AN EVALUATION OF PSYCHOLOGICAL AND SOCIO-DEMOGRAPHIC FACTORS ASSOCIATED WITH METABOLIC SYNDROME AND CARDIOVASCULAR RISK IN POLYCYSTIC OVARY SYNDROME CASES AND CONTROLS

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Background: Major aims of the psychological research in PCOS were: (1) to compare the prevalence of depressive symptoms in women with PCOS to controls; (2) to determine whether depression and psychological traits (anger, anxiety, hostility/cynicism) and satisfaction with life are associated with PCOS (3) to determine the prevalence of Metabolic Syndrome (MS) in PCOS cases and controls (4) to determine if psychological factors are risk factors for Metabolic Syndrome independent of age, marital status, education, and parity (5) to determine if psychological factors, independent of baseline cardiovascular risk factors, are a risk factor for IMT in women with PCOS.

Design: Prospective and cross sectional.

Methods: Cases (n=161) and controls (n=161) matched on age, race, and neighborhood a subset of the Cardiovascular Health and Risk Measurement study (CHARM) investigating coronary heart disease risk factors in women with PCOS. Psychological measures were Beck Depression Inventory I (BDI I), Speilberger Trait Anger and Anxiety Scales, Cook-Medley Scale, Diener Satisfaction with Life Scale.

Results: PCOS women had a higher prevalence of depression (BDI scores > 9; predominately a mild level of depression): 31% vs. 17% in controls (P=.016; OR 1.9; CI 1.55-2.16). Within cases, BMI, education, and parity were statistically significant predictors of depression, $p<.05$. The odds of being depressed (at least mild severity) increased by 6%

for each unit increase of BMI, the odds of being depressed decreased by 20% for each year of education, and the odds of being depressed increased by 44% for parity (*per live birth*). The odds of having PCOS increased with each unit of BDI score by 1.06 times, adjusting for marital status, BMI, smoking, and education (entire sample).

Results from MS, 27% (n=40) of the cases and 9.9% (n=15) of the controls had MS ($p<.05$; OR 3.4; CI 1.726-6.400. The odds of having MS increased by 10% for each year of age and threefold for PCOS cases.

There were no effects from the psychological factors independent baseline cardiovascular risk factors on IMT.

Conclusions: Depression is a major psychological concern in PCOS.

Public Health Significance: Women with PCOS should be screened on diagnosis and monitored closely for depression.

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1.0 DISSERTATION OVERVIEW AND OBJECTIVE

Polycystic Ovary Syndrome (PCOS) is the most common reproductive endocrine condition with a prevalence rate between 6-10%. Features of PCOS, a heterogeneous disorder, include chronic anovulation, hyperandrogenism, and insulin resistance. Metabolic abnormalities often occur in women with PCOS and have been identified as Metabolic Syndrome or Metabolic Cardiovascular Syndrome. The abnormalities include central adiposity, increased triglycerides, low levels of high density lipoproteins (HDLc), hypertension, impaired glucose tolerance and Diabetes. Subclinical cardiovascular disease has been identified as a major concern. PCOS affects not only the physical functioning of women with the disorder, but also has multiple emotional consequences. Although limited, some studies have investigated the relationship of mental health disorders in women with PCOS.

The purpose of this dissertation is to evaluate the psychological factors associated with PCOS. Specifically, the following aims are the foci in a series of three papers.

1. Associations among Depressive Symptoms, Anxiety, Anger, Hostility, and Satisfaction with Life in Women with Polycystic Ovary Disease (PCOS)

1. Women with PCOS have been identified as individuals that are at risk for depression due to the physiological and body image changes that occur from this syndrome. Studies

primarily utilizing small samples have supported the finding that depressive symptoms are more prevalent in PCOS women. This paper focuses on the following research questions:

a. What is the relationship between PCOS and depressive symptoms?
b. What is the point prevalence of clinically significant self-reported depressive symptoms in PCOS women when compared to controls?
c. What is the relationship between satisfaction with life and other psychological characteristics (personality traits), anxiety, anger, and hostility, in women with PCOS?
d. Are age, BMI, education, parity, testosterone levels, and marital and smoking status potential covariates in this relationship?

2. PCOS, Psychological Manifestations, and the Metabolic Syndrome. What is the relationship?

1. Metabolic Syndrome (MS) and its components are often found in women with PCOS. An association between depression and insulin resistance, a characteristic of MS, has been reported. The literature describing MS in women with PCOS and its relationship with psychological variables are limited.

This paper focuses on the following research questions:

a. What is the point prevalence of Metabolic Syndrome (MS) in PCOS cases and controls?
b. Are psychological factors (depressive symptoms, anger, anxiety, hostility/cynicism, and satisfaction with life) risk factors for Metabolic Syndrome independent of age, marital status, education, and parity?

3. PCOS, Psychological Factors, and IMT

1. Earlier work has shown that women with PCOS have increased subclinical atherosclerosis as measured by IMT. Thus far, there has been little attention paid to the investigation of psychological risk factors as predictors of cardiovascular disease (measuring carotid intima-media thickness [IMT]) in women with PCOS.

This paper focuses on the question:

a. Are psychological factors (independent of baseline cardiovascular risk factors) predictors for IMT in women with PCOS?

Research questions for all three papers were evaluated from the CHARM Study, a large matched-pair study of 161 PCOS cases and controls. Paper one was the foundation for the subsequent papers, at is was a descriptive study determining the prevalence of psychological factors in women with PCOS as compared to controls.

Paper two explored the relationship between psychological factors and Metabolic Syndrome, a common medical condition in women with PCOS.

Finally, paper three investigated the relationship between PCOS, psychological factors, and IMT.

2.0 INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous reproductive disorder that has a known prevalence of up to 20% in women. Beyond the physiological sequela of PCOS, psychological consequences coexist and need further study. The purpose of this dissertation is to evaluate the psychological characteristics (i.e. depression, anxiety, anger, hostility, and satisfaction with life) in individuals with PCOS compared to controls. In doing so, it is also intended to determine the point prevalence of depression in this population by utilizing a self-report screening questionnaire to assess depressive symptoms. Because the physiological and psychological features of PCOS are complex and interrelated, health correlates (i.e. cardiovascular disease, obesity, type II diabetes, and insulin resistance) and their relationship to the psychological characteristics will be explored. Finally, it will be determined whether in women with PCOS, the psychological characteristics of depression or satisfaction with life are independent risk factors for subclinical atherosclerosis (measured by intima-media wall thickness and the prevalence of plaque) over and above the traditional cardiovascular risk factors.

The basis for this secondary analysis of the data from the Cardiovascular Health and Risk Measurement Study (CHARM) originated in 1992-1994 with the goal of comparing cardiovascular heart disease risk factors in women with and without PCOS. From this case control study, results published in 1995 revealed that after controlling for age, body mass index

(BMI), and other confounding variables, differences in cardiovascular risk factors were elevated in PCOS women who were largely premenopausal (age 15-55) compared to similar aged controls. In CHARM I, the psychological data was presented at several meetings and univariate analyses of data were completed, (American Heart Association, AHA, 1998), but these data were not examined within the context of the full cardiovascular profile.

In 1998 Talbott and colleagues reported when compared to controls, PCOS women had substantially higher low density lipoprotein (LDL-C) and total cholesterol levels at each age group under 45 years of age after adjustment for BMI, hormone use and insulin levels and other health correlates of PCOS (1). Further research continued in the same population, with a follow-up phase to CHARM II from1996-1999, but no longer in a matched-pair format. This case control study found evidence for an association between PCOS and premature carotid atherosclerosis in middle-aged women through measurements of carotid plaque distribution and intima media thickness. More recently, published findings in 2004 and 2007 highlighted the association between metabolic cardiovascular syndrome (2) in PCOS and incidence and prevalence of Type II diabetes in PCOS, respectively. To add to advances in clinical treatment of PCOS, further knowledge of the psychological effects of this syndrome is essential. The mind–body connection is paramount in the understanding of PCOS in order to ultimately provide comprehensive treatment (emotional and medical) to women with PCOS. The findings from the secondary analyses of the baseline data focusing on the psychological aspects of PCOS may be useful to the future psychological treatment of PCOS women, a much needed aspect of their care.

For this dissertation the following series of three research papers will take advantage of data from CHARM I and CHARM II:

1. Associations among Depressive Symptoms, Anxiety, Anger, Hostility, and Satisfaction with Life in Women with Polycystic Ovary Disease (PCOS).

   Women with PCOS have been identified as individuals that are at risk for depression due to the physiological and body image changes that occur from this syndrome. Studies primarily utilizing small samples have supported the finding that depressive symptoms are more prevalent in PCOS women. This paper focuses on the following research questions:

   a. What is the relationship between PCOS and depressive symptoms?

   b. What is the point prevalence of clinically significant self-reported depressive symptoms in PCOS women when compared to controls?

   c. What is the relationship between satisfaction with life and other psychological characteristics (personality traits): anxiety, anger, hostility in women with PCOS?

   d. Are age, BMI, education, parity, testosterone levels, marital and smoking status potential covariates in this relationship?

2. PCOS, Psychological Manifestations and the Metabolic Syndrome. What is the relationship?

   Metabolic Syndrome (MS) and its components are often found in women with PCOS. An association between depression and insulin resistance, a characteristic of MS, has been reported. The literature describing the MS in women with PCOS and the relationship between psychological effects are limited. This paper focuses on the following research questions:

   a. What is the point prevalence of Metabolic Syndrome (MS) in PCOS cases and controls?

b. Are psychological factors (depressive symptoms, anger, anxiety, hostility/cynicism, and satisfaction with life) risk factors for Metabolic Syndrome independent of age, marital status, education and parity?

3. PCOS, Psychological Factors and IMT

Earlier work has shown that women with PCOS have increased subclinical atherosclerosis as measured by IMT. Thus far there has been little attention in the investigation to the psychological risk factors as predictors of cardiovascular diseas (measuring carotid intima-media thickness [IMT]) in women with PCOS. This paper focuses on the question:

a. Are psychological factors (independent of baseline cardiovascular risk factors) predictors for IMT in women with PCOS?

3.0 LITERATURE REVIEW

Polycystic ovary syndrome (PCOS) is a common heterogeneous reproductive disorder with a known prevalence of 5% to 10% in women (3-7). PCOS manifests in puberty, typically with chronic anovulation, hirsutism, acne and obesity (5, 7-12). Other features include infertility, male-pattern balding, ovarian enlargement, and signs of insulin resistance, ie. central obesity and acanthosis nigricans (7, 9-11, 13). As this is a lifetime disorder, other medical problems may surface such as cardiovascular disease, dyslipidemia and Type II Diabetes (8, 9, 14-16). There is no known cure for PCOS and the goal of treatment is to reduce the symptoms and risk factors for other health problems(17).

The etiology of PCOS is unclear and the natural history of the disease is unpredictable. PCOS has been known as one of the most confusing and complicated diseases. This is probably due to the multiple manifestations of the syndrome, the various definitions given it, as well as the differing diagnostic criteria (18). Early on, PCOS was referred to as the Stein-Leventhal syndrome (10).

In 1990, the National Institute of Health met to investigate PCOS. However, there was no consensus regarding the definition of the disorder (19). For research purposes, though, PCOS has been defined by using the recommendations from the conference (16, 20). These recommendations suggested that PCOS be defined, in order of importance, as: 1.) hyperandrogenism (increased levels of male sexual hormones) and or hyperandrogenemia (an

excess of androgens, which is identified by external changes, i.e. acne, hirsutism), 2.) ovulatory dysfunction, and 3.) the exclusion of related disorders such as hyperprolactinemia (19).

Later in 2003, an expert panel developed diagnostic criteria for PCOS, called the Rotterdam criteria (20). They concluded that the presence of 2 of the 3 criteria, oligo/anovulation, hyperandrogenism, and polycystic ovaries, in the absence of secondary causes is sufficient for diagnosis (6, 20). Talbott et al. in 1995 (4) utilized the definition of PCOS to include a history of chronic anovulation in association with either clinical evidence of androgen excess (hirsutism) or if total testosterone level was >2 nm/L or the luteinizing hormone/follicle-stimulating hormone ratio was greater then 2. As of today, the exact definition of PCOS is still controversial.

3.1 HORMONE IMBALANCE

Hormone dysregulation of PCOS (hyperandrogenism and menstrual irregularities) represents the major medical complaint in young women and in cases of infertility in adults with PCOS (6, 20). Initially, there are outward physical changes that begin to occur early in adolescence (onset approximately age 14) progressing to more severe insults such as infertility, insulin resistance, and cardiovascular health problems. In a recent study, Matar, (21) reported that women with PCOS experience infertility (mean incidence of 74%), hyperandrogenism (69%), amenorrhea (29%), dysfunctional bleeding (29%), and sterilization (21%). In PCOS, there is a chronic presence of increased testosterone levels concurrent with low levels of progesterone and estradiol (22, 23). Further, it has been found that the sex-hormone binding globulin (SHBG) can be significantly lowered which then results in increased levels of free

testosterone (FT) (24). Along with FT, others have reported increased androstenedione (free androgen index) which occurs in 70-90% of women (24). Serum leutenizing hormone levels are also raised (24).

A multitude of gynecological problems can result from hormonal dysfunction in women of all ages with PCOS, as noted earlier by Matar (21). Probably the most serious repercussion is infertility. Reports reveal that pregnant PCOS women have a miscarriage rate of approximately 30%, twice the rate of early miscarriages in non-PCOS women (25).

Menstrual irregularities and its association with cardiovascular disease are also considered a serious complication of PCOS. Solomon et al. in 2002, (26) reported on menstrual cycle irregularity and the risk for future cardiac disease. He highlighted the results of the Nurses' Health Study (n = 82,439) (27). It was found that women with a history of menstrual irregularity, or chronic anovulation, had increased relative risk of fatal and nonfatal coronary heart disease of 1.25 and 1.67, respectively, after a 14 year follow up. After adjusting for BMI, the increased risk for coronary heart disease was slightly attenuated, but still remained statistically significant.

3.2 CARDIOVASCULAR EFFECTS

In addition to a diagnosis of PCOS, women are now being monitored for cardiovascular disease as the research has shown that there is an association between PCOS and cardiovascular disease (4, 14, 16, 28). PCOS is often associated with several cardiovascular risk factors such as decreased HDL cholesterol (HDLc), increased levels of LDL cholesterol (LDLc), increased triglycerides, increased obesity, increased waist-hip ratio, increased hypertension, increased

insulin resistance and abnormalities of coagulation (4, 14, 29). Further, PCOS has been associated with endothelial dysfunction and subclinical cardiovascular disease (30).

Dyslipidemia is a term utilized to describe abnormal levels in HDLc, triglycerides, LDLc, and LDL to HDL ratios (4). Both obese and lean women with PCOS have dyslipidemia.(31) Lean women tend to present with reduced levels of HDLc and the HDL subfraction known as HDL-2 (31). A low HDLc level has been identified as a strong predictor of cardiovascular disease in women (30). Many researchers have contended that prolonged exposure to dyslipidemia can result in increased cardiovascular risk (1, 4, 14, 15, 29).

Hypertension is one of the major cardiovascular risk factors for cardiovascular disease. In 1992, Zimmerman et al.(32) reported that most of the premenopausal women with PCOS have blood pressure readings in the normal range. Of concern, when PCOS women were compared with controls, Holte et al., (33) found that PCOS subjects had higher ambulatory daytime systolic and mean arterial pressures. In the same study, they reported that PCOS subjects compared to controls had a higher prevalence of labile blood pressure independent of insulin sensitivity. Talbott et al., 1995, (4) reported that mean systolic and diastolic blood pressures were greater in women with PCOS than control subjects. Further, in this study, they found that mean systolic blood pressure among case subjects was 113 ± 14.3 mm Hg and among control subjects, 110.3 ± 14.3 mm Hg (p=.025). Mean diastolic pressure was not significantly different. The prevalence of mean diastolic readings ≥ 90mmHg was 5.9% in women with PCOS and only 3.3% of controls.

Abnormalities in coagulation also contribute to the risk of cardiovascular disease in women with PCOS (1, 29). Talbott et al. (15) measured a panel of coagulation and fibrinolytic factors in the Pittsburgh cohort in the CHARM II study. Included markers were: tissue plasminogen activator (TPA), Factor VII, D-Dimer, C-reactive protein and Fragment 1.2 in

addition to PAI-1 levels. When adjusting for BMI and age, only PAI-1 remained significantly different between PCOS cases and controls. Further, the addition of log insulin to a PCOS-BMI regression model, the difference between cases and controls remained significant. This suggests that the higher PAI-1 levels were not completely explained by increased BMI and insulin levels.

Vascular dysfunction is seen an early occurrence in the process of atherosclerosis and therefore its assessment serves as a useful prognostic tool prior to the development of cardiovascular risk factors (34). Endothelial function of flow and resistance (i.e. impaired arterial vasodilatation, increased arterial stiffness, and increased hemostasis) are often identified as cardiovascular endpoints studied in PCOS (28). Arterial endothelial dysfunction is one of the earliest markers of arterial damage and plaque formation in atherosclerosis (35). The endothelial layer of the artery has many homeostatic functions, one being control over thrombosis (36). Abnormalities in the endothelium have been identified as a precursor of atherosclerosis. Mather et al.(37), conducted a cross-sectional study of endothelium-dependent and independent vascular function using brachial ultrasound on women with PCOS and matched controls. In the sample of 18 PCOS women and 19 age-matched controls they reported no evidence of impaired endothelial function in women with PCOS as compared to controls. On the other hand, more recent studies have reported abnormal arterial stiffness and abnormal endothelial function in PCOS case control studies (38-42).

