical markers of metabolic status.

Design: Cross-sectional.

Methods: Accelerometer data were collected from 29 women and processed through three algorithms using an in-house Excel model to generate wear minute data. Mixed-effects linear regression models and bivariate correlation analyses were used to examine associations between accelerometer data with weight, age or clinical markers of metabolic status across algorithms.

Results: The Crouter algorithm estimated significantly more wear minutes in Moderate intensity compared to the Sasaki and Santos-Lozano algorithms [+384(SE 33) and +356(SE 33) min]. Significant interactions between the Crouter algorithm with weight

and age were observed in Sedentary/Light and Moderate wear minutes, with the Santos-Lozano algorithm as the reference (all $p_{interaction} \leq 0.001$). Algorithm selection also provided inconsistent findings in the prevalence of adults meeting PA guidelines and associations between Sedentary/Light and Moderate PA estimates with truncal fat and systolic blood pressure.

Conclusions: Recently proposed data reduction algorithms varied in their estimates of PA in women of reproductive age. Algorithm selection interacted with weight and age to influence PA estimates, contributing to inconsistent findings in the prevalence of women who met PA guidelines and associations between PA and clinical markers.

INTRODUCTION

Objective measures of physical activity (PA) garnered from accelerometers are used widely in research to capture the impact of PA on human health.[1,2] Accelerometer counts can be converted into different types of PA estimates, such as time spent within variable PA intensities (wear minutes).[3] PA is typically classified into intensity categories, with higher intensity activities assigned greater metabolic equivalent (MET) values: Sedentary (MET=1), Light (MET >1 to <3), Moderate (MET 3 to <6) or Vigorous (MET ≥6).[4] These PA estimates are later applied to evaluate the prevalence of adults meeting national PA guidelines and/or gauge whether PA behaviors correlate with clinical markers and the overall health of a target population.[1]

Selection of a regression model that converts count data (data reduction algorithm) into PA estimates can impact findings.[1,5] Algorithm selection has been shown to influence wear minute classification into different MET intensities, thereby providing inconsistent prevalence estimates of adults that meet PA recommendations.[6,7]

Prior studies have compared algorithms developed using counts from one plane given the nature of the technology available at that time.[4,6,8] However, evidence suggests that vector magnitude (VM) counts, which use data collected from three different planes, may yield more precise data since a greater range of motion is captured[5,9], though this concept is still controversial.[10,11] By continuing to use older algorithms, data captured by newer accelerometers may be underutilized despite advancements in the field.[12]

Three data reduction algorithms have emerged within the last seven years: the 2010 Crouter two-regression model, the Sasaki algorithm and the Santos-Lozano algorithm.[6,9,13] The Crouter and Sasaki algorithms have been cited most frequently, in part due to the recent development of the Santos-Lozano algorithm. We are unaware of any published studies that have directly compared PA estimates among these three recent algorithms in women of reproductive age. Multiple studies have shown that women are less physically active compared to men[14–16] and are more likely to engage in unstructured and intermittent PA (such as household cleaning and walking).[17,18] Since the Crouter algorithm differentiates between walk/run and lifestyle activities to calculate PA, it is possible this two-regression model provides significantly different PA estimates in a female population compared to other recently developed algorithms. Additional factors, such as weight and age, may also impact PA estimates across algorithms.[12] However, the implications of these factors remain unknown when interpreting the health benefits of PA.

To that end, the primary objectives of this study were to compare PA estimates across the Crouter, Sasaki and Santos Lozano algorithms in reproductive-aged women and to assess how algorithm selection impacts prevalence of meeting PA guidelines and

associations with clinical markers of metabolic status. A secondary objective was to examine the modifying effect of weight and/or age on wear minutes derived from counts used across algorithms. We hypothesized that the Crouter algorithm would provide different wear minute classification compared to the other algorithms, contributing to inconsistent findings regarding meeting PA guidelines and associations with clinical markers across algorithms.

METHODS

Data were obtained from an observational study aimed at comparing diet and physical activity between women with and without polycystic ovary syndrome (ClinicalTrial.gov Identifier: NCT01859663). The study was approved by the Institutional Review Boards at Cornell University and University of Rochester, and all participants provided written informed consent. Female participants, ages 18 to 38 years, were recruited in Tompkins and Monroe counties, New York. Exclusion criteria included not wearing the accelerometer for ≥ 4 days, participation in a diet or PA intervention and a weight exceeding 300 pounds. Of the 30 participants, one woman was excluded for not meeting the minimum requirement of valid wear days. Partial funding was provided by Cornell University Human Ecology Alumni Association, but they had no role in the finished manuscript.

Triaxial accelerometer models GT3X (27 g; 3.8cm x 3.7cm x 1.8cm) and wGT3X+ (19g; 4.6cm x 3.3cm x 1.5 cm) were initialized to measure seven days of physical activity in 10-second intervals without a low frequency extension (Actigraph LLC, Pensacola, Florida, USA). Accelerometers were worn on an elastic belt around the left hip, except when involved in sleep or water-based activities. Acceleration

sampling rates were set at either 30 or 50 Hertz. Participants recorded periods of wear and non-wear in a daily log to establish the accuracy of the accelerometer data. Accelerometer datasets were downloaded for participants using the commercial software ActiLife Version 6.5.4 (Actigraph, LLC, Pensacola, Florida, USA). Data derived from GT3X and wGT3X+ models were combined, given the previous demonstration of strong agreement between the two accelerometers models.[19] Vector magnitude counts per minute (cpm) were generated using counts from three planes: vertical, medio-lateral and antero-posterior. The raw cpm were copied into an AutocalcMET Excel model developed in-house by the investigators to generate wear minutes across three recent data reduction algorithms simultaneously: Crouter, Sasaki and Santos-Lozano (all populations).

The AutocalcMET model first categorized raw accelerometer cpm into wear and non-wear. Non-wear was assessed according to the method developed by Choi et al.[20] If participants reported wearing the accelerometer during sleep, daily logs were used to confirm non-wear periods. All non-wear cpm were converted to zero and excluded from analysis. Counts were excluded one minute before and after periods of non-wear to remove noise triggered by repositioning of the device. An entire day was categorized as non-wear if participants wore the accelerometer for less than 10 hours. The AutocalcMET model then converted each wear cpm into wear minutes for three MET intensity categories: Sedentary/Light, Moderate and Vigorous. Sedentary and Light activities were collapsed into one category to standardize pre-specified PA intensity category definitions across the three algorithms. Each minute of data was aggregated to provide total wear minutes for the participant across three data reduction algorithms for

each intensity. Intra-rater reliability was verified by an agreement analyses where the participants' raw cpm were copied into the model twice, one week apart. Perfect agreement was noted between both weeks for wear minutes and within each MET intensity category (ICC = 1.0 for all results).

Truncal body fat was estimated using whole body dual energy X-ray absorptiometry (Discovery QDR Series; Hologic Inc., Bedford, Massachusetts, USA), while weight was measured by a calibrated digital scale (Seca; Chino, California, USA). Fasting blood glucose (FBG) was analyzed from whole blood during a 2-hour oral glucose tolerance test (ACCU-CHEK ® Aviva; Roche Diagnostics, Indianapolis, Indiana, USA), while systolic blood pressure (SBP) was measured using an automated digital sphygmomanometer (LabTron 847 Series; Graham-Field, Atlanta, Georgia, USA).

Statistical analyses were performed using SPSS 23.0 (IBM, Armonk, New York, USA) with the significance level threshold at $p<0.05$. Agreement in wear minutes between data reduction algorithms was determined using Cohen's kappa statistics for individual participants and for the overall sample. Linear mixed-effects regression models were used to investigate wear minute differences (calculated from cpm) between the Santos-Lozano and other data reduction algorithms. Bonferroni correction method was applied to the partial models to compare across algorithms.[21] Models were further adjusted to include weight, age and the interaction effects between cpm used in data reduction algorithms with these covariates. Adherence to the 2008 PA guidelines was analogous to performing 150 minutes of moderate and/or 75 minutes of vigorous activity over 4 – 7 days.[22] Pearson's correlations were used to examine associations

between PA estimates and markers of metabolic status, including truncal fat (kg), FBG (mg/dL) and SPB (mmHg).

RESULTS

Table A.1 presents the descriptive characteristics of the participants included in the analyses. The study sample was comprised of young adult females (age range: 19 to 36 years), with a weight range from 47 to 104 kg. Total wear time for the study sample averaged approximately 97 hours per week, and a majority of participants (76%) completed seven valid days of wear. Overall, participants spent the majority of their PA at Sedentary/Light intensity.