The research has identified two major anatomical markers for subclinical cardiovascular disease dealing with endothelial flow. They are coronary artery calcification and carotid intima thickness (14, 43). Coronary artery calcification is associated with atherosclerotic plaque (44) and also predicts an increased risk of cardiac events.

Epidemiological studies in the 1990's focused on cardiovascular disease in PCOS (29, 45, 46). These studies investigated lipid abnormalities in hirsute women (29), the role of hyperinsulinemia in the development of lipid disturbances in non-obese and obese women with PCOS (45), and the risk of myocardial infarction in PCOS women (46). Wild and colleagues (47) investigated coronary artery disease (CAD) in relationship to hyperandrogenism in 102 women through case series. He utilized cardiac catheterization to measure cardiac status. In this cross-sectional study, he found that the CAD cases had twice the amount of excess hair (OR; 3.7; 95% CI, 1.5-9.1). Although this study did not diagnose PCOS it alluded to the possible relationship between PCOS features and cardiovascular disease.

More refined epidemiological studies continued, as Talbott et al.(4) conducted a large scale epidemiological study, (244 PCOS cases and 244 controls), matched on age, race, and neighborhood. They investigated the coronary heart disease (CHD) risk factors in women with PCOS and demonstrated that women with PCOS have adverse lipid profiles, (i.e. increased LDLc and triglycerides) and decreased HDLc in comparison to controls. It was found that the cardiovascular risk profiles were worse among PCOS cases than controls. HDL cholesterol was lower, and total cholesterol and LDL cholesterol were higher among cases than controls ($P < .05$). Triglycerides were also significantly higher in cases than controls ($P < 0.001$)(4). Mean systolic and diastolic blood pressures were greater in PCOS cases than controls ($P = .009$, $P = .04$). Diastolic readings were $\geq$ 90mmHg in 6.1% of cases and 2.6% of controls ($P = .03$). Additionally, fasting insulin and were greater in cases than controls ($P < .001$). Women with PCOS had significantly higher lipid levels than controls when adjusting for potentially confounding variables (48). When adjusting for BMI, fasting insulin independently contributed

to the variation in HDLc, LDLc and triglycerides. In PCOS cases, decreased estradiol levels were independently associated with increased LDLc (4).

Using this same population, Talbott et al.(1998) also evaluated the age-specific coronary heart disease risk profiles in women with PCOS compared with matched controls in four specific age groups (19-24 years; 25-34 years; 35-44 years and 45+ years). The average age of cases and controls was 35.3 ± 7.4 and 36.7 ± 7.7, respectively. Women with PCOS compared to controls had substantially higher LDLc and total cholesterol levels at each age group under 45 years after adjusting for BMI, hormone use and insulin levels. These findings suggest that women with PCOS exhibit significantly adverse lipid profiles and CHD at a young age. Such findings raise the concern that when compared with normally menstruating women, women with PCOS could be more vulnerable to premature coronary heart disease because of their exposure to excess LDLc and HDLc.

Further research by Talbott et al.(2002)(14) continued, and they investigated the association between PCOS and premature carotid atherosclerosis in middle-aged women. The purpose of this study was to evaluate subclinical atherosclerosis among women with PCOS and controls matched by age. One hundred and twenty five white women with PCOS and 142 controls ≥ 30 years of age were recruited. In this follow-up study (approximately 5 years after the initial study reported in 1995), subjects underwent B-mode ultrasonography of the carotid arteries for the evaluation of carotid intima-media wall thickness (IMT) and the prevalence of plaque. A significant difference was observed in the distribution of carotid plaque among women with PCOS when compared with controls (7.2% (9/125) had a plaque index of ≥ 3 compared to 0.7% (1/ 142) in age-matched controls (P = .05). No difference was noted in mean carotid IMT between PCOS cases and controls overall and in the group aged 30-44 years. On the other hand,

in women in the age group ≥ 45 years PCOS cases had significantly greater mean IMT than did controls (P= 0.05). This difference remained significant after adjustment for age and BMI. These results suggest that women with PCOS who are exposed to adverse cardiovascular profiles develop premature cardiovascular disease. The PCOS relationship to IMT can be explained to some degree by weight and fat distribution and other related risk factors.

Others continued to investigate the cardiovascular risk associated with PCOS. Christian et al. (43) examined the prevalence of coronary artery calcification (CAC) in a cohort of 36 women with PCOS. They found that the women aged 30-45 years of age had a higher rate of CAC than the control group of 71 women who were matched for body mass index (BMI) and age (39% vs. 21%, respectively; odds ratio (OR) = 2.4; confidence interval (CI) 0.99-5.73; P = 0.05). Women with PCOS had a greater mean CAC score when compared to controls (P = 0.04). When adjusting for BMI, PCOS was no longer a significant predictor of CAC (OR = 1.99; P = 0.21).

More recently, the cardiovascular risk attributed to metabolic cardiovascular syndrome (MCS) has been of great concern (15, 49). The prevalence of metabolic syndrome has been reported from 33.4% to 46% in women with PCOS (50, 51). In 2004, Talbott et al.(15) studied the association between MCS and coronary and aortic calcification among women with PCOS. In this study, MCS was characterized as the clustering within an individual of 3 or more of the following risk factors: abnormal central adiposity (waist circumference > 88cm), increased triglycerides (>150mg/dl), low levels of high-density lipoprotein cholesterol (<50 mg/dl), hypertension (130/85 mm Hg or more or treated for hypertension), or increased fasting glucose (≥110mg/dl) or diagnosed with type 2 diabetes (52-54) . In this prospective study by Talbott et al. (2004)(15), 61 PCOS cases and 85 similarly aged controls were screened for risk factors and

were reevaluated 5 years later. The purpose of the study was to determine the prevalence of coronary artery (CAC) and aortic (AC) calcification among middle aged women with PCOS and controls. They also explored the relationship among calcification and MCS, and other cardiovascular risk factors assessed 9 years earlier. CAC and AC were measured by electron beam tomography. They found that when compared to controls, women with PCOS had a higher prevalence of CAC (45.9% vs. 30.6%, respectively) and AC (68.9%vs 55.3%, respectively). When adjusting for age and body mass index, PCOS was a significant predictor of CAC (odds ratio = 2.31; 95% confidence interval (CI) = 1.00, 5.33; P = 0.049). Total testosterone was an independent risk factor for AC in subjects after controlling for PCOS, age and body mass index (P= 0.034). High-density lipoprotein cholesterol and insulin appeared to mediate the influence of PCOS on CAC.

Since 2004, several studies have reported an increased prevalence of metabolic syndrome in women with PCOS when compared to controls (16, 55-57). In these studies, the term metabolic syndrome was used versus the metabolic cardiac syndrome (MCS). Results may differ in studies based on differences in definitions. Nevertheless, it is important to address the role obesity plays in the relationship with metabolic syndrome and or MCS. Faloia et al.(56) evaluated the effects of metabolic characteristics of PCOS and found no lean subjects exhibiting the metabolic syndrome compared with the 37% of overweight/obese PCOS subjects and 33% of the overweight/obese controls. Consistent with these findings, Dokras et al.(55) found that the prevalence of metabolic syndrome did not differ when comparing women with PCOS and age-matched controls did not differ significantly after controlling for BMI. Disputing the findings of the two previous studies mentioned, Azziz et al (2006) (57), found a higher prevalence of metabolic syndrome in obese women with PCOS independent of age and BMI. One of the most

striking findings with BMI and MCS was by Talbott et al.(16) in 2004. MCS was evaluated at baseline between relatively young women with PCOS and controls (mean age 38.7 and 40.4 years respectively) with similar BMI (<35kg/m²). They found that women with PCOS were approximately 4.4 times more likely to exhibit MCS than controls.

Studies linking PCOS to primary cardiovascular events such as stroke and myocardial infarction are speculative (58). Wild et al.(54) studied cardiovascular mortality and morbidity in middle aged women previously diagnosed with PCOS and age-matched controls. In this retrospective cohort study of women diagnosed with PCOS in the United Kingdom, they collected data on 319 women with PCOS and 1060 age-matched controls. Data was collected by death certificates, general practitioners' records and questionnaires with measurement of cardiovascular risk factors in a sub-sample of questionnaire respondents. Results indicated that all-cause and cardiovascular mortality in the cohort were similar to the women in the general population (standardized mortality ratios (95% CI): 93 (72-117) and 78 (45-124), respectively. They reported that women with PCOS had higher levels of diabetes (P = 0.002); hypertension (P = 0.04); hypercholesterolemia (P < 0.001); hypertriglyceridemia (P =0.02) and increased waist: hip ratio (P = 0.004). When adjusting for BMI, odds ratios (OR) were 2.2 (CI: 0.9-5.2) for diabetes, 1.4 (CI: 0.9-2.0) for hypertension and 3.2 (CI: 1.7-6.0) for hypercholesterolemia. A history of cerebrovascular disease was significantly more common in women with PCOS with a crude OR (95% CI) of 2.8 (CI: 1.1-7.1) as opposed to the history of CHD which was not significantly more common in women with PCOS; OR (95% CI) 1.5 (0.07- 2.9).

Pierpoint et al.(59) in 1998 studied cardiovascular mortality in PCOS over long-term follow-up. There were 786 women with a history of PCOS identified through hospital records and the investigated through the National Health Service Registry over a 42 year period. In this

study the ratio of observed-to-expected deaths as a result of all circulatory disease was not increased (standard mortality ratio of SMR, 0.83; (95% CI); (0.46-1.37). In this study it was questioned whether unopposed estrogen in PCOS might be protective against cardiovascular disease.

In the second follow-up period of the Cardiovascular Health and Risk Measurement Study (CHARM II) by Talbott et al.(14) (1997-99), a medical history of cardiovascular events including myocardial infarction, doctor diagnosed angina pectoris, coronary insufficiency, bypass angioplasty as well as stroke was obtained. This cohort was comprised of 127 PCOS cases and 142 Caucasian controls. The population represented 75% of the original cohort. In this sample, there were a total of 5 cardiovascular events representing one myocardial infarction with bypass surgery, one angina pectoris with bypass surgery and three doctor-diagnosed angina pectoris (medically treated). When compared to controls of similar age, no events were observed. The result yielded an odds ratio (OR) 5.86: $P < .05$.

More recently, in 2007, Cussons et al. (34) critiqued the literature on the epidemiology of cardiovascular disease in PCOS and noted that definitive evidence of an increased incidence is unproven due to the short periods of follow-up, the use of highly selected clinic populations, small sample size, and confounding factors such as treatment effects at baseline.

3.3 INSULIN RESISTANCE AND TYPE II DIABETES

Another major health problem in women with PCOS is insulin resistance, which is often associated with Type II Diabetes (60). While it is difficult to find a universal definition for

Insulin Resistance (IR), some (61) have defined IR as the failure of target cells to respond to ordinary levels of circulating insulin. In 2004, Legro (62) reported a 50-75% prevalence rate for insulin resistance in women with PCOS. When IR occurs in women, it puts them at a greater risk not only for developing PCOS, but also for Type II Diabetes, essential hypertension, nonalcoholic steatohepatitis, dyslipidemia, and certain cancers (62, 63). Research has also linked insulin resistance with cardiovascular disease in women with PCOS (62). Although insulin resistance is not recognized as an independent risk factor for cardiovascular disease, it is associated with known cardiovascular risk factors (64). Insulin resistance is also associated with the metabolic syndrome in women with PCOS (30).

Type II Diabetes is a heterogeneous metabolic disorder characterized by hyperglycemia which is due to a combination of resistance to insulin and an inadequate compensatory insulin secretory response (65). The prevalence of Type II Diabetes in the general population according to the U.S. Third National Health and Nutrition Examination Survey (NHANES III) (66) is 7.8% in adults ≥ 20 years of age. Rates increase with age to 18.8% in individuals ≥ 60 years old.(66). Type 2 diabetes, associated with insulin resistance, affects a large proportion of the female population, although generally at an older mean age than in PCOS women (65). Among women with PCOS, 7.5% to 10% have type Type II Diabetes by their fourth decade (52, 67).

Menopausal status has also been researched in relationship to the prevalence of Type II Diabetes in women with PCOS. A retrospective study (68) found an increased prevalence of Type II Diabetes in both premenopausal and postmenopausal women with PCOS. Two studies have reported a higher prevalence of PCOS among women with Type II Diabetes (69, 70). Others(52, 60, 71-73) have found that women with PCOS appeared to develop Type II Diabetes at a younger age than women without PCOS. In 2007, Talbott (8) reported that 15% to 35.6% of

all incident cases of Diabetes Type II in Caucasian women may be attributable to PCOS. The prevalence and incidence of Type II Diabetes is reportedly on the increase in young women between the ages of 20-35 (4, 59, 74). Research on Type II Diabetes Type 2 in women with PCOS continues to be of interest as diabetes itself is becoming a major epidemic world wide. Even though many of the prospective or retrospective studies investigating the relationship women with PCOS were performed with matched controls and adequate sample sizes, (8, 58, 67, 74), longitudinal studies should be considered in order to address the lifetime incidence of Diabetes Type 2 in women with PCOS, particularly across the wide age range in PCOS women.

3.4 OBESITY

Yet another physiological implication of PCOS is obesity. Obesity is a comorbid occurrence with the previously described clinical features such as MCS, infertility, insulin resistance and Diabetes II. Obesity has not been included in the definition or the diagnoses of PCOS, but is a major contributor to body dissatisfaction in women with PCOS. In a large sample of women, Carmina (58) reported that 70% of women with PCOS had increased body weight (body mass index) BMI > 25kg/m^2. Categories of obesity are seen below in Table 1. Obesity is known to worsen insulin resistance, which can ultimately lead to cardiovascular disease (58).

Early studies have substantiated that women with PCOS have a higher prevalence of obesity (2, 50). Depending on ethnicity, genetics, other medical problems, lifestyle and geography, the presence of obesity varies. Carmina (75) noted that overall obesity is present in approximately 44% of PCOS women. More recently, the prevalence of obesity in women with

PCOS has ranged between 38% and 88%(76, 77). As one might expect, obesity worsens the manifestations of PCOS. Some features of PCOS that worsen are insulin resistance and androgen levels. Insulin resistance increases and there is a further elevation of ovarian and adrenal androgens and unbound testosterone (78). When obesity is present, it is usually of the android type, with increased waist-to-hip ratio (1). The mechanism of weight gain in PCOS is attributed to both genetic predisposition and environment (i.e., poor diet and reduced exercise)(79).

In 1995, Talbott et al.(4) highlighted the differences in BMI between women with PCOS and controls. They reported that cases weighed more than controls (176.9 ± 49 versus 153.76 ± 35.7 pounds, respectively, P< .001). Almost 50% of the cases and 27.8% of the controls weighed 170 pounds or more (P < .01). Mean BMI for cases was 30.5 ± 8.3 versus 26.3 ± 6.5 for controls; (P< .001). In the Pittsburgh study cohort by Talbott et al.(14) approximately 40% of the PCOS Caucasian women were not overweight/obese by the criterion of a BMI of 27.3kg/m² proposed by the national standards. In 2005, a compelling finding was reported from a study by Glueck et al.(80) on women with PCOS from the ages of 20-41. Utilizing a sample of 401 PCOS women matched with population controls, they found that major weight gain manifested by the age of 20-24 and continued through 32-41 years. Moreover, 91%, were overweight, obese, or extremely obese. As women age, obesity continues to be a major concern and struggle for women with PCOS.

Most early and more recent research studies (4, 12, 75, 81) have examined obesity along with the major features of PCOS and in some studies have found obesity to be a confounding variable. Many studies have reported controlling for BMI to determine independent associations with PCOS physiological determinants (1, 4, 14, 16). Talbott et al.(4, 15), after controlling for BMI, found that cardiovascular risk factors differed significantly between PCOS cases and

controls. Women with PCOS were more than twice as likely as controls to exhibit coronary artery calcification(4). In a later study by Talbott and colleagues (14) women with PCOS ≥ 45 years of age compared to controls of similar age had significantly greater IMT readings. In a later study that investigated the association between MCS and CAC in women with PCOS, Talbott and colleagues (15) found that components of MCS mediate the association between PCOS and CAC, independent of obesity. On the other hand, in prior work examining premature cardiovascular disease in middle aged women, Talbott et al.(14) found BMI to be a powerful predictor of IMT, particularly in women with PCOS. Similarly, in a 1998 study investigating the adverse lipid and CHD risk profiles in young women with PCOS, Talbott et al.(1) reported that BMI predicted both systolic and diastolic blood pressure in younger PCOS women. In addition to BMI, fasting insulin level has been found to be a significant predictor of blood pressure levels in older PCOS women (1).

The parameters for BMI measurement have been fairly consistent with the categories for BMI as listed below in **Table 3-1**. However, it is important to consider the definitions of BMI by categories before interpreting the results of research studies. Additionally, the link between obesity and PCOS is a complex interplay between many organ and endocrine systems. Research studies have moved toward trying to understand this phenomena through stratification of samples by age (82). As the obesity epidemic continues world-wide, this clinical correlate will likely remain a central issue for future studies of PCOS.

Table 3-1 Categories of excessive body mass index, BMI *

BMI 18.5-24.9 kg/mg²	Normal weight
BMI 25-29.9 kg/mg²	Overweight
BMI 30-34.9 kg/mg²	Obesity Class 1
BMI 35-39.9 kg/mg²	Obesity Class 2
BMI ≥40 kg/mg²	Obesity Class 3

*BMI categories based on criteria from the National Heart, Lung, and Blood Institute (83)

3.5 PSYCHOLOGICAL/MENTAL HEALTH PERSPECTIVE OF PCOS

In addition to the medical ramifications of PCOS, mental health consequences may also manifest as a result of this condition. Most research has been primarily focused on the biophysiological characteristics without sufficient attention to the psychological outcomes. As described by many researchers (84-89), the medical features of PCOS make them particularly susceptible to the psychological effects that result from changes in body image related to insulin resistance and hyperandrogenism. These psychological effects may consist of symptoms of depression, reduction in life satisfaction, as well as increased anxiety, anger and hostility in everyday life. These changes are depicted in **Figure 3-1**. Clinical Significance of PCOS with Physiological changes and Psychological consequences.

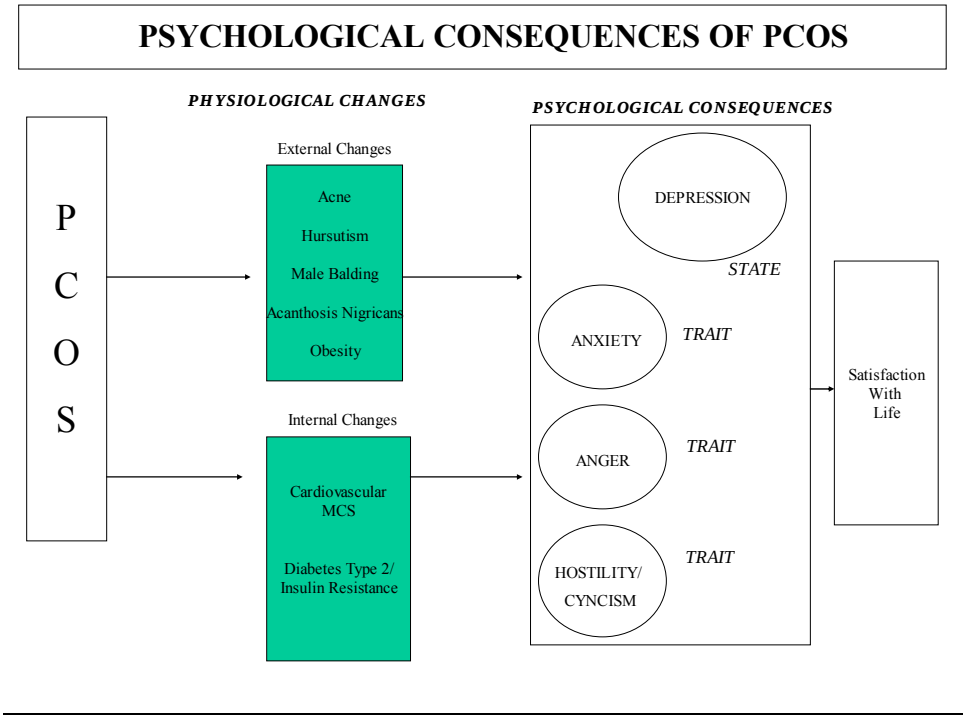

Figure 3-1 Clinical Significance of PCOS with Physiological changes and Psychological consequences

3.6 PSYCHOLOGICAL CONSEQUENCES OF PCOS: DEPRESSION

One psychological consequence of the physical changes associated with is depression. The term 'depression' has varied definitions when used in both clinical and research contexts. Some research studies use the term 'depression' to refer to depressive symptoms that are measured by a self-report of interviewer-administered questionnaire. These studies often use a pre-determined score or cutpoint on the scale to identify persons with symptoms that are above the 'normal range.' It is important to differentiate between the assessment of depressive symptoms and the diagnosis of a clinical illness. Symptom scales cannot be used to diagnose clinical depression. One common form of clinical depression is Major Depressive Disorder (MDD). MDD consists of a sad mood or loss of interest or pleasure in one's life combined in

addition to other symptoms such as sleep disturbance, low energy, decreased appetite, poor concentration, feelings of worthlessness, and guilt that are persistent over a two week period (90). In addition to the presence of at least five of these symptoms, a key aspect of the diagnosis of this clinical illness is that these symptoms impair the person's ability to function. Although major depression can occur only once in an individual's lifetime, it also an illness that can recur repeatedly. Other forms of clinical depression include dysthymia, which is a milder but more chronic form of clinical depression that last at least two years, and bipolar disorder, in which an individual experiences periods of major depression as well as periods of mania.

Currently, the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR) (90) is the accepted standard resource which provides guidelines in determining psychiatric diagnoses. It includes the criteria for the diagnosis of Major Depressive Disorder (MDD) (Single Episode and Recurrent); Dysthymia, and Bipolar Disorder. i.e. depression.

It is well documented that women are at a greater risk for depression as reported in a community epidemiological study, the National Comorbidity Survey (NCS) (91, 92). Women were found to be approximately (21.3% in women and 12.7% in men) 1.7 times as likely as men to report a Major Depressive Episode (MDE) in their lifetime (91). Even though this study is criticized for only sampling subjects less than 55 years of age, it is precisely that age group that is most affected with PCOS. In another well known community study by (93), The Epidemiologic Catchment Area Study, (ECA) it was also found that when compared to men, women women were more than twice as likely to experience major depression (2.7: 1) in their lifetime (93).

Other studies have also identified women as being more vulnerable to depression than men (94, 95). Internationally, others have posited that women suffer from higher rates of

depression due to biological determinants(95). From this large community study, Bebbington et al. (1998) (95) reported that there was a clear reversal of the sex difference in the prevalence of depression in women over the age of 55 as compared to men. The prevalence of depression in women decreased from an OR (2.07 to 0.78).

There are numerous screening tools that are utilized to identify individuals who may be at risk for depression. In 2003, Nease and Malouin (96) evaluated depression screening instruments for primary care settings . They recommended 4 screening instruments for assessing depression, the Primary Care Evaluation of Mental Disorders (PRIME- MD) the PRIME-MD Patient Health Questionnaire (PHQ), Symptom-Driven Diagnostic System for Primary Care (SDDS-PC), and the PRIME_MD Patient Health Questionnaire (PHQ-9) (96).

The BDI is a self-report inventory, which measures characteristic attitudes and symptoms of depression. It contains 21 questions with a cutoff of >9 (total score) to identify potential clinically significant symptoms of depression. The psychometric properties of the BDI have been reported as high with internal consistency estimates that range from .73 to .92 with a mean of .86. The split-half reliability coefficient reported was .93. Concurrent validity, determined by correlations with clinician ratings of depression using the revised BDI ranged from .62 to .66 (97). The BDI has been used in prior research studies on the PCOS population (87, 89), as well as research studies on women with obesity.

As one would expect, it is well known that there are higher rates of depression in the medical population (those with medical illnesses) ranging from 21-47 % (98-100). Others have reported point prevalence rates of major depression in primary care outpatients to range from 2-16% and from 9-20% for all depressive disorders (101-106). The incidence and prevalence of depression in the PCOS population is still debatable.

The prevalence of depression in women with PCOS is unknown because there are few studies that have investigated the psychological sequela of PCOS as well as the lack of appropriate methods to obtain psychiatric diagnoses. More importantly have used symptoms inventories, rather than DSM criteria to determine diagnoses of depression. Therefore, related studies that have investigated the prevalence of depression in women may provide the framework and insights into understanding the association between PCOS and depression.

Early on, research on the psychiatric morbidity associated with PCOS was reported using case studies. One of the first investigations of psychological morbidity in women with PCOS was done in London in 1993 by Bruce-Jones et al.(84). This was a modest case series in which Bruce-Jones and colleagues noted that a significant proportion of their sample exhibited "psychological problems". It is flawed in that it is a small sample within a psychiatric practice. A case series of 10 patients with both significant psychological problems and PCOS were discussed. The patients were referred to a hospital liaison psychiatry service. Psychiatric diagnoses were defined according to the DSM III-R (107). The diagnosis of PCOS was made by endocrinologists or gynecologists based on the clinical presentations and endocrine profile. Seven cases of PCOS were actually diagnosed after their psychiatric disorder Of these case reports, 70% had a diagnosis of a depressive syndrome (5 had Major Depression, 1 had Dysthymia, and 1 had Bipolar Depression), while most of the others were anxiety disorders (general anxiety disorder, obsessive compulsive disorder and panic disorder).

Rasgon et al. (86) in 2003, also investigated the prevalence of depression in women with PCOS. This pilot study done in Los Angeles, California in 2003 evaluated 32 women with PCOS in a Reproductive Endocrinology Clinic. Similar to the previous study, there was no control group. The subjects completed the Center for Epidemiological Studies Rating Scale

(CES-D) during the initial visit and had subsequent diagnostic work-ups to establish a correlation between clinical and biochemical markers of PCOS and the CES-D scores. It was found that 16 women had clinically significant CES-D scores (CES-D scores $\geq$16). They reported that depression was associated with greater insulin resistance (p=0.02), and with a higher body mass index (p=0.05). Limitations of this study were small sample size, sample selection bias, the use of a screening tool versus diagnostic measures to identify depression, and lack of a comparison group. This was the first reported pilot study to examine the rate of depression among women with documented PCOS (with clinical and biochemical markers) and to correlate them with scores from a screening tool for depression (CES-D).

In a recent cross-sectional study done in Iowa by Hollinrake et al.(87) 2007, 103 women with PCOS (Rotterdam Criteria)(20) and 103 controls without PCOS seen during the same time period for an annual exam were studied to estimate the prevalence of depressive disorders in women with PCOS. This study also investigated the role of androgens and other metabolic markers associated with PCOS in the development of depression. It was the first case control study to examine the risk of depressive disorders in women with PCOS based on the DSM IV diagnostic criteria. Depression was screened for using the Primary Care Evaluations of Mental Disorders Patient Health Questionnaire (Prime-MD PHQ) and the Beck Depression Inventory (BDI). The Prime-MD PHQ is a self-report screening measure which provides a simple way to assess both diagnostic criteria and severity.(108) This scale demonstrates a sensitivity of 73% and specificity of 93(108). Subjects were women 18-50 years of age. Women with PCOS were at an increased risk of depression (new cases) compared with controls (21% versus 3%, OR 5.11; (95%; (CI: 1.26-20.69); p<.03). The overall risk of depressive disorders in this sample was OR; 4.23; (95% CI 1.49-11.98; p<.01), independent of obesity and infertility. When compared with

the non-depressed PCOS subjects, the depressed PCOS subjects had a higher body mass index (BMI) and evidence of insulin resistance ($p<.02$). Although the Prime-MD PHQ .(108) was used to screen for depression, it is not fully recognized as a diagnostic measure for depression, which may affect the interpretation of the results of this study.

3.7 DEPRESSION AND BODY IMAGE IN PCOS

Body image is a salient variable that can affect mood negatively in PCOS. Two-thirds of the women with PCOS are overweight and over three-fourths exhibit significant hirsutism(6). Acne and male balding are also common physical disturbances seen in women with PCOS women(4, 6, 85, 89). In 2002, Mc Cook et al. in (109) found that body satisfaction (defined as satisfaction with the size and shape of one's body) was lower in women with PCOS than in a nationally representative sample of college women.

A qualitative study, "The thief of womanhood: a women's experience of polycystic ovarian syndrome", reported by Kitzinger and Willmott in 2002,(85) reported findings from interviews of women with PCOS. Thirty women were recruited through a self-help organization in London. In depth, semi-structured, tape-recorded interviews were conducted. Twenty-four white and 6 non-white heterosexual subjects (age 21-42) with a mean age of 29 participated. The thematic analysis of the interviews revealed the women felt "freakish", "abnormal" and not "proper" women. These feelings were related to excess hair growth, irregular or absent periods, and infertility. In this study, one area of focus was hirsutism (an overproduction of hair), a feature women with PCOS experience, and which psychologically can induce profound feelings

of despair and alienation. Kitzinger and Willmott (85) found that women with hirsutism also referred to themselves as unfeminine.

The research on hirsutism and psychological disturbances is limited. Some studies have reported on women with depression and idiopathic hirsutism(110) and found that 7 of the 20 women studied had clinically significant levels of depressive symptoms. Others dating back to 1993 (111) report psychological morbidity for hirsute women at no greater degree than other hospital outpatients.

Androgens play a part in distorting the body image of women with PCOS because hyperandrogenism can exacerbate an increased amount of superficial and facial hair as well as male patterned baldness. In PCOS, hyperandrogenism and hyperinsulinemia are comorbid features. Hyperinsulinemia is linked to acanthosis nigracans as well as central adiposity. In addition it has been theorized that abnormal gonadal hormones (androgens) can contribute to the manifestation of dysfunctional mood states in women through activational effects on the brain(112). PCOS is a hormonal disorder that begins in puberty and is characterized by chronically augmented free testosterone (113). Increased free testosterone (FT) has been associated with depression in women.(114) and testosterone has correlated with anger and depression in women during both the pre and post partum period (115).

Recently, Weiner et al. in 2004 (113), examined androgens and mood dysfunction in women with PCOS. Weiner and colleagues compared studied 27 women with PCOS with 27 normally menstruating women, all of whom were matched on BMI. The PCOS cases were referred from the Department of Endocrinology at the University of Chicago. PCOS was diagnosed by (1)oligo/amenorrhea, (2) hyperandrogenemia (increased free testosterone level), (3) hyperandrogenism (infertility, hirsutism, acne and or alopecia), and (4) exclusion of non-

classic congenital adrenal hyperplasia, Cushing's syndrome, hypothyroidism, or significant elevations in serum prolactin. Controls were obtained through advertisements and also matched on age, education, and race. Subjects with PCOS had a mean age of 28.19 ± 4.84 and controls had a mean age of 30.07 ± 6.48. Mean BMI for women with PCOS was 37.70 ± 8.46 and 36.89 ± 7.24 for controls. Serum levels of FT, total testosterone, and other labs were taken. Self-reported depression, anger, anxiety and aggression were analyzed and compared across hormonal values. A curvilinear relationship between FT and negative affect across groups was suggested. The most elevated negative mood-scale scores were associated with FT values just beyond the upper limits of normal, while lower negative mood levels corresponded to the normal and extremely high values of FT. These findings support the activational influences of testosterone.

Self reported depression, anger, anxiety and aggression were analyzed and compared across hormonal values. The State-Trait Depression Adjective Check List (116); the State-Trait Anger Expression Inventory (STAXI)(117); the State-Trait Anxiety Inventory (STAI)(118); and the Aggression Questionnaire (AQ) (119) were administered. Depression was significantly increased in the PCOS group $P < .01$; and was significantly greater in the PCOS group for both state and trait univariate analyses. Results from the STAXI, STAI and the AQ did not show any significant differences between groups. Limitations of this study included self report measures and small sample size. These findings suggest that a relationship exists between androgen levels and negative mood states, particularly depression.

Others continued to study the psychological consequences of PCOS. In 2006, Himelein and Thatcher (120) compared 40 women with PCOS with controls without PCOS who were infertile, and to a third group who had neither PCOS or infertility problems. PCOS was defined in this study as women having at least 2 of the following clinical symptoms (ovulatory

dysfunction, hyperandrogenism, biochemical markers such as elevated androgen). The groups did not differ in age, race, education, income, or religious affiliation. The majority (98%) were white with a mean age of 32.1 ± 5.5 years. They were well educated with a mean of 15.6 ± 2.2 years of education, and represented a variety of income levels. The groups differed in marital status as the PCOS and infertility groups were more likely to be married (88% and 95% respectively) than the women in the convenience control group. Subjects with PCOS had typically known about their diagnosis for a considerable length of time (mean of 36.7 ± 54.7 months) which may have affected potential depressive symptoms. Individuals may have adjusted to PCOS and thus depressive symptoms may have decreased. Subjects were recruited from 2 separate offices of south-eastern clinics in the United States that specialized in treating women with reproductive and endocrine disorders. All participants were administered 3 questionnaires, the 13-item short form of the Beck Depression Inventory, BDI, (121) the Multidimensional Body-Self Relations Questionnaire-Appearance Scales, (MBSRQ-AS)(122) and the Body Feature Satisfaction, adapted from the Body Satisfaction Questionnaire.(123) In the PCOS group, 78% reported receiving some type of treatment for PCOS. Fifteen percent of the PCOS group was considered to be normal weight. The PCOS women reported higher depression scores and greater body dissatisfaction ($p<.001$) than comparison group women. Post-hoc comparisons revealed that women with PCOS reported significantly more depressive symptoms than women in either the infertility or convenience control groups. The mean depression score for the PCOS group fell within the mildly depressed range of the short form of the Beck Depression Inventory, compared with mean scores in the normal range for both comparison groups. Furthermore, scores in the moderate to severe level of depression (totals of 12 or greater) were reported by 28% of women with PCOS, compared to 10% in women with infertility and 2 % in the

convenience control group. When controlling for body mass (BMI), body image (defined as overall looks and discrete physical characteristics and measured by the MBSRQ-AS) was strongly associated with depression scores on the BDI. They also found that women with PCOS expressed more dissatisfaction than comparison group women with four additional body characteristics: skin complexion; visible facial hair; general hair features; and overall appearance. Limitations of this study included the cross-sectional design and bias due to the sampling bias. As well, a convenience sample was used and 98% were Caucasian. Furthermore, another limitation that may have affected the findings was that the PCOS subjects knew about their disorder for approximately 3 years prior to the study and thus may have developed strategies to cope with or adapt to the emotional repercussions associated with PCOS.

The research studies on PCOS and depression are limited to 6 investigations from 1993 to 2007. See **Table 3-2** for the studies investigating PCOS and depression.