The Crouter algorithm reported fewer wear minutes in Sedentary/Light intensity compared to Sasaki [-387(SE 31) min, $p \leq 0.001$] and Santos Lozano [-388(SE 31) min, $p \leq 0.001$] algorithms. For Moderate intensity, the Crouter algorithm reported additional wear minutes compared to the Sasaki and Santos-Lozano algorithms [+384(SE 33) and +356(SE 33) min; both $p \leq 0.001$], and more Vigorous wear minutes compared to the Santos-Lozano algorithm [+31(SE 6) min, $p \leq 0.001$]. The Sasaki and Santos-Lozano algorithms had comparable estimates of wear minutes in Sedentary/Light and Moderate intensities, but differed in their estimation of Vigorous intensity (29 min mean difference, $p \leq 0.001$).

Agreement in wear minutes across data reduction algorithms was consistent with findings from the linear mixed-effects regression models. The range of wear minute agreement (κ) for each participant was widest when comparing estimates for the Crouter vs. Santos-Lozano algorithm (κ=0.18-0.84) followed by Crouter vs. Sasaki (κ=0.30-0.73) and Sasaki vs. Santos-Lozano (κ=0.66-0.97) algorithms. Agreement in wear

Table A.1. Descriptive characteristics of study sample (n = 29)

Characteristics	Overall
Age (years)	29 ± 5
Weight (kg)	74 ± 18
Truncal fat mass (kg)	4 ± 7
Fasting blood glucose (mg/dL)	81 ± 6
Systolic blood pressure (mmHg)	76 ± 16
Wear minutes per week in each MET intensity	
Sedentary/Light	
Crouter algorithm	5014 ± 845
Sasaki algorithm	5401 ± 908
Santos-Lozano algorithm	5402 ± 931
Moderate	
Crouter algorithm	737 ± 278
Sasaki algorithm	352 ± 170
Santos-Lozano algorithm	380 ± 192
Vigorous	
Crouter algorithm	45 ± 43
Sasaki algorithm	42 ± 51
Santos-Lozano algorithm	13 ± 27

Data are expressed as mean ± SD or n (%).
Abbreviations: MET, metabolic equivalents

minutes for the overall sample was highest between the Sasaki vs. Santos-Lozano algorithm comparison (κ=0.84), followed by Crouter vs. Santos-Lozano (κ=0.58) and Crouter vs. Sasaki (κ=0.57). When examining the proportion of agreement in wear minutes for each intensity classification across all data reduction algorithms, there was almost perfect agreement for Sedentary/Light intensity (99%). Agreement was poorer in Moderate and Vigorous intensities, with less than 50% agreement with the Crouter vs. Sasaki and Crouter vs. Santos-Lozano algorithm comparisons. The Sasaki and Santos-Lozano algorithms exhibited better agreement, with consistent classification of wear minutes in Moderate (82% of the time) and Vigorous intensities (100% of the time).

Wear minutes were significantly different between the Crouter and Santos-Lozano algorithms across weight in Sedentary/Light and Moderate intensities (Table A.2, all $p_{interaction} \leq 0.001$). Similarly, differences in PA estimates across weight were detected between the Sasaki and Santos-Lozano algorithms (all $p_{interaction} \leq 0.001$). Age interacted with cpm used in the Crouter algorithm in Sedentary/Light and Moderate intensities (all $p_{interaction} \leq 0.001$). No significant interactions were found between cpm from any algorithm with weight and age within Vigorous intensity.

The prevalence of women who met PA guidelines varied according to data reduction algorithm. The Crouter algorithm classified 100% of the sample as having met PA guidelines. The Sasaki and Santos-Lozano algorithms both reported a lower prevalence of meeting PA guidelines (90% of the sample), but disagreed on four individuals that did not meet PA guidelines (14%).

Table A.2. Mixed-effect estimates of wear minutes classified by MET intensity and accelerometer algorithms among reproductive-aged women: full model (n = 29)[a]

Fixed effects	**Sedentary/Light**		**Moderate**		**Vigorous**	
	β	**SE**	**β**	**SE**	**β**	**SE**
Intercept	**2884**[†]	**1155**	**762**[†]	**280**	21	56
Main effects						
Algorithm						
Crouter	**733**[‡]	**155**	**-819**[‡]	**163**	86	44
Sasaki	**478**[†]	**155**	**-546**[‡]	**163**	68	44
Santos-Lozano	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Weight (kg)	18	9	-4	2	0	0
Age (years)	42	34	-4	8	0	2
Interactions						
Algorithm x weight						
Crouter	**-7**[‡]	**1**	**7**[‡]	**1**	0	0
Sasaki	**-5**[‡]	**1**	**5**[‡]	**1**	0	0
Santos-Lozano	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Algorithm x age						
Crouter	**-20**[‡]	**5**	**22**[‡]	**5**	-2	1
Sasaki	-3	5	5	5	-2	2
Santos-Lozano	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*

[†]$p<0.05$; [‡]$p\leq0.001$. *Abbreviations: MET, metabolic equivalents.*

[a] Model: Algorithm, weight and age interactions as fixed effects; Participant as random effect.

Algorithm selection influenced associations between wear minutes and clinical markers of metabolic status. Associations among estimates of Sedentary/Light wear minutes and SBP were consistent across all algorithms (Table A.3). Only the Moderate wear minutes as estimated by the Santos-Lozano algorithm were negatively correlated with truncal fat ($r=-0.53$, $p\leq0.01$). No significant associations were observed with other PA intensity levels and features of metabolic status (e.g., FBG).

DISCUSSION

To the best of our knowledge, this was the first study to investigate agreement in PA estimates across the recently proposed Crouter, Sasaski and Santos-Lozano algorithms in a sample of reproductive- aged women. We anticipated that PA estimates from the Crouter algorithm would have the greatest deviation from the other algorithms given the unique assumptions used to develop the regression model. Unlike Sasaki and Santos-Lozano, the Crouter algorithm used vertical rather than VM cpm, which has been proposed to reduce the accuracy of predicted measures of PA.[5,9,13] Further, Crouter et al. varied in their approach to algorithm development by using indirect calorimetry under unstructured simulated free-living activities in bouts rather than structured activities in laboratory conditions as used Sasaki and Santos-Lozano.[23] Depending on the type and phase of PA bouts, indirect calorimetry can under- or overestimate energy expenditure.[24] Free-living conditions provide different types and phases of activity compared to structured activities conducted in laboratory conditions, which may contribute to significantly different results between the Crouter and other algorithms. Ultimately, the Crouter algorithm classified fewer PA estimates in Sedentary/Light intensity and more PA estimates in higher MET intensities. Differences in PA estimates

Table A.3. Correlation coefficients (*r*) between wear minutes and clinical markers of metabolic status (n = 24)[a]

	Sedentary/Light	Moderate	Vigorous
Truncal fat (kg)			
Crouter algorithm	0.18	0.01	-0.33
Sasaki algorithm	0.18	-0.10	-0.13
Santos-Lozano algorithm	0.29	**-0.53**‡	-0.16
Fasting blood glucose (mg/dL)			
Crouter algorithm	-0.12	-0.12	0.03
Sasaki algorithm	-0.17	0.13	-0.09
Santos-Lozano algorithm	-0.14	0.00	-0.18
Systolic blood pressure (mmHg)			
Crouter algorithm	**0.49**†	0.13	0.09
Sasaki algorithm	**0.49**†	0.01	0.23
Santos-Lozano algorithm	**0.57**‡	-0.34	0.25

†$p<0.05$; ‡$p\leq0.01$.

across algorithms were similar to a prior study that reported the Crouter algorithm significantly underestimated Sedentary[24] and overestimated Moderate and Vigorous wear minutes compared to other MET intensity classification approaches (i.e. indirect calorimetry, accelerometer cutpoints).[7] The overestimation of PA estimates likely resulted from the misclassification of walking versus lifestyle activities. Kuffel et al. [25] showed that the 2006 Crouter two-regression model misclassified more wear minutes as lifestyle activity, resulting in higher calculated MET. In response, Crouter et al. established a coefficient of variation (CV) threshold of 10% across different combinations of six 10-second intervals to improve classification between walk/run and lifestyle activities with the modified version of the Crouter algorithm.[6] However, despite this adjustment, we found that the current Crouter algorithm continued to classify more wear minutes as Moderate and Vigorous lifestyle activities even though participants recorded bouts of walking during those intervals in their accelerometer logs.