Table 3-2 Studies Investigating PCOS and Depression

Study	Year	N	Design	Findings	Comments
Bruce Jones et al. (84)	1993	PCOS Cases n=10	Case series referred for medical in-patient consultation	Majority 50% had Major Depression	Small sample; no standardized tools
Kitzinger & Wilmott (85)	2002	PCOS Cases n=30	Semi-structured tape recorded interviews	Analyses revealed women saw themselves as different and less feminine.	qualitative
Rasgon et al. (86)	2003	PCOS Cases n=32	Descriptive	50% had scores indicative de-pression (not on OCP*) p=.03;De-pression was associated with > insulin-resistance and BMI	Pilot study No control group CES-D used
Weiner et al. (113)	2004	PCOS Cases n=27 & controls n=27	Case Control Matched on BMI, age, education, and race	Depressive symptoms were significantly increased in PCOS group. State and trait depression = P<.01	measured testosterone & relationship to depression; used State-Trait Depression Adjective Checklist
Himelein & Thatcher (89)	2006	PCOS Cases n=40 & 2 control groups n=120	Case control Did not identify matching; but stated no difference in age, race, education, income, or religion in results	PCOS women reported higher depression scores and body dis-satisfaction p<.05.	Case control Compared PCOS women to: 2 groups infertile/no PCOS; and to normal women BDI 13 item used
Hollinrake et al. (124)	2007	PCOS Cases n=103 & controls n= 103	Case Control No matching Multivariate analysis Was performed on BMI and fasting glucose	OR 5.11 (CI-1.26-20.69), p<.03 risk of depression for PCOS cases compared to controls; OR 4.23 (CI-1.49-11.98)p<.01 independent of obesity and infertility	Prime-MD PHQ used for diagnostic measure of depression BDI also used.

*OCP= oral contraceptives

3.8 DEPRESSION AND SUBCLINICAL CARDIOVASCULAR DISEASE

Subclinical cardiovascular disease, also known as cardiovascular disease that has not reached a clinical presentation, has been identified by the presence of underlying disease such as atherosclerosis(125). B-mode ultrasonography, a measurement of carotid wall intima-media thickness (IMT) is utilized as a diagnostic tool to measure atherosclerosis(126). IMT correlates substantially with atherosclerosis in the coronary arteries and can predict clinical coronary events(125).

Epidemiological studies dating back to 1993 have demonstrated that there is a link between depression and the risk of developing cardiovascular disease (127, 128). Patients with depression have a twofold to fourfold increased risk of developing cardiovascular disease (127, 129). In a review article by Musselman et al.(1998)(130) they reported that symptoms of depression predict future coronary events for initially health individuals. Although there are a multitude of studies reporting on depression and different aspects of cardiovascular disease,(127-131) there are none known that have described the possible independent relationship between depression and subclinical cardiovascular disease in PCOS. Since cardiovascular disease is an important concern in PCOS, (e.g., sub-clinical disease noted by Talbott et al.(2000)(14) and Christian et al. (2003)(43), it is important to examine the studies linking depression and cardiovascular disease, specifically those sub-clinical in nature.

There are few studies reporting on the relationship between depression and sub-clinical cardiovascular disease (131-133). In 2003, Jones et al.(134) studied the lifetime history of depression and carotid atherosclerosis in middle-aged women in the Study of Women's Health Around the Nation, (SWAN), a 7 site, prospective, longitudinal study of the perimenopausal transition. Age of subjects ranged from 42-52 upon study entry. A cohort of 463 healthy

middle-aged women, predominately white (one-third African Americans) from the parent study of 463 participants, was assessed for depression and subclinical atherosclerosis as measured by B-mode carotid ultrasound scanning of the right and left common carotid arteries, carotid bulb, and the first 1.5 cm of the internal and external carotid arteries were obtained. The ultrasonographer imaged the vessel in several planes for each location and then focused on the interfaces required to measure IMT and on the largest are of focal plaque. The IMT and plaque scores were computed by trained readers at the Pittsburgh site. Both the ultrasonographers and readers were blind to the participant's Structured Clinical Interview (SCID-IV) diagnoses, and the SCID-IV interviewers were blind to the plaque and IMT results. Psychiatric diagnoses were assessed using the Structured Clinical Interview (SCID) for the DSM-IV Axis I disorders-Non-Patient Edition. Subjects were also administered the Center for Epidemiological Studies Depression Scale (CES-D)(135) to ascertain depressive symptoms during the past 7 days. More than one third of the sample met the criteria for a major depressive episode during their lifetime and approximately 23% of the subjects reported clinically significant depressive symptoms during the past week on the CES-D (score $\geq$ 16) (132). Women with a lifetime history of recurrent major depressive episodes demonstrated a twofold risk of plaque relative to women with no history of depression (odds ratio = 2.30; 95% confidence interval, 1.10-4.82). The lifetime history of a single major depression episode was not associated with plaque (OR = 0.63; 95% CI, 0.20-1.98). Current depressive symptoms (CES-D scores $\geq$ 16) were not significantly associated with plaque (P =.70) or IMT (P =.50). The findings remained the same when the current depressive symptoms were used as a continuous variable rather than a dichotomous one. Covariates included systolic BP, insulin and race. A lifetime history of recurrent major depressive episodes remained significantly associated with plaque after controlling for age,

diastolic blood pressure, smoking history, and race. Lastly, the covariate, tricyclic antidepressants, was analyzed to determine if the tricyclic antidepressants mediated the association between recurrent major depression and plaque. This association remained statistically significant after controlling for the use of tricyclic antidepressants (OR = 2.56; CI, 1.18-5.57).

In another study, Agatisa et al. (2005)(132) (using the women in the SWAN study site in Pittsburgh) investigated coronary and aortic calcification in women with a history of major depression. Fifty-eight African American women and 152 Caucasian women participated in the study. A history of major depression was diagnosed using the SCID, administered at baseline and annually to assess participant's mental health. The Center for Epidemiological Studies Depression Scale, (CESD) (135) was used to identify potential clinically significant symptoms of depression. At the beginning of the third year of the annual visits, electron beam tomography (EBT) measures of calcification of the coronary arteries and aorta were obtained. Of the 210 women in the study, 53 (25%) met criteria for a history of recurrent major depression. Most of the subjects were Caucasian. Coronary calcification was identified in 103 women (49%) and aortic calcification in 144 women (54%); high calcification scores were classified at approximately 75% of the sample distribution (i.e. ≥10 for coronary calcium score (n = 49) and >100 for the aorta calcium score (n = 53). Women with a history of recurrent major depression (n = 53) were more likely to have any coronary calcification or calcification in the high category at either site compared with women with a history of a single episode of depression or no depression. When adjusting for cardiovascular risk factors (age, race, education, BMI, triglycerides, smoking status) and sociodemographic characteristics, a history of recurrent major depression, compared with a single episode or no history was associated with increased risk (OR

2.46; 95% CI: 1.06–5.67) for any coronary calcification; with high coronary calcification (OR 2.71; 95% CI: 1.08-6.81) and with high aortic calcification (OR 3.39; 95% CI :1.34-8.63). Adjusting for waist-hip ratio reduced the association (was no longer statistically significant) between history of recurrent depression and any calcification or with high calcification.

In a recent study by Stewart et al. (2007)(133) from the Pittsburgh Healthy Heart Project, an ongoing prospective cohort study of healthy older men and women from the general community, negative emotions and a 3 year progression of subclinical atherosclerosis was studied. Three hundred and twenty-four subjects participated to determine a three year change in mean carotid intima-media thickness. This study was unique in that it simultaneously studied the effects of depressive symptoms, anxiety, and hostility/anger, on coronary artery disease (CAD). Participants were healthy adults with a mean age of 60.6 ± 4.7 years. Approximately 50% were women. The Beck Depression Inventory II, (BDI II) (97) was administered as one of the negative emotion scales along with the Cook-Medley Hostility Scale (136) and the State-Trait Anger Expression Inventory.(117) Carotid intima-media thickness (IMT) was measured by ultrasonography. Regression analyses indicated that higher depressive symptoms at baseline were associated with greater 3-year change in carotid intima-media thickness (ΔR^2=0.026, P=.002) even when controlling for demographic factors, cardiovascular risk factors (blood pressure, BMI, total cholesterol, high-density lipoprotein cholesterol, triglycerides, low density lipoprotein cholesterol, fasting glucose, fasting insulin), medication use, medical conditions, and other correlated negative emotions. Additionally, mild to moderate depressive symptoms, as assessed by the BDI II, were associated with greater 3 year change in carotid IMT. Anxiety symptoms, hostility, anger experience and anger expression were each unrelated to IMT changes. Post hoc analyses showed that the somatic-vegetative symptoms (primarily included items

assessing the physical symptoms (i.e. anhedonia, fatigue, and sleep/appetite disturbance) of depression (ΔR^2=0.027, P=.002) were positively associated with intima-media thickness change, while the cognitive-affective symptoms of depression were not. Limitations to this study included asking participants to rate their symptoms on the BDI II during the past week instead of the past 2 weeks (recommended time frame for the BDI II) which may have underestimated the severity of depressive symptoms reported. In addition, the age range of the sample was older which limits generalizability. Despite the older population in this study, these findings evoke further questions regarding the relationship between depression and subclinical cardiovascular disease in women with PCOS.

3.9 DEPRESSION AND CLINICAL CARDIOVASCULAR DISEASE

Other large studies (137, 138) have examined depressive symptoms and their association with heart disease and cardiac symptoms in women. Ferketich et al. (2000)(137) studied depressive symptoms as an antecedent to heart disease among women and men in the National Health and Nutrition Examination Survey (NHANES I) Study (139). From the initial National Health and Nutrition Examination Follow-up Survey (NHEFS)(140) 5006 women were studied who were free of coronary heart disease (CHD). Participants were evaluated from 1982 until 1992 or until an occurrence of a CHD event. Subjects were given the Center for Epidemiologic Studies Depression Scale (CES- D). CHD incidence and CHD mortality were the outcome variables. The mean age for women was 53.7 ± 13.9 and 55.9 ± 14.4 for men. The mean scores for the CES-D were 8.79 ± 8.60 and 6.77 ± 7.13 for women and men, respectively. The cut point for defining clinically significant depressive symptoms on the CES-D was 16, classifying 17.5%

of women and 9.7% of men as depressed. Depressed women had a higher BMI than women who were not depressed. Women experienced 187 nonfatal and 137 fatal events, compared with 187 nonfatal and 129 fatal events among the men. The adjusted RR of CHD incidence among depressed women was 1.73 (95% confidence interval (CI: 1.11-2.68) compared with nondepressed women. One important limitation of this study is that it was not prospective. Because this was a prevalence study, it is difficult to discern if clinically significant depressive symptoms preceded the increased CHD risk or if the CHD risk preceded increased depressive symptoms.

In another large multi-site study by Ruttledge et al. (2007)(138), Women's Ischemia Syndrome Evaluation (WISE), sponsored by the National Heart, Lung, and Blood Institute (NHLBI), 750 women with a mean age of 53.4, were studied to determine the association between depressive symptoms and cardiac symptoms, mortality and hospitalization. Five-hundred and five subjects completed the BDI at baseline. Approximately 18% of the women reported depression scores consistent with the presence of at least moderate depression at the time of baseline assessment. Depression symptom severity was linked to an increased mortality risk over follow-up. (RR = 1.05; 95% CI, 1.01-1.09). Limitations of this study include not obtaining past depression history and severity, treatment or response to treatment. Like the NHANES I study, the sample population of the WISE study enrolled women who were older women than those typically seen in the PCOS population. However, these studies highlight the need to consider the effect of depression and depressive symptoms on the cardiovascular status of women at all ages with PCOS.

In all, there is empirical evidence for depression as a risk factor for cardiovascular disease. In Coronary Artery Disease (CAD), numerous cross-sectional studies have documented

a high prevalence of depressive symptoms in patients. Depression confers a relative risk (RR of 1.5-2.0) for the onset of CAD in healthy individuals (141). In a review article by Rugulies (142) in 2002 cohort studies on depression and Coronary Heart Disease were searched from 1997-2000 to review and quantify the impact of depression on the development of CHD initially healthy subjects. The overall RR for the development of CHD in depressed subjects (of the 11 studies evaluated) was 1.64 (95% confidence interval (CI) =1.29-2.08, P< 0.001). The recently published results from a large study, Women's Health Initiative (WHI) Observation Study (143), followed 93,676 postmenopausal women for an average of 4.1 years. None of the subjects had cardiovascular disease. When adjusting for other cardiac risk factors, results indicated that depression was an independent risk factor for developing and dying from CVD. These findings give support to further investigate the effects of depression not only on cardiovascular disease in PCOS, but the silent precursor to CHD and CAD, subclinical cardiovascular disease.

3.10 ANXIETY AND CARDIOVASCULAR DISEASE

A meta-analysis of articles concerning anxiety and the pathogenesis leading to heart disease published between 1980 and 1998 concluded that anxiety plays a role in the onset of coronary heart disease (144). Further, in this analysis, when investigating negative emotions and coronary heart disease, anxiety was the strongest predictor in comparison to anger and depression. Yet, in other studies (145, 146) there was a lack of association or correlation between anxiety and sub-clinical heart disease, which suggests that future research examine the role of anxiety and the temporal nature of its onset in predicting cardiovascular disease and associated mortality.

Although the relationship between anxiety and cardiovascular disease has been less frequently studied when compared to depression, there is evidence that anxiety has been associated with increased mortality in cardiac patients (147, 148).. In one study looking at carotid atherosclerosis in postmenopausal women, (145) anxiety along with other psychological variables were evaluated for the prospective association with carotid atherosclerosis. A total of 200 women underwent carotid ultrasound, intima media thickness (IMT), an indirect measurement for coronary risk. Using the Spielberger Trait Anxiety Scale, anxiety scores were not associated with subsequent IMT in univariate and multivariate analyses. The absence of a significant association between anxiety and IMT was due to the possibility that anxiety triggers clinical events (such as myocardial infarction) as opposed to contributing to atherosclerosis itself (145). On the other hand, phobic anxiety, defined as anxiety symptoms related to agoraphobia and simple phobias, (149) has been associated with ventricular arrhythmias in patients with coronary heart disease. Although only 20% of the total sample (940) was female, women reported higher phobic anxiety than men and the correlation with female gender was $r = .024$, $p < .0001$). To date, research findings are not precise in determining whether anxiety is a predictor of cardiovascular disease as the relationship with other psychosocial variables is complex. Moreover, in the past anxiety has been shown to predict depression in both men and women with heart disease (150) and may be an early prelude to sub-clinical cardiovascular disease.

3.11 ANGER, HOSTILITY, AND CARDIOVASCULAR DISEASE

Anger and hostility are psychosocial traits that have often been studied simultaneously. Their relationship to cardiovascular disease has been studied predominately in men and both traits may be predictive of coronary artery disease in younger men(151). In one of the earliest studies, the Framingham Heart Study (152) conducted between 1965 and 1967, psychosocial measures were administered to 1674 healthy men and women to investigate the development of coronary heart disease (CHD). Women between the ages of 45-64 who developed CHD scored significantly higher on the Framingham Type A behavior, suppressed hostility (holding in anger) than women who were free of CHD. In a multivariate analysis, Framingham Type A behavior and not discussing anger were independent predictors of CHD incidence when controlling for the standard coronary risk factors. This study suggested that Type A behavior and suppressed hostility may be associated in the pathogenesis of CHD in women.

In another study, The Women's Ischemia Syndrome Evaluation Study (WISE)(153) the relationship between anger and hostility to angiographic coronary artery (CAD) was investigated. Women (636) with suspected CAD were assessed for hostility/anger by the Cook-Medley Hostility Inventory and the Speilberger Anger Expression Scale. Anger and hostility were higher in the women who reported increased cardiovascular symptoms. Logistic regression revealed that anger-out (aggressive behavior in response to angry feelings) was associated independently with the absence or presence of angiographic CAD (OR =1.09, CI 1.01-1.17). Further, the women who did not have angiographic CAD (women without cardiac symptoms) had the highest anger-out, anger expression, hostile affect, and aggressive responding scores. This study concluded that the relationship between the psychological factors, cardiac symptoms, and angiographic CAD are potentially important in providing care to those with suspected CAD.

Studies have also investigated the association between hostility and carotid atherosclerosis measured by ultrasound(154, 155). In the study by Matthews and colleagues (154) 200 healthy middle-aged postmenopausal women were studied to determine the prospective association between measures of trait anger, hostility and anxiety. Women with high Trait Anger and Anger-In had high IMT on average 10 years later. The women with high Cook-Medley scores reflective of hostility/cynicism had high IMT scores on an average of 1.5 years later. Multivariate analyses that adjusted for standard cardiovascular risk factors (that are highly recognized as predictors of IMT) indicated that holding anger in, being self-aware and having hostile attitudes were significant predictors of IMT.

A similar study in 2006 (156) investigated the relationship between several positive and negative attributes (i.e. hostility and anger) and the risk for coronary and aortic calcification in healthy women. Hostility was measured by the Cook-Medley Hostility Scale and anger was measured by the Anger-In Scale. From the multivariate binary logistic regression analyses indicated that negative attributes were related to extent of aortic calcification. For hostility the OR was 1.77 (95% CI, 1.15-2.74 ; $p<.01$) and for the Spielberger Anger-In: OR=1.49; (95% CI, 0.98-2.26; $p<.06$). These findings concluded that women's overall psychosocial attributes were not related to coronary calcification, thereby suggesting that psychosocial attributes might be less important for early than late stages of coronary atherosclerosis. This study was cross sectional which may have also affected the results.

Lastly, numerous epidemiological studies have identified that there are psychosocial risk factors for CAD (153-155) , and that hostility/cynicism is one of the most consistent predictors of CAD (157).

3.12 RELATED AREAS OF DEPRESSION RELEVANT TO PCOS

In 2006, Himelein and Thatcher (158) reviewed 2100 PubMed citations on PCOS and Mental Health and reported that only 3% addressed psychological concerns. Research studies on depression in women with PCOS have been varied; they've included the study of risk and prevalence of depressive disorders (86, 124), investigation of depression secondary to the clinical features(84, 85), and chronicity of PCOS(59) as it relates to quality of life (159, 160).

3.13 DEPRESSION AND CHRONIC ILLNESS

Depression continues to be studied to determine if it is a predictor of chronic illness or whether it is a result of the chronicity of an illness. PCOS has been classified as a chronic illness, based on it's diagnosis at an early age and the fact that there is no cure. The Center for Disease Control (CDC) had addressed the link between chronic disease and depression (161) as well as others worldwide. Results from the World Health Surveys (2007) (162) addressed the important public-health problem of depression and chronic diseases. The World Health Survey (WHS) studied adults aged 18 years and older to obtain data for health, health-related outcomes and their determinants. Prevalence of depression based on ICD-10 criteria was estimated. Four chronic physical states were identified for the study and included: angina, arthritis, asthma, and diabetes. Observations on 245,404 participants from 60 countries in all regions of the world were reported. The 1 year prevalence for ICD-10 depressive episode alone was 3.2% (95%, CI, 3.0-3.5); for angina 4.5% (CI, 4.3-4.8); for arthritis 4.1% (CI, 3.8-4.3); for asthma 3.3% (CI, 2.9-3.6); and for diabetes 2.0% (CI,1.8-2.2).

There was an average between 9.3% and 23% of all participants with one or more chronic physical disease and comorbid depression. This result was found to be significantly higher than the likelihood of having depression in the absence of a chronic physical disease ($p<.0001$). When adjusting for socioeconomic factors and health conditions, depression had the greatest effect on worsening chronic health problems. The comorbid state of depression incrementally worsens health compared with depression alone, with any of the chronic diseases alone, and with any combination of chronic diseases without depression. Another finding that was consistent across countries and varied demographic characteristics was that respondents with depression comorbid with one or more chronic diseases had the worst health scores of all the disease states.

Depression has been linked prospectively to various chronic diseases such as known comorbidities of PCOS, cardiovascular disease, diabetes, and obesity. The relationship between subclinical depression and cardiovascular disease was reported by the Women's Health Initiative (143). The study found that depression increases cardiovascular disease independent of risk factors such as smoking or obesity. Other studies have reported that patients with depression have a 2-4 fold increased risk of developing cardiovascular disease (127, 129, 163-165). . Early on, studies have reported that persons who are depressed are much more likely to develop coronary heart disease (166). Meta analyses have revealed that the relative risk for developing heart disease in individuals with depression or depressive symptoms is approximately 1.6 times greater than among non-depressed persons (142, 167).. Further, Ruguilies (2002)(142) found a stronger effect for clinical depression on cardiovascular disease suggesting that the presence of a dose-response relationship. Kindler and colleagues(168) reported that depression has been positively associated with the metabolic syndrome among women younger than 40 years of age.

Diabetes is one of the many chronic diseases that appear to be adversely affected by comorbid depression (169). Studies have shown that patients with diabetes are 1.5 -2 times more likely to have depression compared with individuals who do not (170-173).. In a study by Brown et al.(169) a population- based nested case-control study was done to explore the history of previous depression in people with incident diabetes compared to people without diabetes. Cases of type 2 diabetes based on diagnostic codes and prescription records for individuals were identified. Each case had 2 matched controls (matched on age, sex, and frequency of physician visits) randomly selected from the non-diabetic population during the same index year. Results of the study revealed that individuals with newly diagnosed diabetes (1,622 of 33,257; 4%) were 30% more likely to have had a previous history of depression compared with people without diabetes (2,279 of 59,420; 3.8%). This increased risk did not change after controlling for sex and number of physician visits but was limited to subjects 20-50 years of age (adjusted OR=1.23; 95% CI; 1.10-1.37) and not in those aged ≥ 51 years. In another recent study (a large multiethnic study of White, Black, Hispanic and Chinese men and women aged 45-84), Golden et al.(2007)(174), also noted that depression was associated with a greater odds of treated diabetes (OR= 1.57; 95% CI, 1.27-1.96).

Lastly, obesity is considered a chronic illness itself, but may also be comorbid with many other diseases, such as PCOS. Recently, in 2007 researchers (175) reported that higher BMI's are associated with depression which supports previous findings stating that the severely obese individuals may by more at risk for developing psychological problems (176, 177). It has been reported that there may be a common pathophysiology that exits between obesity and depression (178) and researchers have studied neurotransmitters, serotonin and norepinephrine, which are often altered in depression. Moreover, the relationship between obesity and depression appears

to be reciprocal (175). This relationship can be devastating for PCOS patients as the dose effect (cumulative increase of symptoms over time) of either obesity or depression over the years could lead to clinical mental health disorders and affect one's quality of life.

3.14 PSYCHOLOGICAL OUTCOMES WITH PCOS: QUALITY OF LIFE

In line with investigating the relationship of depression with PCOS in women or other mental health problems, is the concern for one's quality of life with PCOS. Health related quality of life often encompasses a compilation of measurable constructs such as psychological or emotional functioning and physical, social and sexual satisfaction amongst others. In a review article, Jones et al. (131) stated that gynecological conditions like PCOS were major causes of psychological dysfunction that can lead to a decrease in quality of life.

Griffin-McCook (179) in 2005 studied health-related quality of life issues in women with PCOS in a cross-sectional correlational study of 128 women with PCOS. The Health-Related Quality of Life Questionnaire for women with PCOS (PCOSQ) was used in this study (180). The PCOSQ is the first instrument designed to measure specific PCOS-related psychological dysfunction. This instrument identifies emotional, physical, and social problems that women with PCOS experienced as a result of having this condition and asks respondents to rate how the severity of the symptoms affects their daily lives (179) . Validity reliability ratings are not reported, however the scales' authors assert that there is construct and content validity.

A convenience sample of 128 women from private reproductive practices in two southeast United States cities was obtained. One half of the sample was attempting to conceive in addition to being treated for PCOS. Most were white (97%), and married (78%), with a mean

age of (30.4 ± 5.5 years). PCOS was determined by the Rotterdam Criteria (20), as previously defined on page 6. They examined clinical measures such as BMI, waist-to-hip ratio and degree of hirsutism. The main outcome measure was quality of life measured by the (PCOSQ). Result indicated that the most common health-related quality of life concern was weight, followed by menstrual problems, infertility, emotions, and body hair. BMI was significantly and negatively correlated with the weight subscale of the PCOSQ ($r = -.33$, $p = .001$). Limitations of this study include the absence of a control group and possible sample bias (i.e., the sample was a convenience sample, primarily comprised of Caucasian women, and biased geographically, representing 2 small cities in Appalachia). It does, however, point to the need for assessment of the quality of life and evaluation of the comprehensive biological insults on the PCOS population, which can also lead to disturbances in mental/emotional functioning.

One international study by Hahn et al. in 2005 (181) studied the extent of different PCOS symptoms on quality of life, psychosocial well-being and sexual satisfaction. Metabolic, hormonal, clinical and psychosocial data were examined in 120 women with PCOS and were compared to 50 healthy women in order to quantify quality-of-life and emotional well-being. Patients were recruited from the Department of Medicine outpatient clinics at the University of Duisburg-Essen, Germany. Diagnosis of PCOS was made by the 1990 NIH conference criteria(20). Patients were compared to 50 healthy women recruited through a health screening program at the University of Duisburg-Essen, Germany and to normative data. Psychosocial variables and major clinical PCOS features, such as obesity (body mass index (BMI)), excessive hair (hirsutism), and others were analyzed. Quality-of- life was assessed with the German version of the SF-36 (182).. The SF-36 contains a total of 8 subscales, 3 of which are pertinent scales to PCOS; these are: Physical Function, Emotional Role Function, and Mental Health.

Results indicated that PCOS subjects showed significant reductions in quality-of-life, increased psychological disturbances and decreased sexual satisfaction when compared to healthy controls. Apart from other features of PCOS, only BMI and hirsutism scores showed significant reductions in quality-of-life, increased psychological disturbances, and decreased sexual satisfaction when compared with healthy controls. PCOS patients reported significantly lower quality-of-life as measured by the SF-36 Health Survey in all dimensions except General Health when compared to normative data. Severity of depressive symptoms was significant at $p<0.001$ as measured by the SCL-90-R scale when compared to normative data. This study, however, did not reveal the demographics of the sample except for their mean age. Therefore, caution must be considered in interpreting the results.

In another prospective intervention study by Hahn et al.(183) (2006), the effects of metformin treatment on health related quality of life (HRQL), emotional distress and sexuality of women with PCOS was investigated. Metformin improves biochemical, clinical and reproductive functions in women with PCOS. In this prospective, observational study, they assessed the PCOS patient's before, during, and 6 months after of treatment with Metformin. A convenience sample of 85 patients was recruited from outpatient clinics in the Division of Endocrinology at the University of Duisburg-Essen and 64 patients with PCOS participated in the study. The diagnosis of PCOS was made using the 1990 NIH conference criteria. HRLQ was measured by the German version of the SF-36 (182). The Symptom Check List-90-Revised (SCL-90-R)(184) was used to determine psychological symptoms. Subject results were compared with published German normative data. Prior to treatment, patients with PCOS demonstrated significantly higher SCL-90-R scale scores, indicating greater psychological disturbances in dimensions such as depression and aggression when compared to the German

normative data. During treatment with Metformin, the psychosocial aspects of health related quality of life, (i.e. Emotional Role Function, Mental Health, and the Psychological Sum scale from the SF-36 and the emotional well-being scale from the SCL-90-R) improved. Limitations to this study included small sample size and the lack of a randomized placebo-controlled clinical trial.

In a case control study by Elsenbruch, et al. (2003)(185) quality of life, psychosocial well-being, and sexual satisfaction in women with PCOS was also studied. This study used recruitment strategies and determination of diagnostic criteria for PCOS similar to the previously described study by Hahn et al. 2005 (181), with the exception that the controls were matched on age. Fifty women and their controls were evaluated with standardized questionnaires (36-Item Short-Form Health Survey (SF-36), Symptom Checklist Revised (SCL-90-R), and Life Satisfaction Questionnaire (186). The features of PCOS, hirsutism, obesity, and infertility were assessed. Patients showed increased psychological disturbances on the symptom checklist revised dimensions in areas such as depression, anxiety, interpersonal sensitivity and aggression. Patients with PCOS patients also had a lower level of life satisfaction on the life satisfaction questionnaire scales which were related to health, self, and sex. Even though this study has its limitations in reference to generalizability due to selection bias, it has its merits in attempting to address the comprehensive aspects of one's quality of life, inclusive of sexual satisfaction.

Elsenbruch et al.(187) in 2006 further investigated the determinants of emotional distress in women with PCOS. The goals of this study were to investigate the incidence of mental distress in women with untreated PCOS (had no medical treatment) using self-report measures, to identify PCOS cases who were at risk for psychiatric disorder and to assess the impact of emotional distress on quality of life in affected patients. A sample of 143 women with untreated

PCOS were administered the SCL-90-R and the SF-36. The SCL-90-R (184) is used to assess mental well-being. It assesses symptomatology in 9 areas (Somatization, Obsessive Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Aggression, Phobia, Paranoid Ideation, and Psychoticism). The global severity index (GSI) represents the overall level of distress.(184) GSI t scores ≥ 63 identify cases with possible mental disorder (SCL cases). Psychological disorder was based on the SCL-90-R. Twenty-two patients (15.4%) had a possible psychological disorder with a global severity index of ≥ 63 (SCL cases). Cases also had significantly elevated body mass index (BMI). These findings support the hypothesis that subclinical levels of psychological disturbances may exist in patients with PCOS which often affects their quality of life. Limitations of this study included lack of a control group, self-report questionnaires, and the lack of diagnostic measurements to identify a psychiatric diagnosis.

Quality of life and its relationship to Body Mass Index (BMI) has been an interest in PCOS as rapid weight gain is a common occurrence and a clinical manifestation of PCOS. A cross-sectional study by Ching et al. in 2007(160) studied Australian women with PCOS. A sample of 203 women between the ages of 15-65 were compared to the Australian population norms (women aged 18-44; (n= 173). Subjects were ascertained through mailings of questionnaires. Of these women, 64% were obese, 18% were overweight, and 18% were normal weight. Diagnosis of PCOS was confirmed by an endocrinologist at a private practice or at a Diabetes Clinic. Diagnostic criteria were used from the NIH standards.(19). Three standardized measures were used to assess quality of life. The Short Form SF-36 (184), the General Health Questionnaire-28 (GHQ28)(188), and the Questionnaire for Women with Polycystic Ovary Syndrome (PCOSQ) (180). The GHQ-28 is a measure of function or disturbance, comprising a global score and four scales for somatic symptoms, anxiety, insomnia, social dysfunction and

severe depression. The GHQ-28 identified psychological morbidity in 62.4%, compared to 26.4% for the matched Australian population ($p<0.001$). BMI was negatively correlated with quality of life ($p<0.01$).

BMI and its relationship to quality of life in PCOS patients is controversial and somewhat inconclusive. Trent (189) reported that when adjusting for BMI, no difference in quality of life was found between adolescent PCOS subjects and healthy controls . Most importantly, however, it is clear that BMI is not the sole reason for determining quality of life in this population.(160) The research by Ching et al. (160), though, lacks a true representation of quality of life as it was cross-sectional. On the other hand, it uses the most currently validated and reliable measures for assessing quality of life in the PCOS population.

Another recent study, (2007) by Barnard et al.(159) addressed the quality of life and psychological well being in PCOS. Aims of this study included determining the quality of life in PCOS women to determine an estimate of the prevalence of depression in a large community sample of women with PCOS. Four groups of women were recruited: 192-224 with PCOS not taking anti-androgen medication (AA), 177-200 women with PCOS taking AA medication, 504-548 healthy women not taking AAs , and 356-387 healthy women taking AAs. The subjects were contacted through the internet by e-mail. The Rotterdam diagnostic criteria (20) was utilized to determine PCOS women. The study also required them to confirm diagnosis. The Polycystic ovary syndrome health-related quality of life questionnaire (PCOSQ)(180) and the Zung depression scale(190) were used to measure quality of life and depression respectively. Of the PCOS women, 71% (taking AA medication) and 67% (not taking AA medication) were classified as depressed. Women with PCOS had lower quality of life on all seven factors of the modified PCOSQ. The PCOSQ was modified adding an additional factor, acne. The 7 factors

were emotional disturbance, weight, infertility, acne, menstrual symptoms, menstrual predictability and hirsutism. Weight was the greatest contributor to decreased quality of life for PCOS women taking or not taking AA medication. Both PCOS groups were significantly more depressed than the control groups (all P-values <0.001). However, there were no significant differences between the 2 PCOS groups and the 2 control groups. There was a significant association between the diagnosis of PCOS and severity of depression P < .001 with more cases of mild, moderate and extreme depression in the 2 PCOS groups. Limitations of this study are the internet samples (selection-bias) and use of self-report measures.

Quality of life in PCOS has been researched not only in those affected, but also in family members. A local study done in Pittsburgh by Malek, (191) in 2006, studied the quality of life and mental health status among family members with PCOS. The aim of the study was to determine whether elevated BMI was associated with quality of life of family members with and without PCOS. Additionally, she investigated whether mental health scores differ among female with PCOS and family members. One hundred and one subjects, 20 PCOS cases, 52 non-PCOS cases and 29 males participated. Quality of life was determined by the SF-36.(184) Quality of life as determined by the SF-36 found that PCOS females did not differ significantly when compared to non-PCOS family members on the total scores of most domains. Self- reported depression was rated as higher in PCOS females, although it was not a statistically significant difference. BMI was a significant predictor for most domain scores among females with and without PCOS. Limitations of this study included small sample size and under representation of the general population as the majority of the sample were white. **Table 3-3** summarizes the relevant PCOS studies on quality of life and depression.

Table 3-3 PCOS Studies and Quality of Life and Measurement of Depression

Study	Year	N	Design	QUA	PSYCH	Comments
Elsenbruch et al. (185) German	2003	50 PCOS cases & controls	Case Control	PCOS causes major Reduction in QOL	PCOS pts showed ↑ depression	Used SCL-90-R; SF-36
Griffin et al. (179) U.S.	2005	128 PCOS women; Convenience sample	Cross-sectional; Correla-tional	Most QOL concerns: obesity; menstrual problems; infertility; emotions; body hair		Used PCOSQ
Hahn et al.(181) German	2005	120 PCOS cases and 50 controls	Case Control	BMI and hirsutism affected physical aspects of QOL & sexual functioning		Used SCL-90-R; SF-36
Elsenbruch et al. (187) German	2006	143 untreated PCOS patients compared to normative data	Cross-sectional compared to normative prevalence		15.4% had a possible Psychological disorder	Used SCL-90-R; SF-36
Hahn et al.(183) German	2006	64 PCOS patients treated with Metformin	Prospec-tive Observa-tional	Metformin appeared to significantly improve psychosocial domains of SF-36		Used SCL-90-R; SF-36
Ching et al. (160) Australia	2007	443 PCOS women compared to population norms	Cross-sectional	GHQ identified psycholog-ical morbidity in 62.4% of PCOS women compared to 26.4% matched norms		Used SF-36 PCOSQ, GHQ-28, PIQ
Malek (191) US	2006	20 PCOS Cases 52 Non-PCOS cases + 29 males in family	Cross-Sectional	BMI was a significant predictor for a majority of the SF-36 domains in PCOS females and non-PCOS females. Highest was in physical Functioning p< 0.001	Self report depression was higher in PCOS adults compared to non PCOS adults although not statistically significant	Used SF-36
Barnard et al. (159) London	2007	4 Groups of women Large community sample: approx 400 PCOS compared to approx 800+ controls	Cross-sectional Internet	PCOS women had lower qol on all seven factors Wt most affected QOA	Both PCOS group more depressed than controls P<.001	Self-report PCOSQ Zung Depression Scale

SF-36 used in study *
PCOSQ = Polycystic Ovary Syndrome health related Questionnaire
QUA = Quality of Life

As can be seen, the literature is limited in investigating psychological implications of PCOS. To date, the studies investigating the impact of PCOS primarily on mental health i.e. (depression) are limited as there are 1 case report, 1 qualitative study, 1 descriptive study and only 3 case-control studies that have been reported. Likewise, there are only 8 relevant studies that have measured quality of life in women with PCOS which began in 2003 until present. Until more recently, the focus of this incurable syndrome has been on the biophysiological ramifications of PCOS. An explanation for this lack of psychological research on PCOS may be in part because the syndrome is extremely complex in its presentation, inclusive of body image disturbances, i.e.hirsutism and obesity, infertility, insulin resistance, and hyperandrogenism (85).