We also noted significant differences in PA estimates between the Sasaki and Santos-Lozano algorithms. Differences in PA estimates between these two algorithms were indirectly observed by Santos-Lozano et al., who reported different MET estimates for each algorithm compared to indirect calorimetry results.[9] Variations in algorithm development may have contributed to the wear minute differences between the Sasaki and Santos-Lozano algorithms. Unlike the Sasaki algorithm, the Santos-Lozano algorithm uses ANN models, which may provide greater precision in estimating METs because they rely on biological pattern recognition.[9,26] Further, Santos-Lozano et al. developed their algorithm with a sample of adolescents aged 12 to 16 years and adults over 40 years. This was in direct contrast to Sasaki et al. who developed their algorithm

in participants of reproductive age (mean age: 28.0 ± 9.0 years). Given that age may influence PA levels and that participants in this study were of reproductive age, the heterogeneous conditions under which Santos-Lozano *et al.* validated their algorithm may have contributed to differences in wear minutes.[27]

We observed interactions between weight and age with cpm derived from algorithms, particularly between the Crouter and Santos-Lozano algorithms. The interactions noted in this study are supported by previous findings on the biological interactions between weight and age with energy expenditure. Wilms et al. reported that participants in overweight and obese BMI categories had a resting metabolic equivalent below 1 MET, suggesting that the current standard for the resting MET estimate may be an overestimation for this population.[28] Age was also shown to alter daily resting metabolic rate, consequently altering resting MET estimates.[29] Thus, significant differences in PA estimates among algorithms, particularly between the Crouter and Santos-Lozano algorithms, may also be attributed to the incorporation of weight and age into the Santos-Lozano algorithm.[9] Examination in a larger sample size with indirect calorimetry may help elucidate the statistical and biological interactions between algorithm selection with weight and age observed in this study.

Others have also reported differences in the percentage of participants meeting PA guidelines depending upon the data reduction algorithm selected.[7,30] Similar to our findings, the Crouter algorithm universally classified more participants as meeting PA guidelines compared to other accelerometer MET intensity classification approaches.[7] Weaver et al.[30] reported that the Sasaki algorithm classified four additional participants as meeting guidelines compared to the Santos-Lozano algorithm; however, it was

unclear whether there was agreement in how individual participants were classified by the two algorithms. Our results also revealed discrepancies in associations between PA estimates and clinical markers of metabolic status across algorithms. We noted that the algorithms reported different correlations between Moderate PA estimates with truncal fat. This lack of consensus may result in mixed interpretations on the health benefits of PA and slow progress in formulating effective health recommendations.[1]

Strengths of this study included the use of the AutoCalcMET Model, which we developed as a transparent platform on which to process accelerometer data. In contrast to manufacturer computer software, the model documents decisions taken during the processing stages for each cpm and provides multiple options on how PA estimates can be reported (e.g., day of the week, units, walk-run for the Crouter algorithm). The model also provided the ability to filter accelerometer data, resulting in greater expediency when comparing against accelerometer logs. These functions allowed us to classify PA estimates into different intensity by epoch, in contrast to entering the data into a program without understanding how the MET were categorized. The AutoCalcMET Model also provides greater confidence in the results since it uses Excel formulas to double check the generated data. Further, our use of a targeted sample of reproductive-aged women limited the potential confounding effect of gender since exercise habits may differ between males and females.[15,16] However, the study was designed to address inter-algorithm reliability of PA estimates, and therefore, the validity of data reduction algorithms was not examined against an independent criterion (such as indirect calorimetry data). Another limitation of the study was the small sample size, which may underestimate the effects that weight and age have on algorithm agreement. Last, this

study used a convenient sample and included a subset of women with reproductive dysfunction; thus, the results may not be applicable to all populations. Despite the study limitations, these results highlight potential factors that may explain the differences in PA estimates across algorithms.

CONCLUSIONS

Despite the increasing use of accelerometers in population-based studies, there are currently no standardized data reduction algorithm recommendations. This study investigated agreement across three recently developed algorithms in women of reproductive age in order to further understanding on how algorithm selection may impact data interpretation. The Crouter algorithm reported higher MET intensity PA estimates compared to the Sasaki and Santos-Lozano algorithms. Our findings also suggest that weight and age merit further consideration when selecting algorithms. Algorithm selection impacted the interpretation of PA results, leading to different conclusions about the proportion of adults meeting PA guidelines and the associations between PA and clinical markers of metabolic status. As such, interpretations on the impact of PA on health outcomes should be viewed in light of any effects of algorithm selection across studies. Expert consensus is needed to inform algorithm selection for specific populations in order to improve health-related population based studies.

PRACTICAL IMPLICATIONS

- Recently proposed data reduction algorithms yield different estimates of PA. As such, direct comparisons of PA estimates across studies may be inappropriate.
- When selecting a data reduction algorithm for use, researchers should consider the approach used to develop the algorithm.

- Weight and age emerged as important factors to consider when selecting a data reduction algorithm.

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APPENDIX B

Development and Distributed Instrument for PCOS: Knowledge, Health-Related Beliefs, and Self-Efficacy (I-PCOSK)

* Submitted as Supplementary Material to Human Reproduction.

I-PCOSK: DEVELOPMENT

The preliminary draft comprised of 91 items designed using SCT and HBM constructs to assess 1) reproduction-, nutrition-, and PCOS-related knowledge, 2) beliefs about health outcomes and confidence in lifestyle behaviors, and 3) self-evaluation of current lifestyle (Supplemental Table S4.1). Items were developed using semi-structured interviews conducted by our research group, existing literature about women's experiences with PCOS (Weiss and Bulmer, n.d.; Humphreys and Costarelli, 2008; Moran *et al.*, 2010) and published instruments about health-related beliefs (Bandura, 1990; Wang *et al.*, 2009; Centers for Disease Control and Prevention (CDC), 2011). The draft instrument underwent three rounds of peer review before testing with participants. Peers with expertise in instrument design reviewed a draft instrument to determine clarity and organization (N=2). In a second review, professors with expertise in reproductive physiology and nutrition sociology provided input on the relevance to the domains of interest (N = 2). In a third review, colleagues with expertise on survey development, physiology and nutrition provided additional feedback about the domains of interest and clarity of the items (N = 10).

I-PCOSK: VALIDATION

Methods

An equal number of women with and without PCOS enrolled in one of three rounds of semi-structured interviews where they completed a preliminary I-PCOSK draft (n=36; n=12 per round). Interviews were conducted using an iterative process to assess content validity and potential misinterpretation of items in the I-PCOSK. Each participant was asked to repeat the item prompt in her own words to assess her understanding of the item and then to evaluate its importance. Participants were also asked to determine the appropriateness of response options and the perceived difficulty level for items in the knowledge construct. Only women with PCOS were asked knowledge items specific to PCOS. Test-retest reliability and internal consistency were examined during the final interview round (PCOS n=6, comparison n=6). During this round, the preliminary I-PCOSK was administered twice to each participant, two weeks apart. The total score of each construct was calculated at each time and compared in the test-retest reliability analyses. An evaluation of internal consistency was performed with data from the second administration of the I-PCOSK in this participant sample. After applying the I-PCOSK in the nationwide sample, preliminary analysis was performed with data from the PCOS group to confirm internal consistency results from the interviews and to identify the valid I-PCOSK items.

Test-retest reliability of the I-PCOSK constructs were determined using intraclass correlation coefficient (ICC) analyses, with an ICC ≥0.5 considered as acceptable (Cicchetti, 1994). Internal consistency of the I-PCOSK was evaluated for each construct covered by the instrument and a coefficient of 0.70 was considered as acceptable (Bland and Altman, 1997). Exploratory factor analysis with varimax rotation was used to examine the construct validity of I-PCOSK items for women with PCOS

(N=255). Factors with eigenvalues >1 were retained (Kaiser, 1960). If the item loadings for the retained factors were <0.50, items were removed in a stepwise fashion until all loadings were ≥0.50.

Results

Test-retest reliability was acceptable for all health-related knowledge, beliefs, and self-efficacy constructs (ICC 0.56-0.97). When examining internal consistency of the preliminary I-PCOSK draft, perceived inevitability, susceptibility of adverse health outcomes, evaluation of lifestyle behaviors, and self-efficacy constructs had high internal consistency (α=0.71-0.93). Estimates of worry about adverse health outcomes approached, but did not meet, the acceptable internal consistency threshold (α=0. 66). Low internal consistency was observed for perceived severity of adverse health outcomes, suggesting that select items were not closely related to others in the construct (α=0.25). Cronbach's alpha was not performed for items within the knowledge constructs since knowledge was considered a non-latent variable. When examining construct validity in the health-related beliefs and self-efficacy constructs, factor analysis in the nationwide sample of women with PCOS confirmed results from the Cronbach's α tests in the interview round. Seven items were identified as being unrelated to latent factors in each psychosocial construct. Consequently, 14 items were eliminated and the 77 retained items with high commonality were observed to have high construct validity.

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DISTRIBUTED I-PCOSK

[Author comments are in italicized blue. Logic statements were built into the instrument in order to streamline the response process. Unless otherwise stated, items were asked for both comparison and PCOS groups.]

Q1 Thank you for taking the time to complete this survey by Cornell University. Your responses are very important in helping us examine current health-related knowledge and beliefs of adult women.

Your answers will be confidential and participation is voluntary. You can stop the survey at any time.

Completion time: 10 - 20 minutes
Honorarium: Raffle for one of eight $50 Amazon gift cards upon completion.

Please do not look up the answers to these questions.

We anticipate that your participation in this survey presents no greater risk than everyday use of the Internet. If you have any questions about the survey, please contact us at womensimaging@gmail.com.Participants may also report their concerns or complaints anonymously through Ethicspoint by calling toll free at (866)293-3077 or emailing www.hotline.cornell.edu.

By selecting the "I agree" button, you are indicating that you are willing to participate in this survey.

❍ I agree
❍ I do not agree

Q2 How old are you (years)?

Q3 Which race(s) do you identify with most?

❑ American Indian or Alaskan Native
❑ Asian
❑ Black or African American
❑ White
❑ Other _____

Q4 What is your highest completed education?
- ❍ 1st to 5th grade
- ❍ 6th to 8th grade
- ❍ 9th to 12th grade
- ❍ High school graduate or GED
- ❍ Associate's degree
- ❍ College graduate
- ❍ Advanced degree

Q5 What is your yearly household income (e.g., yourself or with significant other)?
- ❍ ≤ $19,999
- ❍ $20,000 to $39,999
- ❍ $40,000 to $59,999
- ❍ $60,000 to $79,999
- ❍ $80,000 to $99,999
- ❍ ≥ $100,000

Q6 What is your current height (in inches)?

Q7 What is your current weight (in pounds)?

Q8 When did you last weigh yourself (number of days from today)?

Q9 Are you currently on birth control pills or intrauterine devices (IUD)?
- ❍ No
- ❍ Yes
- ❍ Unsure

Q10 How would you classify your fertility status (ability to become pregnant within a year)?
- ❍ Fertile
- ❍ Infertile
- ❍ Unsure

Q11 How familiar are you with the term "polycystic ovary syndrome" (PCOS)?
- ❍ Not at all
- ❍ Somewhat familiar
- ❍ Familiar
- ❍ Very familiar

Q12 Have you been diagnosed with PCOS by a medical professional?
- ❍ No
- ❍ Yes
- ❍ Unsure

Q13 Can you usually predict when your period would start at least half of the time?
- ❍ No
- ❍ Yes
- ❍ Unsure

Q14 On average, what is the smallest number of days between the beginning of one period to the beginning of the next one? *[If answered "No" to Q13]*
- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q15 On average, what is the greatest number of days between the beginning of one period to the beginning of the next one? *[If answered "No" to Q13]*
- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q16 On average, what is the smallest number of days between the beginning of one period to the beginning of the next one? *[If answered "Yes" to Q13]*
- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q17 On average, what is the greatest number of days between the beginning of one period to the beginning of the next one? *[If answered "Yes" to Q13]*
- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q18 On average, what is the smallest number of days between the beginning of one period to the beginning of the next one? *[If answered "Unsure" to Q13]*

- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q19 On average, what is the greatest number of days between the beginning of one period to the beginning of the next one? *[If answered "Unsure" to Q13]*

- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q20 How old were you when diagnosed with PCOS? *[For PCOS Group]*

- ❍ Between 9 to 15 years old
- ❍ Between 16 to 17 years old
- ❍ Between 18 to 29 years old
- ❍ Between 30 to 38 years old

Q21 What PCOS symptoms did you have that led to a diagnosis? Put "DK" if unsure. *[For PCOS Group]*

Q22 Were you ever diagnosed with the following? Mark all that apply.

- ❑ Heart disease (e.g., coronary artery disease, stroke)
- ❑ Diabetes (high blood sugar)
- ❑ Thyroid disease (e.g., hypothyroidism)
- ❑ Cancer
- ❑ Kidney disease
- ❑ None

Q23 Are you a New York State resident? If yes, please list the city. If no, please list the state where you live.

- ❍ Yes _____
- ❍ No _____

Q24 We will now ask about the reproductive system and nutrition. Please indicate whether the following statements are True or False.

Q25 Ovaries are female reproductive organs.

- ❍ True
- ❍ False
- ❍ Unsure

Q26 An egg is released during ovulation.

- ❍ True
- ❍ False
- ❍ Unsure

Q27 Ovaries do not produce hormones.

- ❍ True
- ❍ False
- ❍ Unsure

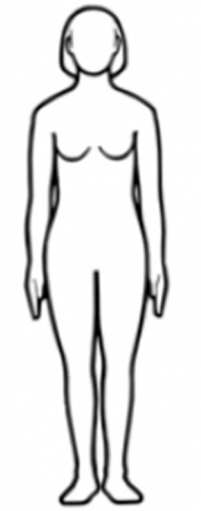
Q28 Women do not usually produce testosterone.

- ❍ True
- ❍ False
- ❍ Unsure

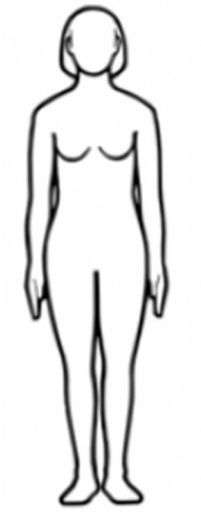
Q29 Ovarian cysts are unusual growths on the ovaries.

- ❍ True
- ❍ False
- ❍ Unsure

Q30 Please click on the 2 areas where the right and left ovaries are located.
[For Comparison Group]



Q31 Please click on the 2 areas where the right and left ovaries are located.
[For PCOS Group]



Q32 How confident are you about your knowledge on the reproductive system?

- ❍ 1 (Not confident)
- ❍ 2 (Somewhat confident)
- ❍ 3 (Confident)
- ❍ 4 (Very confident)

Q33 Have you heard of the Dietary Guidelines for Americans?
- ❍ No
- ❍ Yes
- ❍ Unsure

Q34 It is said that for a healthy diet, at least a _____ of your total grains should be whole grains.
- ❍ Quarter (25%)
- ❍ Half (50%)
- ❍ Three-fourths (75%)
- ❍ Unsure

Q35 It is said that for a healthy diet, you should fill your plate with at least how much fruits and vegetables?
- ❍ Quarter (25%)
- ❍ Half (50%)
- ❍ Three- fourths (75%)
- ❍ Unsure

Q36 Please select all the nutrients to limit in the average diet.
- ☐ Sodium
- ☐ Saturated fat
- ☐ All carbohydrates
- ☐ Protein
- ☐ Added sugars
- ☐ Unsure

Q37 Please select all the foods that contain fiber. Mark all that apply.
- ☐ Fruits
- ☐ Whole grains
- ☐ Meats
- ☐ Vegetables
- ☐ Dairy
- ☐ Unsure

Q38 Protein has a higher number of calories per gram, compared to carbohydrate and fat.
- ❍ True
- ❍ False
- ❍ Unsure

Q39 According to exercise recommendations, how much weekly exercise should adults do for substantial health benefits?

- ❍ 15 minutes, 5 days a week
- ❍ 30 minutes, 5 days a week
- ❍ Unsure

Q40 How confident are you about your knowledge on nutrition and exercise?

- ❍ 1 (Not confident)
- ❍ 2 (Somewhat confident)
- ❍ 3 (Confident)
- ❍ 4 (Very confident)

Q41 We will now ask about PCOS. Please choose the answer you feel is most appropriate.