From the available literature it would appear that there are few large well characterized case control studies of women with PCOS and controls on whom data was collected prospectively on both cardiovascular risk factors and psychological characteristics. The present study will seek to determine if women with PCOS compared to controls exhibit increased psychological sequela and cardiovascular risk factors in addition to a reduction in life satisfaction related to the syndrome. Moreover, the present design will permit an investigation of whether the psychological characteristics have an independent effect on the prevalence of subclinical atherosclerosis in PCOS cases compared to controls.

4.0 ASSOCIATIONS AMONG DEPRESSIVE SYMPTOMS, ANXIETY, ANGER, HOSTILITY, AND SATISFACTION WITH LIFE IN WOMEN WITH POLYCYSTIC OVARY DISEASE (PCOS)

Background: Polycystic Ovary Syndrome (PCOS) is associated with many physical and physiological changes and can affect women's psychological functioning and satisfaction with life. Previous research has focused mainly on cardiovascular risk factors, with few studies investigating the psychological effects of the condition. The aims of this study were: (1.) to compare the prevalence of depressive symptoms in women with PCOS compared to controls; (2.) to determine whether depression and psychological traits (anger, anxiety, hostility/cynicism) and satisfaction with life are associated with PCOS; (3.) to examine within PCOS cases factors associated with depressive symptoms: specifically BMI, education, marital and smoking status, and parity

Design: The subjects examined in this study were selected from those in a previous case-control study, with observational follow-up over a 12 year period, 1995 to 2006.

Methods: A total of 161 cases and controls were matched on age, race, and neighborhood and participated in the baseline psychological assessment arm of our original study. They were part of the original Cardiovascular Health and Risk Measurement study (CHARM) study by Talbott et al. conducted in 1992-4 to investigate coronary heart disease risk factors in women with PCOS. Psychological characteristics of the women were assessed using

the Beck Depression Inventory I (BDI I), the Speilberger Trait Anger and Anxiety Scales, the Cook-Medley Scale and the Diener Satisfaction with Life Scale.

Results: Women with PCOS had a higher prevalence of depression (BDI scores>9; at predominately a mild level of depression): 31% vs. 17% in controls; P=.016: OR 1.9 (CI 1.55-2.16). The difference between cases and controls for the BDI scale was statistically significant P=.002. Within cases, results of logistic regression analysis showed that BMI, education, and parity were statistically significant predictors of depression p<.05. The odds of being depressed of at least mild severity increased by 6% for each unit increase of BMI, the odds of being depressed decreased by 20% for each year of education and increased by 44% for parity (*per live birth*). When conditional logistic regression (for the entire sample) was performed, the odds of having PCOS increased with each unit of BDI score by 1.06 times, adjusting for marital status, BMI, smoking, and education.

Conclusions: Depression is a major psychological concern in PCOS. Women should be screened at regular intervals to detect and treat depression as a risk factor.

Public Health Significance: The public health implications of this study center around primary and secondary prevention. With secondary prevention, case finding is paramount as women are known to have 2 times the prevalence of depression than men even before being diagnosed with PCOS. Finally, implementing a high-risk prevention approach would be a strategy to decrease the prevalence of depression in the PCOS population.

4.1 INTRODUCTION

Polycystic ovary syndrome is the most common reproductive endocrine condition among women. Estimates in the US reflect a prevalence of 6-10% and in England, the addition of ultrasound to the criteria for evidence of polycystic ovaries results in a prevalence rate that is higher (1). PCOS manifests at puberty and is a lifelong condition (2-5). It is characterized by chronic anovulation, obesity, and clinical hyperandrogenism. Other manifestations include infertility, male-pattern balding, ovarian enlargement, and signs of insulin resistance, ie. central obesity (5-8). As this is a lifetime disorder, other medical problems may surface such as cardiovascular disease and Type 2 Diabetes (1, 4, 5, 9). To date, there is no known cure for PCOS. The goal of treatment is to reduce the symptoms and risk factors for complications and comorbid conditions.

Until recently, research and clinical management for PCOS women have been primarily focused on the physiological consequences. However, as a result of the numerous physical and metabolic changes, PCOS women may be at high risk for psychological problems, such as depression and decreased satisfaction with life (10, 11). Previous studies have lacked sufficient sample sizes, case-control studies, and a complete psychological profile of what mental health issues and or personality traits are associated with women with PCOS.

In general, women are twice as prone to depressive symptoms and disorders when compared with men (12) and several studies have reported the total lifetime prevalence of major depression in women to be approximately 21% (12-14). Furthermore, research examining the psychological effects of PCOS has been largely lacking.

Previous psychological research in women with PCOS has been conducted utilizing small sample sizes and case reports (15-17). One study (17) reported that depressive symptoms, as measured by the Center for Epidemiological Studies Depression Rating Scale (CES-D) (18), was associated with greater insulin resistance ($p< 0.02$) and with a higher body mass index ($p<0.05$) in a sample of 32 PCOS women. However, there was no control group.

In a recent cross-sectional study of women 18 – 50 years of age, Hollinrake et al. (19) studied PCOS women and controls to estimate the prevalence of depressive disorders in women with PCOS. Androgens and other metabolic markers associated with PCOS and depression were also studied. DSM IV (20) diagnostic criteria were used. Depression was determined based on Primary Care Evaluations of Mental Disorders Patient Health Questionnaire (Prime-MD PHQ) (21) and the Beck Depression Inventory (BDI) (22). Women with PCOS were at an increased risk of depression (new cases) compared with controls (21% versus 3%, OR 5.11; (95% CI: 1.26-20.69, $p<.03$)). The overall risk of depressive disorders in this sample of PCOS women compared to controls was OR; 4.23 (95% CI 1.49-11.98; $p<.01$), independent of obesity and infertility. When compared with the non-depressed PCOS subjects, the depressed PCOS subjects had a higher body mass index (BMI) and evidence of insulin resistance ($p<.02$).

Body image was also the focus of psychological research in women with PCOS (23). Several studies have supported the existence of increased emotional problems concurrent with the physical changes seen in PCOS. Himelein and Thatcher (23) reported that in comparing PCOS women to non-PCOS women with infertility, and to women with neither PCOS nor infertility, that PCOS women had higher depression scores and body dissatisfaction ($p<.001$). Further, body image was strongly associated with depression overall, even after controlling for body mass index. The affective self-evaluation measures proved more important in the

prediction of depression than other measures of body image. Some longitudinal studies have demonstrated that poor body image in adolescent females is related to later onset of depression (24, 25). Although the association is controversial and inconsistent, obesity in PCOS women has been linked to depression (26). It is generally accepted that up to two thirds of PCOS women are overweight or obese, that three fourths have significant hirsutism (3, 4), and that obesity has been associated with depression in women in the general population (27).

A longitudinal study by Hollinrake et al.(19) further investigated the risk of depression and other mental health disorders in women with PCOS (28). A total of 60 women from the original sample of 103 were resurveyed within a two year period (mean time was 22 months). There were 11 new cases identified in the second survey (19%). Thirty-four of the 60 subjects (56.6%) had mood disorders which also included those with anxiety disorders. Among these depressed subjects, 11.6% also had an anxiety disorder while 23.3% had binge-eating disorders.

Other psychological ramifications of PCOS are found in the research on quality of life (QOL). Barnard et al. (29) found that women with PCOS had lower QOL on all seven factors of the modified Polycystic Ovary Syndrome Health-related QOL Questionnaire (PCOSQ) (30) (i.e. emotional disturbance, weight, infertility, acne, menstrual symptoms, menstrual predictability, and hirsutism). Others have also investigated the quality of life in PCOS women and their families (31). Using the SF-36 to measure quality of life, there was no statistically significant difference in PCOS females compared to family members, which may have been reflective of the small sample size (20 PCOS cases) compared to 81 family members.

Acne, hirsutism, and obesity are among the most frequent changes in physical appearance among PCOS women. The major medical changes that frequently occur with PCOS are cardiovascular disease, metabolic cardiovascular disease (MCS), Diabetes Type 2, and insulin

resistance. As women attempt to cope and adapt to PCOS, depression may develop. Anxiety and anger have been studied among these women (28, 29, 32). In a study examining androgens and mood dysfunction (32), the state trait anxiety inventory (33) and the state-trait anger expression inventory (34) did not demonstrate a group difference or the difference became non-significant when other mood and symptoms were covaried in the MANCOVA. The authors (32) suggested that the mood states were related to general negative affectivity (measured by a visual analog scale (35) and physical symptomatology).

In a recent Qol study (29), using the Zung anxiety scale (36), both PCOS groups who were on anti-androgens and those without anti-androgens reported almost a threefold higher score in anxiety as compared to their controls. Similarly, findings from a longitudinal study in 2008 (28) indicated that 11.6% of the 60 had an anxiety disorder. To date, hostility and cynicism have not been studied in persons with PCOS. Lastly, overall satisfaction with life in relationship to PCOS is often compromised (29, 31, 37).

In the present study, the overall goal is to: (1.) Determine the prevalence of clinically significant depressive symptoms in PCOS cases and controls using the BDI; (2.) To determine if depressive symptoms, psychological traits (anxiety, anger, hostility/cynicism), and satisfaction with life are associated with PCOS; and (3.) To investigate within cases, factors associated with depressive symptoms, controlling for BMI, education, marital and smoking status, and parity.

4.2 SUBJECTS AND METHODS

4.2.1 Case Recruitment

The study sample is comprised of a subset of the original " Cardiovascular Health and Risk Measurement" study (CHARM) investigation conducted by Talbott et al. (3). This study's main aim was to investigate coronary heart disease risk factors in women with PCOS. A total of 243 PCOS cases and controls were recruited for the primary study. Complete data on the psychological profile was available on 212 cases and 202 controls, but only 161 cases and 161 controls had complete psychological data for this analysis.

Subjects with PCOS were recruited from the Pittsburgh area through the reproductive endocrine department/private practices at Magee-Women's Hospital for the period 1970-1993. As a result, a presumptive clinical diagnosis of PCOS was made if there was a history of chronic anovulation in association with either clinical evidence of androgen access (hirsutism) and or biochemical diagnosis comprising of total testosterone concentration >2nmol/L or the LH/follicle-stimulating hormone (FSH) ratio was greater than 2.

The current group (academic practice group, 1970-93) was comprised of 243 women with PCOS. Details are published elsewhere (3).

4.2.2 Control Subject Recruitment

Controls were matched on race, age ± 5 years, and neighborhood. They were selected by using a combination of voters' registration tapes for 1992 for the greater Pittsburgh area and Cole's Cross Reference Directory of households (38). The major sources of control candidates

were the Allegheny County voters' registration tapes. A nonrepeating random selection process was used that matched on date of birth, sex, race, and zip code of the case subject. For each PCOS case subject, five control subjects were randomly drawn and contacted by mail. The letter explained the nature of the study and invited the individuals to participate. A preaddressed, stamped postcard was included. After 2 weeks, a follow-up letter was sent to the same address.

Those participants living in the greater Pittsburgh area were asked to participate in the clinical phase of the study located at Magee-Women's Hospital. Subjects were evaluated after a 12 hour fast. Another questionnaire was administered on site which included a repeat medical history, medication history, current medical practices, and family history of PCOS.

4.2.3 Psychological Measurement

The psychological characteristics of the women were assessed using the Beck Depression Inventory I (22), the Speilberger Trait Anger (34) and Anxiety Scales (33), the Cook-Medley Scale (39), and the Diener Satisfaction with Life Scale (40). A total of 243 PCOS cases and controls were recruited for the primary study. Data on the psychological profile was available on 212 cases and 202 controls, but only 161 cases and 161 controls had complete psychological data for this analysis.

4.2.4 Psychological Measures

Depression Assessment: The Beck Depression Inventory I (BDI I) (22) is a self-report inventory measuring symptoms of depression. It contains 21 questions; a cutoff of >9 (total score) was used to identify potential clinically significant symptoms of depression and to define

cases in these analyses (22). In this study, the BDI was used as a screening measure for depression. The psychometric properties of the BDI have been reported as high with internal consistency ranging from .73 to .92 with a mean of .86 (41). The split-half reliability coefficient reported was .93. Concurrent validity was determined by correlations with clinician ratings of depression using the revised BDI and ranged from .62 to .66 (42). The BDI was previously tested on the PCOS population in other research studies (10, 23).

Anxiety and Anger Assessments: The Spielberger Trait Anger/Anxiety Scales are two of six subscales of the State-Trait Personality Inventory by Spielberger (STPI) (33, 34). Both anger and anxiety scales are comprised of 10 items each. Responses are rated on a 4-point likert scale with response categories ranging from categories "almost never" to "almost always." The six STPI scales demonstrate good internal consistency as evidenced by alpha coefficients of .80 to .87 (43). Reliability testing revealed internal consistency (alpha coefficient = .81-.87) (33, 34) Cronbach alphas were .82-.85 and .80-.85 for anger and anxiety, respectively.

Hostility/Cynicism Assessment: This 13 item scale derived from the Cook-Medley Hostility Scale, measures cynical attitudes and hostile feelings and behaviors rather than overt expressions of anger and aggression. Each item is rated as "probably true" or "probably false." Higher scores indicate greater hostility (range 9-13). Cronbach's alpha for the scale was .79, indicating good internal consistency (39).

Diener Satisfaction With Life Scale: This scale was developed as a measure of the judgmental aspect of satisfaction with life. It measures the cognitive component of subjective well-being. The scale consists of 5 questions each rated on a 7 point likert scale ranging from "strongly disagree" to "strongly agree." A higher score reflects a greater satisfaction with life.

Test retest reliability was .84 (44). The scale is brief, yet it offers as high or higher predictive validity than several longer measures of life satisfaction.

4.2.4.1 Covariates

BMI was measured in kg/m^2. Education was measured by each year of education. Parity was measured by each live birth. Marital status was coded yes (married) and no (not married). Smoking status was also binary. Current smoking was yes and never or ever smoked was no.

4.3 STATISTICAL ANALYSES

All data collected for the original study were entered and verified by using SPSS data-entry software. All data were analyzed using SPSS FOR WINDOWS version 15.0 (SPSS Inc., Chicago, IL, USA).

Descriptive statistics, including measures of central tendency and dispersion, were computed for all variables of interest for PCOS cases and controls. Non-normally distributed continuous data were logarithmically transformed before performing statistical comparisons. Continuous variables of interest were compared using Student's t test or the Mann-Whitney U test. For categorical data, the χ^2 test or Fisher's exact test was used.

Group differences were assessed using paired and two-sample t-tests. Spearman correlation and logistic regression were used to determine predictors of depression within cases. Conditional logistic regression was also performed to determine the association between select variables, covariates, and PCOS status.

4.4 RESULTS

4.4.1 Sample characteristics

One hundred and sixty-one pairs formed the cohort studied. Pairs were matched on age, race, and neighborhood. The average age of the sample was 35.8 years at baseline (SD = 7.5 years). The sample was predominately white (94.7%) and 3.4% black with a large proportion married (65.2%), with most of the PCOS cases being married (72%). Education was similar between cases and controls with each group completing approximately 14 years of schooling. Fifty percent of the cases and controls were predominately professionals, while the other 50% were either laborers or homemakers in both groups, although the differences between groups were not statistically significant. The mean for parity was higher for the control group at 1.22 ± (SD 1.6) compared to the cases at .89 ± (SD 1.6) p< .01. (**Table 4-1**)

There was no significant difference between the proportion of cases and controls on oral contraceptives (P=.06) or hormone use. Of the cases, 15.5% were on hormones as well as 15.5% of the controls. Seventy percent of the cases and 82% of the controls were not on oral contraception. Only 4 categories of psychiatric medications were reported by the total sample as being prescribed at baseline: major tranquilizers, minor tranquilizers, sedatives, and antidepressants. One case was on an antidepressant and 2 controls were on a tranquilzer. Smoking history did not significantly differ between cases and controls. Cases reported 23% as current smokers and 47.8% for controls. BMI was statistically significant between cases and controls p<.01. The mean for cases was 30.3 ± 8.2 and 26.3 ± 6.3 for controls. (**Table 4-1**)

4.4.2 Prevalence of Depression

Cases scored higher than controls on the BDI, indicating significantly more severe depressive symptoms (mean of 7.8 ± SD 7.0) compared to the non-depressed cases (mean of 5.7 ± SD 5) even though they did not fall into the depressive range. (Table 2) The mean scores for both groups were not in the clinically significant range. The prevalence for clinically significant depressive symptoms (score of > 9) was 31.1% for cases and 17.4% for controls.

The prevalence of clinically significant mild depression was 24% for cases and 15% for controls. Clinically significant moderate depression was only 5% for cases and 2.5% for controls. Only cases exhibited any significant severe depression (3%). Within cases (between groups), 31% of the sample had a BDI score >9. As expected, the BDI score differed significantly between depressed and non-depressed groups with a mean of 15.7 ± SD 6.6 for depressed and a mean 3.9 ± SD 2.7 for non-depressed women. **(Table 4-2)**

4.4.3 Association of Depression and Psychological Traits (anger, anxiety, hostility/cynicism) and Satisfaction with Life

Cases scored higher on the trait anger scale with a mean of 9.1 ± SD 4.2 compared to controls (mean=8.2 ± SD 3.6, $p<.02$). For anxiety, the mean for cases was 9.6 ± SD 5.5 compared to controls (mean of 8.7 ± SD 5.2, $p<.01$). Cases scored lower (were less hostile/cynical) on the hostility/cynicism measure compared to controls with a mean score of 7.3 ± SD 2.9 and 7.9 ± SD 2.6, respectively ($p< .01$). Only satisfaction with life was not statistically significant between cases and controls. Cases also reported a lower mean score satisfaction with life compared to controls, 23.9 ± 6.8 and 24.2 ± 6.2 respectively. (**Table 4-2**)

Conditional logistic regression analysis on the matched-pair data set for psychological measures is illustrated below. (**Table 4-4**) Candidate variables that were considered for the multivariate model were BMI, marital status, parity, education, smoking status, occupation, and hormones. The candidate variables were assessed by univariate analysis using logistic regression. P values were obtained using likelihood ratio tests. After forward stepwise conditional logistic regression, the final model included BMI, marital status, and BDI I score as significant predictors. PCOS status was the dependent variable. The odds of having PCOS increased with each unit of BDI score by 1.12 times when marital status, BMI, smoking status, and education were included in the model. All of the psychological variables were significant in univariate models except for satisfaction with life. When adjusting for BMI, marital status, smoking, and education, anger and cynicism/hostility were significant. BMI remained significant ($p<.01$) in the models with anger and cynicism/hostility. In the model with cynicism/hostility, marital status also remained significant $p<.009$.

4.4.4 Comparison of Depressed and Non-depressed PCOS Cases

Demographics: The results of the demographics and health variables were similar to the total sample. Both groups were predominately white, 90% in the depressed group, 92.2% in the non-depressed group. Mean age was similar for both groups. Of the depressed group, 72% were married and less educated than the non-depressed group. More depressed women were identified in non-professional occupations (60%). PCOS cases in the depression group had higher BMI scores (mean 32.8, $P<.01$) than the non-depressed cases (28.9). Smoking history was higher in the depressed versus non depressed group, 58% and 45% respectively. Twenty-six percent of the

group with depression were on hormones compared to 12% of the non-depressed group (**Table 4-3**).

Association of psychological traits (anger, anxiety, hostility/cynicism) and satisfaction with life: Depressed women scored higher trait anxiety and anger scores. Anxiety means and SD were 14.5 ± SD 5.0 for cases and 7.1 5 ± SD 4.0 for controls. Anger means and SD were 11.7 ± SD 5.1 for the depressed group and 7.8 ± SD 3.2 for the non-depressed group. Both anxiety and anger compared between the depressed and non-depressed were statistically significant p <.01. Non-depressed women reported significantly greater satisfaction with life (mean 26.1 ± SD 5.7) compared to the depressed group mean (mean 19.6 ± SD 7.2, p<.01). The depressed group was less hostile/cynical when compared to the non-depressed group. Results were significant between both groups at <.01 with mean 6.4 ± SD 3.0 for the depressed group and 7.8 ± SD 2.8 for the non-depressed.

Logistic regression **(Table 4-5)** was performed within cases to determine predictors of depressive symptoms. BMI, education, and parity were statistically significant predictors of depression when smoking status and marital status were forced into the model. The odds of being depressed increased by 6% for each unit increase of BMI. The odds of being depressed decreased by 20% for each year of increased education and increased by 44% for parity (***per live birth***). BMI and education remained consistently significant with the model building. Parity was near statistical significance when marital status was added to the model and when smoking was added to the model, parity became significant. There was no interaction between marital status and smoking or between marital status and parity.

Table 4-1 Sociodemographic and Health Related Variables in PCOS Case and Matched Control Subjects

Variable	Case Subjects (n =161)	Control Subjects (n =161)	Total	Range	p value
Age (years) (M ± SD)	35.2 7.3	36.4 7.8	35.8 7.5	18 to 53	0.01
BMI (M ± SD)	30.3 8.2	26.3 6.3	28.3 7.6	17.6-58.6	0.01
Education (highest level completed) (M ± SD)	14.2 2.2	14.4 2.0	14.3 2.1	9 to 17	0.42
Parity (M ± SD)	.89 1.6	1.6 1.5	1.2 1.6	1 to 16	0.01
Race	n %	n %	n %		0.06
White	148 91.9	157 97.5	305 94.7		
Black	7 4.3	4 2.5	11 3.4		
Other	6 3.7		6 1.9		
Marital Status	n %	n %	n %		0.17
Married	116 72	94 58.4	210 65.2		
Living alone	29 18	38 23.6	67 20.8		
Living with a partner	5 3.1	13 8.1	18 5.6		
Other	8 5	8 5	16 5		
Missing	3 1.9	8 5	11 3.4		
Occupation	n %	n %	n %		0.79
Professional	83 51.6	81 50.3	164 50.9		
Laborer	47 29.2	45 28	92 28.6		
Homemaker	23 14.3	30 18.6	53 16.5		
Other	8 5	5 3.1	13 4		

Table 4-1 Continued

Variable	Case Subjects (n =161) n	%	Control Subjects (n =161) n	%	Total n	%	*Range*	P
MEDICATIONS Self Report								
Oral Contraceptives							1-10+	
Months on Oral Contraceptives								.06
0	124	77.0	13	82.0	256	79.5		
1-4 months	14	8.7	8	5.0	23	6.8		
5-9 months	18	11.2	18	11.2	36	11.2		
10 or more months	2	1.2	3	1.9	7	2.2		
Missing	1	0.6	0	0	1	0.3		
HORMONES Self Report								
(currently taking)								.58
Yes	25	15.5	25	15.5	50	15.5		
No	134	83.2	136	84.5	270	83.9		
Unknown	2	1.2	0	0	2	1.2		
OTHER MEDICATIONS								
Psychiatric medications								
Major tranquilizer	0		0		0			
Minor tranquilizer	0		1	.6	1	.3		
Sedative	2	1.0	1	.6	3	.9		
Other Antidepressant	1	.6	0		1	.3		
Steroids	5	3.0	1	.6	6	1.8		
SMOKING HISTORY								
Never	83	51.6	77	47.8	160	49.7		.66
Current	37	23.0	44	27.3	81	25.2		
Ever	41	25.5	40	24.8	81	25.2		

Table 4-2 Psychological Variables in PCOS Case and Matched Control Subjects

Variable	Case Subjects (n =161)		Control Subjects (n =161)		Total		*Range*	p value
BDI Total Score								
Beck Depression Inventory *							0-63	
(M ± SD)	7.8	7.0	5.7	5.0	6.8	6.2		
Missing	9		14		23			.02
Category of Depressive sx Subscale ***		%		%		%		
<9	102	63.4	119	73.9	221	68.6	0-9	
>9	50	31.1	28	17.4	78	24.2	10-63	.04
Missing	9	5.6	14	8.7	23	7.1		
Severity of Depressive Sx								
Mild	39	24.2	24	14.9	63	19.6	10-18	
Moderate	8	5.0	4	2.5	12	3.7	19-29	
Severe	3	1.9	0		3	.9	30-63	
Deiner Satisfaction Total*								
(M ± SD)	23.9	6.8	24.2	6.2	24	6.5	5 to 35	.74
Missing	5		9		14	4.3		
Spielberger Trait Anger*								
(M ± SD)	9.1	4.2	8.2	3.6	8.6	4.0		.02
missing	9		14		23		10 to 36	
Speilberger Trait Anxiety*								
(M ± SD)	9.6	5.5	8.7	5.2	9.2	5.4		.01
missing	10		16		26		10 to 39	
Cook-Medley*								
Subscale								.01
Cynicism	7.3	2.9	7.9	2.6	7.6	2.8	14 to 26	
(M ± SD)	8		14		14			
missing								

*** continuous variables**
**** categorical variables**

Table 4-3 Comparison of Demographic, Health, and Psychological Variables within PCOS Cases Only

		PCOS Cases with depression BDI>9 n=50		PCOS Cases without depression BDI≤9 n=102*		P Value
Age	M±SD	3.0	(7.3)	35.27	(7.2)	.88
Parity	M±SD	.96	(1.2)	.68	(.91)	.13
Education	M±SD	13.72	(2.1)	14.66	(1.9)	<.01
Race		%		%		.82
White		45	90	94	92.2	
Black		3	6	4	3.9	
Other*		2	4	4	3.9	
Marital Status						
Married		36	72	76	74.5	<.01
Not Married		14	28	26	25.4	
Occupation						< .04
Professional		20	40	60	58.8	
Sales		12	24	26	25.5	
Laborer		4	8	3	2.9	
Homemaker		13	26	10	9.8	
Other		1	2	3	2.9	

*9 missing

Table 4-3 Continued

Comparison of Medical Variables within PCOS Cases Only

	PCOS Cases with depression BDI>9 n=50		PCOS Cases without depression BDI≤9 n=102		P Value
Smoking History	n	%	n	%	.37
never	21	42	56	54.9	
current	16	32	20	19.6	
ever	13	26	26	25.5	
BMI * M±SD	32.8 (8.6)		28.9 (7.6)		.01
Months oral contraceptives	n	%	n	%	.11
0	37	74	81	79.4	
1-4 months	2	4	10	9.8	
5-9 months	8	16	10	9.8	
10 or more months	2	4	1	1.0	
Missing	1	2	0	0	
Hormones	n	%	n	%	.01
yes	13	26	12	11.8	
no	36	72	90	88.2	
missing	1	2	0	0	

*****Range 19.26-50.2 for depressed cases
18.1-58.7 for cases without depression

Table 4-3 Continued

Comparison of Psychological Variables within PCOS Cases Only

	PCOS Cases with depression n=50	**PCOS Cases without depression n=102**	
Psychological Variable	M±SD	M±SD	P Value
BDI I	15.7 6.6	3.9 2.7	<.01
Anger	11.7 5.1	7.8 3.2	<.01
Anxiety	14.5 5.0	7.1 4.0	<.01
Cynicism/Hostility	6.4 3.0	7.8 2.8	<.01
Satisfaction with life	19.6 7.2	26.1 5.7	<.01

Table 4-4 Terms of Conditional Logistic Regression Model Showing association with PCOS Status on the Matched–Pair Data Set (n=161 Pairs)

Variable	ß	SE (ß)	OR (CI)	P
Marital Status	-1.017	.351	.362 (.182-.720)	**.004**
BMI	.066	.20	1.068 (1.027-1.111)	**.001**
BDI I Scale	.062	.028	1.068 (1.007-1.125)	**.028**
Smoking	.298	.354	1.347 (.674-2.695)	.399
Education	.031	.072	1.031 (.896-1.188)	.667

Table 4-5 Logistic Regression Predictors of Depression within PCOS Cases

N=50

	β	SE	OR	95% CI for OR	P value
Education	-.221	.098	.802	.661-.971	**.024**
Smoking Status					
Current	-.255	.454	.802	.318-1.888	.775
Parity	.371	.187	1.449	1.005-2.091	**.047**
Marital Status	-.495	.446	.610	.254-1.461	.267
BMI	.058	.023	1.060	1.013-1.109	**.012**

4.5 DISCUSSION

The Cardiovascular Health and Risk Measurement Study (Charm) is the largest case control study examining the prevalence of depressive symptoms and psychological traits in women with PCOS. One of the major findings from the psychological arm of this study was that the point prevalence of clinically significant high depressive symptoms on a screening instrument (BDI I) >9 was 31.1% compared to 17% in controls (OR = 1.75). Within cases, results of logistic regression analysis showed that BMI, education, and parity were statistically significant predictors of depression $p<.05$. The odds of being depressed of at least mild severity increased by 6% for each unit increase of BMI. The odds of being depressed decreased by 20% for each year of education and increased by 44% for parity (*per live birth*). Other studies have supported the high prevalence of depression in the PCOS population (16, 17, 32, 45). The prevalence rates have been higher, 35% independent of obesity and fertility, as reported by

Hollinrake et al. (10) in a matched control study of PCOS cases and controls and similarly a 40% prevalence rate in another longitudinal study (28).

The depressive symptoms on the BDI scale were also examined within cases. Mean scores for the BDI were significantly higher in the cases. Almost 80% of cases scored within the moderate and severe categories. As expected, the cases had a higher BMI compared to controls.

This finding is supported by the literature on obesity and depression in the general population (27). Large community studies have evaluated the relationship between obesity and depression. The second largest community study on obesity and mood disorders reported that obesity (BMI $\geq$ 30) was associated with major depression in women (OR 1.82, 95% CI = 1.01 to 3.3). More importantly, the severely obese patient is at even greater risk for depression.(46). In this study, 25% of cases with BMI $\geq$ 40 had increased depressive symptoms.

In addition to BMI, education, marital and smoking status, and parity were factors examined to determine whether there was a relationship to depressive symptoms within cases. In this study, education was protective against having increased depressive symptoms.

Studies in the literature reach different conclusions about the association between education and depression. For example, in a recent community study (47) results indicated that the highest rates of depression were reported by those "with other post-secondary" education, which is contrary to the current findings that the odds of being depressed decreased by 20% for each year of education within cases.

Parity was found to be positively associated with depression in the full model. This finding is unexpected in the PCOS population as infertility is often a result of the condition. In the general population, however, studies have reported increased depression during the

childbearing years (48). It is unclear whether this findings regarding parity could be a result of a combination of age and the stress of caretaking.

Marital status was not associated with depression in the logistic analyses. Typically, it has been found that unmarried persons were approximately 1.5 to 2.5 times more likely than married individuals to have had a recent episode of depression.(49). Others have reported that there are lower rates of depression among people living with their marriage partners when compared to divorced individuals (47). Another important aspect of marital status is measuring the quality of the marital relationship, which was not ascertained. This may have contributed to the results.

Likewise, smoking status was not associated with depression. The research has shown that smoking does have an association with depression and has been found in early studies to be related to major depression (50). The analyses only included smoking status and may have changed if more precise data regarding smoking habits were included. Yet, it was left in the model as parity was no longer significant when smoking status was removed.

Findings from the adjusted conditional logistic regression concluded that BMI, marital status, and BDI score were independently associated with PCOS. This highlights the importance of focusing on depressive symptoms concurrently with BMI when attempting to identify PCOS women who may be at risk for depression. It also substantiates the complexity of the disorder, in that weight along with depressive symptoms and other demographic characteristics should be considered when screening for depression.

It was notable that all the psychological variables, depressive symptoms and trait anger, anxiety, and cynicism on univariate analysis were associated with PCOS case status. However, satisfaction with life was not. In retrospect, other measures investigating quality of life that have

been tested on the PCOS population may have been more appropriate, i.e. the Health-Related Quality- of- Life Questionnaire (30).

There were strengths to this study. The matched pair design allowed for more robust results. The sample size of 161 matched pairs was the largest case control study that reported psychological manifestations of PCOS. It also provided a model to predict PCOS women who may have increased depressive symptoms and require treatment. The psychological measures were well known, reliable, and valid measures.

The limitations to the study included its cross-sectional perspective and lack of diagnosis of depression. The BDI I was useful as a screening tool for identifying individuals at risk for depression but did not have the ability to make a clinical diagnosis of depression.

In conclusion, this study has highlighted the high risk and prevalence of depression that is associated with PCOS. The mortality of women with PCOS is concerning not only from a medical standpoint but also from a psychological one. These analyses have also shed light on factors such as BMI, education, and parity that are associated with increased depressive symptoms and which can provide useful clinical information with which to screen and identify women at risk for depression. Additionally, the findings indicate that depression was associated with PCOS status independent of BMI.

Further study is needed to examine the many confounding variables that mediate and moderate depressive symptoms in women with PCOS. Identifying women with increased depressive symptoms, which often can lead to a clinical diagnosis, is implicit not only to provide early treatment for depression but to mitigate the probability of recurrent depression as this is a chronic disorder. With appropriate psychological intervention, women with this condition can improve their quality of life and psychological functioning.

The public health implications of this study center around primary and secondary prevention. With secondary prevention, case finding is paramount as women are known to have 2 times the prevalence of depression than men even before the having the diagnosis of PCOS. Finally, implementing a high-risk prevention approach would be a strategy to decrease the prevalence of depression in the PCOS population.

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5.0 PCOS, PSYCHOLGICAL MANIFESTATIONS, AND THE METABOLIC SYNDROME. WHAT IS THE RELATIONSHIP?

Objective: The aims of this study were: 1) to determine the prevalence of Metabolic Syndrome (MS) in PCOS cases and controls and 2) to determine if psychological factors (depression, anger, anxiety, hostility/cynicism, and satisfaction with life) are risk factors for Metabolic Syndrome independent of age, marital status, education, and parity.

Methods: A cross sectional study consisting of 148 PCOS cases and 151 controls with a mean age of 35.4 years was conducted to determine the prevalence of Metabolic Syndrome (MS) at baseline. A total of 40 (27%) PCOS cases and 15 (9.9%) controls met the criteria for MS according to the Adult Treatment Panel III (ATPIII). In addition, psychological characteristics of the women were collected at baseline using the Beck Depression Inventory I (BDI I), the Spielberger Trait Anger and Anxiety Scales, the Cook-Medley Scale, and the Diener Satisfaction with Life Scale.

Results: In the sample, 27.0% (n=40) of the cases and 9.9% (n=15) of the controls had MS; $p<.05$; OR 3.4 (CI 1.726-6.400). Differences between cases with and without MS for age was statistically significant, $p<.001$ and $<.04$, for cases and controls respectively. Differences between controls with and without MS for education was also statistically significant, $p<.04$.

In univariate analyses, BDI was borderline when associated with MS ($p=.053$). Only PCOS and age were significant predictors for MS when BDI was forced into the model. The

odds of having MS increased by 10% for each year of age and three fold for PCOS cases. Within the subjects who had a BMI>30, the odds of having MS increased by 3% for each year of age.