Q42 Please select the symptoms used to diagnose PCOS. Mark all that apply. *[For PCOS Group]*

- ❑ High testosterone
- ❑ Sudden weight gain
- ❑ Trouble losing weight
- ❑ Above average number of ovarian follicles
- ❑ Excessive body and facial hair
- ❑ Insulin resistance
- ❑ Irregular or absent menstrual periods
- ❑ Acne, male pattern baldness
- ❑ Unsure

Q43 How confident are you about your knowledge on PCOS symptoms? *[For PCOS Group]*

- ❍ 1 (Not confident)
- ❍ 2 (Somewhat confident)
- ❍ 3 (Confident)
- ❍ 4 (Very confident)

Q44 What do you believe causes PCOS? *[For PCOS Group]*

Q45 How confident are you about your knowledge on causes of PCOS? *[For PCOS Group]*

- ❍ 1 (Not confident)
- ❍ 2 (Somewhat confident)
- ❍ 3 (Confident)
- ❍ 4 (Very confident)

Q46 Women with PCOS are at higher risk of _____ compared to women without PCOS. Mark all that apply. *[For PCOS Group]*

- ❑ Heart disease
- ❑ Urinary tract infection (UTI)
- ❑ Diabetes
- ❑ Infertility (not able to have children)
- ❑ Obesity
- ❑ Unsure

Q47 How confident are you about your knowledge on health risks of women with PCOS? *[For PCOS Group]*

- ❍ 1 (Not confident)
- ❍ 2 (Somewhat confident)
- ❍ 3 (Confident)
- ❍ 4 (Very confident)

Q48 We will now ask about PCOS treatments.

Q49 Please select all the treatments used to treat PCOS symptoms. Mark all that apply.*[For PCOS Group]*

- ❑ Diet and exercise
- ❑ Birth control
- ❑ Diabetes medication
- ❑ Fertility medication
- ❑ Anti-testosterone medication
- ❑ Herbal supplements _____
- ❑ Other _____
- ❑ Unsure

Q50 How confident are you about your knowledge on PCOS treatments? *[For PCOS Group]*

- ❍ 1 (Not confident)
- ❍ 2 (Somewhat confident)
- ❍ 3 (Confident)
- ❍ 4 (Very confident)

Q51 We will now ask about resources you have used. Please select the answers you feel are most appropriate.

Q52 Please select the resources you have used to learn about PCOS. Mark all that apply. *[For PCOS Group]*

- ❑ Electronic media (e.g., Facebook, TV, apps, websites)
- ❑ Paper materials (e.g., books, handouts)
- ❑ Health food stores
- ❑ Support groups (in person, phone)
- ❑ None

Q53 Please select the resources you have used to learn about nutrition. Mark all that apply. *[For PCOS Group]*

- ❑ Electronic media (e.g., Facebook, TV, apps, websites)
- ❑ Paper materials (e.g., books, handouts)
- ❑ Health food stores
- ❑ Support groups (in person, phone)
- ❑ None

Q54 How satisfied or dissatisfied are you with the PCOS information from... *[For PCOS Group]*

	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Electronic media	❍	❍	❍	❍	❍
Paper materials	❍	❍	❍	❍	❍
Health food stores	❍	❍	❍	❍	❍
Support groups	❍	❍	❍	❍	❍

Q55 How satisfied or dissatisfied are you with the general nutrition information from... *[For PCOS Group]*

	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Electronic media	❍	❍	❍	❍	❍
Paper materials	❍	❍	❍	❍	❍
Health food stores	❍	❍	❍	❍	❍
Support groups	❍	❍	❍	❍	❍

Q56 We will now ask about your beliefs on health severity, risk, worry and control. Please select the answer you feel is most appropriate.

Q57 _____ is a very serious problem.

	Disagree	Somewhat disagree	Neutral	Somewhat agree	Agree
Heart disease	❍	❍	❍	❍	❍
Diabetes	❍	❍	❍	❍	❍
Endometrial cancer (cancer in uterus lining)	❍	❍	❍	❍	❍
Weight gain	❍	❍	❍	❍	❍
Infertility (not able to have children)	❍	❍	❍	❍	❍

Q58 Compared to most people your age and weight in the United States, what would you say your CHANCES are of getting...
[Scale ranged from 1 (much lower than average) to 5 (much higher than average)]
_____ Heart disease
_____ Diabetes
_____ Endometrial cancer (cancer in uterus lining)
_____ Weight gain
_____ Infertility (not able to have children)

Q59 During the past year, how often have you thought about your CHANCES of getting...*[Scale ranged from 1 (never) to 5 (almost all the time)]*

_____ Heart disease
_____ Diabetes
_____ Endometrial cancer (cancer in uterus lining)
_____ Weight gain
_____ Infertility (not able to have children)

Q60 There is a lot I can do to PREVENT getting...
[Scale ranged from 1 (disagree) to 5 (agree)]

_____ Heart disease
_____ Diabetes
_____ Endometrial cancer (cancer in uterus lining)
_____ Weight gain
_____ Infertility (not able to have children)

Q61 We will now ask about health-related behaviors. Please select the answer you feel is most appropriate.

Q62 In general, how healthy is your overall DIET?

❍ Poor
❍ Fair
❍ Average
❍ Good
❍ Excellent

Q63 In general, how healthy is your overall LIFESTYLE?

❍ Poor
❍ Fair
❍ Average
❍ Good
❍ Excellent

Q64 Have you heard of MyPlate?

❍ No
❍ Yes

Q65 Have you looked at the MyPlate plan on the Internet?

❍ No
❍ Yes

Q66 Have you tried to follow the recommendations in the MyPlate plan?
- ❍ No
- ❍ Yes

Q67 How often do you read nutrition labels?
- ❍ Never
- ❍ Rarely
- ❍ Sometimes
- ❍ Usually
- ❍ Always

Q68 What do you look for on the nutrition label?

Q69 We will now ask about beliefs about health-related behaviors and disease. Please select the answer that matches how much you disagree or agree with the statement.

Q70 It is important for me to meet government dietary recommendations.
- ❍ Disagree
- ❍ Somewhat disagree
- ❍ Neutral
- ❍ Somewhat agree
- ❍ Agree
- ❍ Do not know recommendations

Q71 It is important for me to meet government physical activity recommendations.
- ❍ Disagree
- ❍ Somewhat disagree
- ❍ Neutral
- ❍ Somewhat agree
- ❍ Agree
- ❍ Do not know recommendations

Q72 A HEALTHY DIET will reduce my risk of...
[Scale ranged from 1 (disagree) to 5 (agree)]
_____ Heart disease
_____ Diabetes
_____ Endometrial cancer (cancer in uterus lining)
_____ Weight gain
_____ Infertility (not able to have children)

Q73 BEING PHYSICALLY ACTIVE will reduce my risk of...
[Scale ranged from 1 (disagree) to 5 (agree)]
_____ Heart disease
_____ Diabetes
_____ Endometrial cancer (cancer in uterus lining)
_____ Weight gain
_____ Infertility (not able to have children)

Q74 Please select how confident you are in your ability to do the following things FOR THE NEXT MONTH.

	1 (Cannot do)	2	3 (Possibly can do)	4	5 (Certainly can do)
Incorporate low fat foods into my diet.	❍	❍	❍	❍	❍
Incorporate low salt foods into my diet.	❍	❍	❍	❍	❍
Eat 5 servings of fruits and vegetables per day.	❍	❍	❍	❍	❍
Decrease the amount of refined sugar in my diet.	❍	❍	❍	❍	❍
Eat more high fiber foods.	❍	❍	❍	❍	❍
Eat smaller portions at dinner.	❍	❍	❍	❍	❍
Exercise for 30 minutes for 5 days a week.	❍	❍	❍	❍	❍
Control my eating on weekends.	❍	❍	❍	❍	❍

Q75 Please select how confident you are in your ability to do the following things FOR THE NEXT MONTH.

	1 (Cannot do)	2	3 (Possibly can do)	4	5 (Certainly can do)
Resist eating too much when there are many different kinds of food available.	❍	❍	❍	❍	❍
Resist eating when I am at a party.	❍	❍	❍	❍	❍
Resist eating when I am watching TV.	❍	❍	❍	❍	❍
Resist eating when I am reading.	❍	❍	❍	❍	❍
Resist eating just before going to bed.	❍	❍	❍	❍	❍
Resist eating when I am anxious or nervous.	❍	❍	❍	❍	❍
Resist eating when I am depressed or feel down.	❍	❍	❍	❍	❍
Resist eating when I am angry or irritable.	❍	❍	❍	❍	❍
Resist eating when I am happy.	❍	❍	❍	❍	❍
Resist eating when I experience failure.	❍	❍	❍	❍	❍

Q76 It is easy to eat a healthy diet.

- ❍ Disagree
- ❍ Somewhat disagree
- ❍ Neutral
- ❍ Somewhat agree
- ❍ Agree

APPENDIX C

Development and Distributed Instrument for PCOS: Medical Experiences (I-PCOSM)

* Will submit as Supplementary Material

I-PCOSM: DEVELOPMENT

Forty-eight items were modified from two published instruments to assess perceptions of trust in physicians and social support from healthcare professionals by women with PCOS.[1,2] Items were modified with the goal of collecting perceptions related to medical experiences over a broad range of healthcare providers (primary care physicians (PCP), specialists, and nurse practitioners and physician assistants) and perceptions of care over general and PCOS-related health concerns. The draft instrument of the I-PCOSM (Instrument for Polycystic Ovary Syndrome: Medical Experiences) underwent three rounds of peer review by individuals with expertise in instrument design to ensure clarity and organization of the items prior to administration in research participants.

I-PCOSM: VALIDATION

Methods

Three rounds of semi-structured interviews were conducted to assess the content validity and reliability of the I-PCOSM (n = 36; n = 12 per round). A single interviewer asked a succession of questions to gauge the interpretability, difficulty, and importance of all I-PCOSM items. Test-retest reliability was examined in the final round of interviews with 12 participants (PCOS n = 6, comparison n = 6), where the I-PCOSM was administered twice, two weeks apart. A preliminary analysis of internal consistency

was performed with data from the second administration of the I-PCOSM from the interview rounds. To confirm the preliminary results and identify valid I-PCOSM items for inclusion in the final version, internal consistency analyses were performed with data collected from the nationwide sample.

Intraclass correlation coefficient (ICC) statistics were used to analyze test-retest reliability and an ICC ≥ 0.5 was considered acceptable.[3,4] Internal consistency of each domain was evaluated using Cronbach α, with a coefficient ≥ 0.7 considered acceptable. Construct validity was evaluated using exploratory factor analysis with a varimax rotation and factors with eigenvalues > 1 were selected.[5] Items with factor loadings <0.50 were removed in an iterative process until all items had loadings ≥0.50. Similarly worded trust items were eliminated across both types of physicians [PCPs and specialists] if they were invalid for at least one of the domains. For the purpose of evaluating the test-retest reliability of the I-PCOSM, total scores for items within each domain were averaged and included in the final analyses for instrument validation.

Results

Test-retest reliability was acceptable for all I-PCOSM domains (ICC range = 0.51 to 0.99). Internal consistency analyses could not be performed on items inquiring about PCPs and PCOS health concerns because of the small sample size. Items related to trust in specialists regarding PCOS health concerns did not reach the acceptable threshold for internal consistency ($\alpha = 0.37$). By contrast, similarly worded items on general health concerns with specialists had high internal consistency ($\alpha = 0.78$), though this result was not observed with PCPs ($\alpha = 0.34$). In the comparison group, internal consistency was high for items related to trust in PCPs ($\alpha = 0.71$), but not with specialists

(α = 0.18). The low consistency was likely attributed to the small sample size used in the interview rounds since not every participant visited each type of physicians. When we examined the internal consistency of the trust domain in the nationwide sample (n=332), we found the internal consistency was high in the trust domain across different types of physicians and health concerns (α range = 0.83 to 0.94). Items related to social support provided by healthcare professionals met the acceptable threshold for internal consistency in both the interview and nationwide samples (α = 0.88 and 0.85, respectively). Factor analysis on the nationwide sample identified 20 items as having low factor loadings. The trust domains retained 16 items, while the social support domain retained 12 items. The final version of the I-PCOSM represented 28 items with high construct validity and were used in the final analyses (Supplemental Table S5.1).

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DISTRIBUTED I-PCOSM

[Author comments are in italicized blue. Logic statements were built into the instrument in order to streamline the response process. Unless otherwise stated, items were asked for both comparison and PCOS groups.]

Q1 Thank you for taking the time to complete this 2nd survey by Cornell University. Your responses are very important in helping us examine the medical experiences and social support of adult women. Please complete the survey on a computer. Your answers will be confidential and participation is voluntary. You can stop the survey at any time.

Completion time: 10 - 20 minutes.
Honorarium: Raffle for one of five $50 Amazon gift cards upon completion.We predict this is a 1 in 30 odds. The draw will occur at the end of the study.

We anticipate that your participation in this survey presents no greater risk than everyday use of the Internet. If you have any questions about the survey, please contact us at womensimaging@gmail.com. Participants may also report their concerns or complaints anonymously through Ethicspoint by calling toll free at (866)293-3077 or emailing www.hotline.cornell.edu.

By selecting the "I agree" button, you are indicating that you are willing to participate in this survey.

- ❍ I agree
- ❍ I do not agree

Q2 How old are you?

Q3 What race(s) do you identify with most?

- ☐ American Indian or Alaskan Native
- ☐ Asian
- ☐ Black or African American
- ☐ White
- ☐ Other _____

Q4 What is your highest completed education?

- ❍ 1st to 5th grade
- ❍ 6th to 8th grade
- ❍ 9th to 12th grade
- ❍ High school graduate or GED
- ❍ Associate's degree
- ❍ College graduate
- ❍ Advanced degree

Q5 What is your yearly household income (e.g., yourself, with significant other)?
- ❍ ≤ $19,999
- ❍ $20,000 to $39,999
- ❍ $40,000 to $59,999
- ❍ $60,000 to $79,999
- ❍ $80,000 to $99,999
- ❍ ≥ $100,000

Q6 What is your current height (in feet, inches)?

Q7 What is your current weight (in pounds)?

Q8 When did you last weigh yourself (number of days from today)?

Q9 Are you currently on birth control pills or intrauterine devices (IUD)?
- ❍ No
- ❍ Yes
- ❍ Unsure

Q10 How would you classify your fertility status (ability to become pregnant within a year)?
- ❍ Fertile
- ❍ Infertile
- ❍ Unsure

Q11 How familiar are you with the term "polycystic ovary syndrome" (PCOS)?
- ❍ Not at all
- ❍ Somewhat familiar
- ❍ Familiar
- ❍ Very familiar

Q12 Have you been diagnosed with PCOS by a medical professional?
- ❍ No
- ❍ Yes

Q13 Can you usually predict when your period would start at least half of the time?
- ❍ No
- ❍ Yes
- ❍ Unsure

Q14 On average, what is the smallest number of days between the beginning of one period to the beginning of the next one? *[If answered "No" to Q13]*

- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q15 On average, what is the greatest number of days between the beginning of one period to the beginning of the next one? *[If answered "No" to Q13]*

- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q16 On average, what is the smallest number of days between the beginning of one period to the beginning of the next one? *[If answered "Yes" to Q13]*

- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q17 On average, what is the greatest number of days between the beginning of one period to the beginning of the next one? *[If answered "Yes" to Q13]*

- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q18 On average, what is the smallest number of days between the beginning of one period to the beginning of the next one? *[If answered "Unsure" to Q13]*

- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q19 On average, what is the greatest number of days between the beginning of one period to the beginning of the next one? *[If answered "Unsure" to Q13]*

- ❍ Less than 20 days
- ❍ 20 to 25 days
- ❍ 26 to 35 days
- ❍ Greater than 35 days
- ❍ Unsure

Q20 How old were you when diagnosed with PCOS? *[For PCOS Group]*

- ❍ Between 9 to 15 years old
- ❍ Between 16 to 17 years old
- ❍ Between 18 to 29 years old
- ❍ Between 30 to 38 years old

Q21 What PCOS symptoms did you have that led to a diagnosis? Put "DK" if unsure. *[For PCOS Group]*

Q22 Were you ever diagnosed with the following? Please mark all that apply.

- ❑ Heart disease (e.g., coronary heart disease, stroke)
- ❑ Diabetes (high blood sugar)
- ❑ Thyroid disease
- ❑ Cancer
- ❑ Kidney disease
- ❑ None

Q23 Are you a New York State resident? If yes, please list the city. If no, please list the state where you live.

- ❍ Yes _____
- ❍ No _____

Q24 The next 2 sections will ask about the healthcare professionals you have visited. It will be divided by most recent (within the last 3 years) and past (more than 3 years). These questions will be asked by profession.

Q25 We will now ask about your MOST RECENT healthcare professionals (who are familiar with your health history).**Please think of your experiences for when you were 18 years or older. Choose the answer you feel is most appropriate.**

Q26 In the PAST 3 YEARS, which types of healthcare professionals have you visited? Mark all that apply. *[For Comparison Group]*

- ❑ Primary Doctor
- ❑ Specialized Doctor (e.g., Gynecologist, Dermatologist) _____
- ❑ Nurse Practitioner or Physician Assistant
- ❑ Holistic Professional (Chiropractor, Acupuncturist or Naturopath)
- ❑ Dietitian
- ❑ Other _____
- ❑ None

Q27 In the PAST 3 YEARS, which types of healthcare professionals have you visited for NON-PCOS issues? Mark all that apply. *[For PCOS Group]*

- ❑ Primary Doctor
- ❑ Specialized Doctor (e.g., Gynecologist, Dermatologist) _____
- ❑ Nurse Practitioner or Physician Assistant
- ❑ Holistic Professional (Chiropractor, Acupuncturist or Naturopath)
- ❑ Dietitian
- ❑ Other _____
- ❑ None

Q28 In the PAST 3 YEARS, which types of healthcare professionals have you visited for PCOS issues (e.g., hair growth, infertility)? Mark all that apply.
[For PCOS Group]

- ❑ Primary Doctor
- ❑ Specialized Doctor (e.g., Gynecologist, Dermatologist) _____
- ❑ Nurse Practitioner or Physician Assistant
- ❑ Holistic Professional (Chiropractor, Acupuncturist or Naturopath)
- ❑ Dietitian
- ❑ Other _____
- ❑ None

[Comment: Items 29 to 40 were asked for each healthcare provider. Therefore, only items related to recent primary doctor were provided as examples.]

Q29 About how many times do you visit that most recent Primary Doctor in a YEAR? *[For Comparison Group]*

- ❍ 0-1 time
- ❍ 2-5 times
- ❍ 6-10 times
- ❍ 11-15 times
- ❍ 16-20 times
- ❍ 21-25 times
- ❍ More than 25 times

Q30 Please list all types of treatment that were recommended by that most recent Primary Doctor (e.g., low fat diet, birth control).Put "NA" in the Treatment 1 box if there was no treatment; "DK" if unsure. *[For Comparison Group]*

	How long did you use the recommended treatment?					How satisfied or dissatisfied are you that the treatment improved your health?				
	Did not begin treatment	Less than 1 month	Between 1 to 6 months	Between 6 to 12 months	Greater than 12 months	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Treatment 1	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 2	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 3	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 4	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 5	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q31 We will ask about your trust in that most recent Primary Doctor. Please select the answer you feel is most appropriate. *[For Comparison Group]*

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I doubt that the recent Primary Doctor really cares about me as a person.	❍	❍	❍	❍	❍
The recent Primary Doctor is usually considerate of my needs and puts them first.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor so much, I always try to follow his/her advice.	❍	❍	❍	❍	❍
If the recent Primary Doctor tells me something is so, then it is usually true.	❍	❍	❍	❍	❍
I sometimes distrust the recent Primary Doctor's opinions and would like a second one.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor's judgment about my medical care.	❍	❍	❍	❍	❍

I feel the recent Primary Doctor does not do everything he/she should about my medical care.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor to put my medical needs above all other considerations when treating my medical problems.	❍	❍	❍	❍	❍
The recent Primary Doctor is well qualified to treat medical problems that I experience.	❍	❍	❍	❍	❍

Q32 Does seeing that most recent Primary Doctor give you a sense of control over your health? *[For Comparison Group]*

❍ No
❍ Yes

Q33 For NON-PCOS issues, about how many times do you visit that most recent Primary Doctor in a YEAR? *[For PCOS Group]*

❍ 0-1 time
❍ 2-5 times
❍ 6-10 times
❍ 11-15 times
❍ 16-20 times
❍ 21-25 times
❍ More than 25 times

Q34 Please list all types of NON-PCOS treatment recommended by that most recent Primary Doctor (e.g., low fat diet, birth control). Put "NA" in the Treatment 1 box if there was no treatment, "DK" if unsure.*[For PCOS Group]*

	How long did you use the recommended treatment?					How satisfied or dissatisfied are you that the treatment improved your health?				
	Did not begin treatment	Less than 1 month	Between 1 to 6 months	Between 6 to 12 months	Greater than 12 months	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Treatment 1	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 2	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 3	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 4	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 5	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q35 We will ask about your trust in that most recent Primary Doctor for NON-PCOS issues. Please select the answer you feel is most appropriate. *[For PCOS Group]*

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I doubt that the recent Primary Doctor really cares about me as a person.	❍	❍	❍	❍	❍
The recent Primary Doctor is usually considerate of my needs and puts them first.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor so much, I always try to follow his/her advice.	❍	❍	❍	❍	❍
If the recent Primary Doctor tells me something is so, then it is usually true.	❍	❍	❍	❍	❍
I sometimes distrust the recent Primary Doctor's opinions and would like a second one.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor's judgment about my non-PCOS medical care.	❍	❍	❍	❍	❍

I feel the recent Primary Doctor does not do everything he/she should about my non-PCOS medical care.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor to put my medical needs above all other considerations when treating my non-PCOS medical problems.	❍	❍	❍	❍	❍
The recent Primary Doctor is well qualified to treat non-PCOS medical problems that I experience.	❍	❍	❍	❍	❍

Q36 Does seeing that most recent Primary Doctor for NON-PCOS issues give you a sense of control over your health? *[For PCOS Group]*

❍ No
❍ Yes

Q37 In a YEAR, about how many times do you visit that most recent Primary Doctor for PCOS issues? *[For PCOS Group]*

❍ 0-1 time
❍ 2-5 times
❍ 6-10 times
❍ 11-15 times
❍ 16-20 times
❍ 21-25 times
❍ More than 25 times

Q38 Please list all types of PCOS treatment recommended by that most recent Primary Doctor (e.g., low fat diet, birth control). Put "NA" in the Treatment 1 box if there was no treatment; "DK" if unsure. *[For PCOS Group]*

	How long did you use the recommended PCOS treatment?					How satisfied or dissatisfied are you that the PCOS treatment improved your health?				
	Did not begin treatment	Less than 1 month	Between 1 to 6 months	Between 6 to 12 months	Greater than 12 months	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Treatment 1	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 2	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 3	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 4	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 5	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q39 We will ask about your trust in that most recent Primary Doctor for PCOS issues. Please select the answer you feel is most appropriate. *[For PCOS Group]*

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I doubt that the recent Primary Doctor really cares about me as a person.	❍	❍	❍	❍	❍
The recent Primary Doctor is usually considerate of my needs and puts them first.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor so much, I always try to follow his/her advice.	❍	❍	❍	❍	❍
If the recent Primary Doctor tells me something is so, then it is usually true.	❍	❍	❍	❍	❍
I sometimes distrust the recent Primary Doctor's opinions and would like a second one.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor's judgment about my PCOS medical care.	❍	❍	❍	❍	❍

I feel the recent Primary Doctor does not do everything he/she should about my PCOS medical care.	❍	❍	❍	❍	❍
I trust the recent Primary Doctor to put my medical needs above all other considerations when treating my PCOS medical problems.	❍	❍	❍	❍	❍
The recent Primary Doctor is well qualified to treat PCOS medical problems that I experience.	❍	❍	❍	❍	❍

Q40 Does seeing that recent Primary Doctor for PCOS issues give you a sense of control over your health? *[For PCOS Group]*

❍ No

❍ Yes

[Comment: Items 96 to 110 were asked for each healthcare provider to gauge earlier medical experiences (before the past 3 years). Therefore, only items related to past primary doctor were provided as examples.]

Q96 We will now ask about your PAST healthcare professionals (who are familiar with your health history).**Unless specified, please think of your experiences for when you were 18 years or older.**

Q97 When you were younger than 18, which types of healthcare professionals did you visit for PCOS issues (e.g., hair growth, infertility)? *[For PCOS Group]*

- ❑ Primary Doctors
- ❑ Specialized Doctors (e.g., Gynecologists, Dermatologists)

  _____
- ❑ Nurse Practitioners or Physician Assistants
- ❑ Holistic Professionals (Chiropractors, Acupuncturists or Naturopaths)
- ❑ Dietitians
- ❑ Others _____
- ❑ None

Q98 For when you were younger than 18, please list all types of treatment recommended by past healthcare professionals (e.g., low fat diet, birth control). Put NA" in the Treatment 1 box if there was no treatment; "DK" if unsure. *[For PCOS Group]*

	How long did you use the recommended PCOS treatment?					How satisfied or dissatisfied are you that the PCOS treatment improved your health?				
	Did not begin treatment	Less than 1 month	Between 1 to 6 months	Between 6 to 12 months	Greater than 12 months	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Treatment 1	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 2	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 3	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 4	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 5	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

99 When you were an adult (18 years or older), which types of healthcare professionals did you visit? Do not include the most recent healthcare professionals. *[For Comparison Group]*

- ❑ Primary Doctors
- ❑ Specialized Doctors (e.g., Gynecologists, Dermatologists)

  _____
- ❑ Nurse Practitioners or Physician Assistants
- ❑ Holistic Professionals (Chiropractors, Acupuncturists or Naturopaths)
- ❑ Dietitians
- ❑ Others _____
- ❑ None

Q100 When you were an adult (18 years or older), which types of healthcare professionals did you visit for NON-PCOS issues? Do not include the most recent healthcare professionals. *[For PCOS Group]*

- ❑ Primary Doctors
- ❑ Specialized Doctors (e.g., Gynecologists, Dermatologists)

  _____
- ❑ Nurse Practitioners or Physician Assistants
- ❑ Holistic Professionals (Chiropractors, Acupuncturists or Naturopaths)
- ❑ Dietitians
- ❑ Others _____
- ❑ None

Q101 When you were an adult (18 years or older), which types of healthcare professionals did you visit for PCOS issues (e.g., hair growth, infertility)? Do not include the most recent healthcare professionals. *[For PCOS Group]*

- ❑ Primary Doctors
- ❑ Specialized Doctors (e.g., Gynecologists, Dermatologists)

  _____
- ❑ Nurse Practitioners or Physician Assistants
- ❑ Holistic Professionals (Chiropractors, Acupuncturists or Naturopaths)
- ❑ Dietitians
- ❑ Others _____
- ❑ None

Q102 Please list all types of treatment recommended by past Primary Doctors (e.g., low fat diet, birth control) as an adult. Put "NA" in the Treatment 1 box if there was no treatment; "DK" if unsure. *[For Comparison Group]*

	How long did you use the recommended treatment?					How satisfied or dissatisfied are you that the treatment improved your health?				
	Did not begin treatment	Less than 1 month	Between 1 to 6 months	Between 6 to 12 months	Greater than 12 months	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Treatment 1	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 2	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 3	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 4	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 5	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q103 We will ask about your trust in your past Primary Doctors (NOT your recent). Please select the answer you feel is most appropriate. *[For Comparison Group]*

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I doubted that my past Primary Doctors really cared about me as a person.	❍	❍	❍	❍	❍
My past Primary Doctors were usually considerate of my needs and put them first.	❍	❍	❍	❍	❍
I trusted my past Primary Doctors so much, I always tried to follow their advice.	❍	❍	❍	❍	❍
If my past Primary Doctors told me something is so, then it is usually true.	❍	❍	❍	❍	❍
I sometimes distrusted my past Primary Doctors' opinions and would have liked another one.	❍	❍	❍	❍	❍

I trusted my past Primary Doctors' judgments about my medical care.	❍	❍	❍	❍	❍
I felt my past Primary Doctors did not do everything they should about my medical care.	❍	❍	❍	❍	❍
I trusted my past Primary Doctors to put my medical needs above all other considerations when treating my medical problems.	❍	❍	❍	❍	❍
My past Primary Doctors were well qualified to treat medical problems that I experienced.	❍	❍	❍	❍	❍

Q104 Did seeing your past Primary Doctors give you a sense of control over your health? *[For Comparison Group]*

❍ No

❍ Yes

Q105 Please list all types of NON-PCOS treatment recommended by past Primary Doctors as an adult (e.g., low fat diet, birth control). Put "NA" in the Treatment 1 box if there was no treatment; "DK" if unsure. *[For PCOS Group]*

	How long did you use the recommended treatment?					How satisfied or dissatisfied are you that the treatment improved your health?				
	Did not begin treatment	Less than 1 month	Between 1 to 6 months	Between 6 to 12 months	Greater than 12 months	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Treatment 1	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 2	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 3	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 4	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 5	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q106 We will ask about your trust in your past Primary Doctors for NON-PCOS issues (NOT your recent). Please select the answer you feel is most appropriate. *[For PCOS Group]*

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I doubted that my past Primary Doctors really cared about me as a person.	❍	❍	❍	❍	❍
My past Primary Doctors were usually considerate of my needs and put them first.	❍	❍	❍	❍	❍
I trusted my past Primary Doctors so much, I always tried to follow their advice.	❍	❍	❍	❍	❍
If my past Primary Doctors told me something is so, then it is usually true.	❍	❍	❍	❍	❍
I sometimes distrusted my past Primary Doctors' opinions and would have liked another one.	❍	❍	❍	❍	❍

I trusted my past Primary Doctors' judgment about my non-PCOS medical care.	❍	❍	❍	❍	❍
I felt my past Primary Doctors did not do everything they should about my non-PCOS medical care.	❍	❍	❍	❍	❍
I trusted my past Primary Doctors to put my medical needs above all other considerations when treating my non-PCOS medical problems.	❍	❍	❍	❍	❍
My past Primary Doctors were well qualified to treat non-PCOS medical problems that I experienced.	❍	❍	❍	❍	❍

Q107 Did seeing your past Primary Doctors for NON-PCOS issues give you a sense of control over your health? *[For PCOS Group]*

❍ No

❍ Yes

Q108 Please list all types of PCOS treatment recommended by past Primary Doctors (e.g., low fat diet, birth control). Put "NA" in the Treatment 1 box if there was no treatment; "DK" if unsure. *[For PCOS Group]*

	How long did you use the recommended PCOS treatment?					How satisfied or dissatisfied are you that the PCOS treatment improved your health?				
	Did not begin treatment	Less than 1 month	Between 1 to 6 months	Between 6 to 12 months	Greater than 12 months	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied
Treatment 1	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 2	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 3	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 4	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Treatment 5	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q109 We will ask about your trust in your past Primary Doctors for PCOS issues (NOT your recent). Please select the answer you feel is most appropriate. *[For PCOS Group]*

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I doubted that my past Primary Doctors really cared about me as a person.	❍	❍	❍	❍	❍
My past Primary Doctors were usually considerate of my needs and put them first.	❍	❍	❍	❍	❍
I trusted my past Primary Doctors so much, I always tried to follow their advice.	❍	❍	❍	❍	❍
If my past Primary Doctors told me something is so, then it is usually true.	❍	❍	❍	❍	❍
I sometimes distrusted my past Primary Doctors' opinions and would have liked another one.	❍	❍	❍	❍	❍

I trusted my past Primary Doctors' judgment about my PCOS medical care.	❍	❍	❍	❍	❍
I felt my past Primary Doctors did not do everything they should about my PCOS medical care.	❍	❍	❍	❍	❍
I trusted my past Primary Doctors to put my medical needs above all other considerations when treating my PCOS medical problems.	❍	❍	❍	❍	❍
My past Primary Doctors were well qualified to treat PCOS medical problems that I experienced.	❍	❍	❍	❍	❍

Q110 Did seeing your past Primary Doctors for PCOS issues give you a sense of control over your health? *[For PCOS Group]*

❍ No

❍ Yes

Q151 We will now ask about your social support. Please select the answer you feel is most appropriate.

Q152 Please select the following the people with whom you talk about all health problems.

- ❑ Significant other (e.g., spouse, partner, girlfriend/boyfriend)
- ❑ Adult women in your family (e.g., mother, sister, aunt; NOT PARTNER)
- ❑ Close friends (NOT PARTNER or RELATION)
- ❑ Most recent health professionals (only doctors, nurse practitioners or physician assistants)
- ❑ No one

[Comment: Items 159 to 160 were asked for group of different support systems [significant other, adult women in the family, friends, healthcare providers] to gauge social support. Only items related to healthcare providers were provided as examples.]

Q159 With most recent HEALTHCARE PROFESSIONALS (only doctors, nurse practitioners or physician assistants)...

	Never	Rarely	Sometimes	Usually	Always
How often do they give you advice or information about health (whether you want it or not)?	❍	❍	❍	❍	❍
How often do they give you advice or information about nutrition (whether you want it or not)?	❍	❍	❍	❍	❍

How often do they give you advice or information about PCOS (whether you want it or not)? *[For PCOS Group]*	❍	❍	❍	❍	❍
How often do they give you reassurance, encouragement and emotional support (affection) concerning your health?	❍	❍	❍	❍	❍
How often do they listen to and try to understand your worries about your health?	❍	❍	❍	❍	❍
How often can you relax and be yourself around them?	❍	❍	❍	❍	❍
How often can you open up to them if you need to talk about your worries about your health?	❍	❍	❍	❍	❍
How satisfied are you with the emotional support provided?	❍	❍	❍	❍	❍

Q160 With most recent HEALTHCARE PROFESSIONALS (only doctors, nurse practitioners or physician assistants)...

	Never	Rarely	Sometimes	Usually	Always
How often do they argue with you relating to your health?	❍	❍	❍	❍	❍
How often do they criticize you relating to your health?	❍	❍	❍	❍	❍
How often do they let you down when you are counting on them?	❍	❍	❍	❍	❍
How often do they withdraw from discussions or try to change the topic away from your health?	❍	❍	❍	❍	❍