Conclusions: Metabolic syndrome has been related to premature coronary heart disease. PCOS women have three times the prevalence of MS and should be monitored for a reduction in CHD risk factors as well as for lifestyle modification. The prevalence of depressive symptoms, although greater in cases than controls, is not significantly related to MS after adjusted for age and PCOS status.

Public Health Significance: The presence of MS and depressive symptoms in PCOS has clinical implications in screening for depression and also for evaluating women at intervals as they age so as to prevent the progression of MS. Early identification and treatment of depression in PCOS women could possibly reduce the prevalence of MS as well as other features of MS, such as obesity and diabetes.

6.0 INTRODUCTION

Polycystic ovary syndrome is the most common reproductive endocrine condition with a prevalence rate between 6-10%. Features of PCOS, a heterogeneous disorder, include chronic anovulation, hyperandrogenism, and insulin resistance (1, 2). Metabolic abnormalities often occur in PCOS women and have been identified as Metabolic Syndrome (MS) or Metabolic Cardiovascular Syndrome (3, 4). They include central adiposity, increased triglycerides, low levels of high density lipoproteins (HDLc), hypertension, impaired glucose tolerance, and Diabetes 2 (3, 5, 6). Consensus on the definition and components of the Metabolic Syndrome varies (7, 8).

The literature describing the Metabolic Syndrome (MS) in PCOS and the relationship with psychological characteristics are limited. The association between MS and PCOS has been primarily on the medical features. It is clear that there is a high prevalence of MS in women with PCOS (9, 10). Previous research by Talbott et al. 2004 (10) concluded that women with PCOS are at increased risk for developing MS. In this prospective study of 61 PCOS white women and 85 similarly aged controls, they reported that PCOS cases were 4.4 times more likely to meet the criteria for MS.

Psychological factors may be an important component of MS. In a recent cross-sectional study by Hollinrake et al.(11), 103 women between the ages of 18-50 years with PCOS and controls were studied to estimate the prevalence of depressive disorders in women with PCOS.

They reported the comparison of biochemical variables between cases and controls with and without depression but did not examine those with metabolic syndrome.

Depressive symptoms, stressful life events, and anxiety have been studied in relationship to MS in premenopausal middle-aged women (12). Gender dependent associations (13) were also investigated finding that depression among women was associated with a 1.94-fold risk of having the MS with an elevated risk of having two of its five components: elevated waist circumference (OR=2.23) and elevated glucose levels (OR=2.44) (14). Further, a positive trend was observed toward an association with low high-density lipoprotein, hypertension, and elevated triglycerides suggesting that depression and cardiovascular diseases might be linked via the metabolic processes (14). Findings from a review by Goldbacher and Matthews 2007 (15) suggested that psychological characteristics, predominately depression, hostility, and anger may increase risk for the metabolic syndrome.

Other areas of interest in association with MS are quality of marital status (16) and parity (17). Women in high-quality marriages are at a lower risk of developing MS (16). The presence of MS is significantly higher in women with increasing numbers of children demonstrating a dose-response relationship ($p<0.0001$) (18). After controlling for age, race/ethnicity, income, education, and other sociodemographic and behavioral risk factors, the odds of metabolic syndrome increased 13% (95% CI, 6%-20%) with each additional child (18).

Numerous cross sectional studies have reported on the relationship between psychological variables and MS (13, 14, 19). Likewise, research studies have reported on the association of MS and cardiovascular disease (3, 20) and the association with depression, MS and cardiovascular disease (21).

In longitudinal study investigating antecedents to MS, cynicism and hostility were characteristics identified as predictors of Metabolic Syndrome in older men and women.(22). Similarly, studies have substantiated that baseline anger scores in middle age women predicted increased risk for developing MS (12, 23). However, the association of anxiety and MS is equivocal (23).

Others have reported on the prospective relationship of metabolic syndrome and psychological characteristics in various populations but not with PCOS (12, 23). Research by Raikkonen et al. (23) investigated the reciprocal relationship between psychological risk attributes and Metabolic Syndrome in healthy women. Women who had high levels of depression and anger at baseline and increased anger during the follow-up had an elevated risk of developing MS during the follow-up, $P<.04$. Conversely, MS syndrome at baseline predicted increasing anger and anxiety 7.4 years later, $P<.001$. It was thus concluded that psychological risk factors affect the development of the MS and that the association between anger and the MS is indeed reciprocal.

In another study by Raikkonen and colleagues (2007) (12), women enrolled in the population-based prospective cohort Healthy Women Study were followed for an average of 15 years after baseline. Premenopausal women (n=523) participated with a 3 year follow-up. When women did not have MS at baseline, the risk for developing MS was 1.21 to 2.12 fold ($P<.05$) for more severe depressive symptoms or for very stressful events. This was true even though MS was defined in various ways. Those who at the baseline reported feeling frequently angry measured by the Spielberger Trait Anger Scale had an increased risk for developing the MS at least by one definition (relative risk 1.19-1.166 [1.00-2.39].

A recent study examining the temporal relationship of depression and MS (24) found that non-depressed women with MS at baseline were twice as likely to have depressive symptoms at follow-up (OR 2.2, 95% CI=1.1 to 4.5) as compared to the non-depressed cohort members without Metabolic Syndrome at baseline. This finding underscores the possibility that MS may be an important risk factor for depression in other populations, such as PCOS. Moreover, effective identification and prevention of the MS could aid in the prevention of depression and other psychological symptoms.

In a large matched pair study by Cipkala-Gaffin and colleagues (25) investigating the psychological ramifications of PCOS, the prevalence of depression was 31% for cases as compared to 17% for controls (OR 1.9, CI 1.55-2.16). In continuation of that study, further research was conducted to determine the psychological characteristics related to MS in women with PCOS as there is a paucity of research in this area.

The present study was designed to: 1) determine the prevalence of Metabolic Syndrome (MS) in PCOS cases and controls and 2) to determine if psychological factors (depression, anger, anxiety, hostility/cynicism, and satisfaction with life) are risk factors for Metabolic Syndrome independent of age, marital status, education, and parity.

6.1 SUBJECTS AND METHODS

Case and Control Recruitment: The study population is comprised of a subset of the original Cardiovascular Health and Risk Measurement study (CHARM) investigation conducted by Talbott et al. (l995) (26) . This study's main aim was to investigate coronary heart disease risk factors in women with PCOS. At baseline, psychological characteristics of the women were

collected using the Beck Depression Inventory I, the Spielberger Trait Anger and Anxiety Scales, the Cook-Medley Scale, and the Diener Satisfaction with Life Scale. A total of 243 PCOS cases and controls were to be recruited for the primary study. Approximately 200 cases and controls participated in answering the psychological measures. However, complete data on the psychological profile was available for only 160 cases and controls and forms the basis for this analysis. Details and further information about the participants have been published elsewhere (26). Controls were matched to cases by age ± 5 years, race, and neighborhood.

Those participants living in the greater Pittsburgh area were asked to participate in the clinical phase of the study located at Magee-Women's Hospital. Subjects were evaluated after a 12 hour fast. Another questionnaire was administered on site which included a repeat medical history, medication history, current medical practices, and family history of PCOS.

6.2 MEASURES

Metabolic Syndrome (MS) was defined according to the Adult Treatment Panel III (ATPIII) Criteria. Criteria for MS are listed in **Table 6-1**.

Table 6-1 Metabolic Syndrome

(3 or more of the following)

DIMENSION	CRITERIA
1.Waist	>88cm
2.Elevated fasting glucose /or Type 2 Diabetes (MD diagnosed)/ or receiving treatment for Type 2 Diabetes	>110mg/dl
Dyslipidemia **3**.↑tryglcerides **4**.↓ (HDLc)	 ≥150mg/dl ≤50mg/dl
5.Hypertension* ↑ SBP /or ↑DBP/ or receiving treatment for hypertension	≥ 135mmHg and ≥ 85mmHg

Systolic Blood Pressure=SBP
Diastolic Blood Pressure=DDP
*ATP criteria (2001) includes any three of the components

Lipid and Lipoprotein Measurement

Serum concentrations of total cholesterol, total HDL cholesterol (HDLc), subfractions HDL2, HDL3, triglycerides, LDL and VLDL were measured at the University of Pittsburgh, Heinz Lipid Laboratory. Total cholesterol was determined by the enzymatic method of Allain et al.(27). Duplicate samples with standards, control sera, and serum calibrators were included in each run. The coefficient of variation (CV) runs was 1.3%.

HDL-C was determined after selective precipitation by heparin/manganese chloride and the removal by centrifugation of VLDL and LDL (28). The cholesterol was measured as

described above for total cholesterol. Duplicate samples, standards, and control sera were included in each run. The CV between runs was 2.1%. After precipitation and removal of VLDL and LDL by heparin/manganese chloride as described above, the supernatant was mixed with dextran sulfate (29). The HDL_2 precipitates and the HDL_3 in the supernatant were then measured using the methods described above for cholesterol measurement. The HDL_2 content was estimated by subtracting the HDL_3 level from the total HDL content. Duplicate samples, standards, and control sera were included in each run. The CV between runs was 6.0%. LDL concentration was estimated by using the Friedewald formula (30). Triglycerides were determined by using the enzymatic procedure of Bucolo and David (31). The CV between runs was 1.7%. Blood for glucose and insulin determinations was obtained when the subjects were fasting. Plasma glucose was analyzed by using an enzymatic assay (Yellow Springs Glucose Analyzer, Yellow Springs Instruments) and plasma insulin by radioimmunoassay.

6.2.1 Standardized Psychological Measures

Depression Assessment: The Beck Depression Inventory I (BDI I) (32) is a self-report inventory measuring characteristic attitudes and symptoms of depression. It contains 21 questions with a cutoff of >9 (total score) to identify potential clinically significant symptoms of depression. The psychometric properties of the BDI have been reported as high with internal consistency ranging from .73 to .92 with a mean of .86. The split-half reliability coefficient reported was .93. Concurrent validity was determined by correlations with clinician ratings of depression using the revised BDI and ranged from .62 to .66 (32). The BDI was previously tested on the PCOS population (33, 34) and in other research studies on women with obesity that may be applicable to the PCOS population as obesity is a central feature of this disorder.

Anxiety and Anger Assessments: The Spielberger Trait Anger/Anxiety Scales are components of the State-Trait Personality Inventory by Spielberger (35, 36) (2 of 6 subscales). For reliability testing, alpha coefficients ranged from .80 to .87 and provide evidence for internal consistency of the six STPI scales (37). Reliability testing was done to determine internal consistency, alpha coefficient = .81-.87 (Spielberger manual reports). Cronbach alphas were .82-.85 and .80-.85 for anger and anxiety (35, 36).

Hostility/Cynicism Assessment: This 13 item scale derived from the Cook-Medley Hostility Scale (38) measures cynical attitudes and hostile feelings and behaviors rather than overt expressions of anger and aggression. Higher scores indicate greater hostility (range 9-13). Cronbach's alpha for the scale was .79 indicating good internal consistency (38).

Diener Satisfaction With Life Scale: This scale (39) measures judgmental components of subjective well-being. It is comprised of 2 major components, the emotional or affective component and the judgmental or cognitive component. The scale consist of 5 questions with a 7 point likert scale ranging from strongly disagree to strongly agree. A higher score reflects a greater satisfaction with life. Test retest reliability was .84 (39). While brief, this instrument offers as high or higher predictive validity than several longer measures of life satisfaction.

7.0 STATISTICAL ANALYSES

All data collected for the original study were entered and verified by using SPSS data-entry software. All data were analyzed using SPSS FOR WINDOWS version 15.0 (SPSS Inc., Chicago, IL, USA). Univariate and multivariable analyses were performed.

Descriptive statistics, including measures of central tendency and dispersion, were computed for all variables of interest for PCOS cases and controls. Due to it's non-normally distribution, triglyceride levels were logarithmically transformed before performing statistical comparisons. Variables of interest were compared using the Student's t test or the nonparametric Mann-Whitney U test for continuous data. For categorical data, x^2 or Fisher's exact test was used.

The group differences were determined by using independent t-tests. Spearman correlation and logistic regression were utilized. The logistic regression models examined the relationship between the metabolic syndrome (dependent variable), covariates (PCOS, age, marital status, education, and parity), and depressive symptoms.

7.1 RESULTS

7.1.1 Demographics

One hundred and sixty-one pairs formed the cohort studied. Pairs were initially matched on age, race, and neighborhood. Fifty five subjects met criteria for Metabolic Syndrome. Because of the small number of subjects with MS, it was not possible to retain the matched pairs for all of the analyses without losing sample size.

From the total sample, PCOS cases (n=148) and controls (n=151), 40 cases and 15 controls met criteria for MS, OR 3.4. (**Figure 7-1**) Of those with MS (n=55), 27.0% of the cases and 9.9% of the controls had MS, OR 2.7. (**Table 7-2**) The average age of the initial CHARM matched pair sample (CHARM I) was 35.8 ± 7.5. The average age of the total sample with MS was 39.2 ± SD 5.2. (**Table 7-1**) Cases and controls with MS were similar in age, 39.2 ± 5.2 and 39.7 ± 5.7 respectively. However, the cases and controls without MS were younger in comparison. For the cases, the mean age was 33.9 ± 7.5 and for controls, 36.2 ± 8.0. The age between cases with and without MS was statistically significant, p<.001. Those with MS were older, 39.2 ± 5.2, compared to cases without MS, 33.9 ± 7.5 years. The same was true between controls. The controls with MS were older, 39.9 ± 5.7 years, compared to those without MS, 36.2 ± 5.7years (P<.04).

The sample was predominately White in both the cases and controls with MS (97.5%, 93.3% respectively) with only 1 case and 1 control with MS being Black. Seventy-five to 80% of the MS cases and controls were married, which was higher in comparison to the original cohort (65.2%) in which cases exhibited the greater percentage (72%). PCOS cases with MS had a mean of 1 child compared to controls with MS who had 2. Education within controls, with and

without MS, was statistically significant at p<.04 (13.2 ± 2.2 and 14.5± 2.0 years respectively) but not for cases. No statistically significant differences were found between groups for marital status and hormone use and smoking status. BMI was statistically different between those with MS within cases and controls separately, p<.001 (not shown in table, but relevant for analyses). **Table 7-2** presents the distribution of components of MS among PCOS cases (n=40, 27%) and controls (n=15, 9.9%). At baseline, a total of nine PCOS cases (15.3%) versus three control women (3.5%) had MS defined by the presence of 3 or more critical components (10).

7.2 PSYCHOLOGICAL VARIABLES

The mean BDI score for cases with MS was 9.1 ± 7.4 compared to 6.6 ± 4.3 for controls with MS. (**Table 7-3**) Differences in BDI scores between cases with and without MS and controls with and without MS as well as in the total samples of cases and controls, were not statistically significant. However, differences between BDI scores for the total cases and controls, 8.0 ± 7.2 and 5.8 ± 5.1, was statistically significant, p <.003. Mean scores for anger, anxiety, hostility/cynicism, and satisfaction with life were similar between cases and controls with and without MS and for the total sample, with the exception of hostility/cynicism in regard to the total sample. Hostility/cynicism was borderline significant between cases and controls for the total sample.

7.3 LOGISTIC REGRESSION ANALYSES

To adjust for the matching of the subjects, case status and age were variables kept in the model. (**Table 7-4**) On univariate logistic regression, BDI was borderline significant in predicting MS (p=.053) and no other psychological factor was significant. PCOS status was significant in univariate analysis (P<.001) and in all of the other modeling (P<.001 to P<.002). Age, also, remained significant in all of the models at P<.001. None of the other sociodemographic variables, marital status, parity, or education were significant.

The final model chosen was with PCOS, age, and BDI forced into the model. The sample was also stratified by BMI >30 (**Table 7-5**) in order to examine the relationship between the psychological and sociodemographic on MS. Age was the only significant predictor in the models, most notably with BDI, PCOS, Age, and Education. In this model, age was significant at P<.003. Analyses were not performed on the BMI sample < 30 due to small sample size.

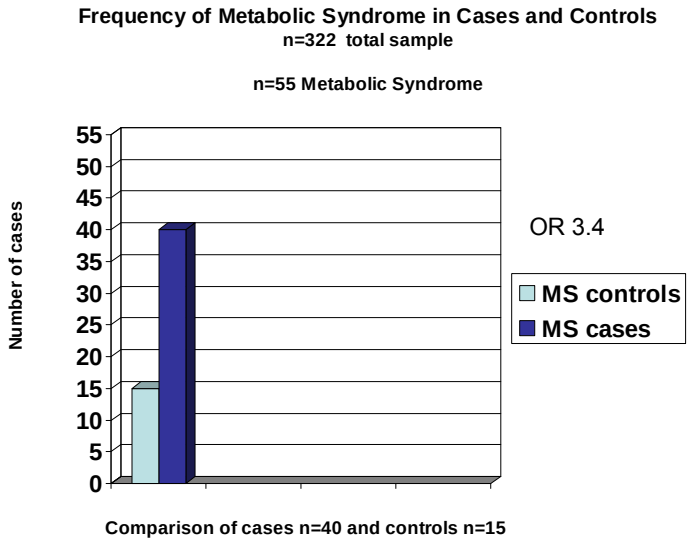

Figure 7-1 Frequency of Metabolic Syndrome in Cases and Controls

Table 7-1 Selected Sociodemographic Variables in PCOS Cases and Controls at Baseline (1993-1994)

	PCOS Cases				Controls					
MS*	Y	n=40	N	n=108	Y	n=15	N	n =136	P**	P***
Variable	M	±SD	M	±SD	M	±SD	M	±SD	Cases	Controls
Age	39.2	(5.2)	33.9	(7.5)	39.7	(5.7)	36.2	(8.0)	**<.001**	**< .04**
Race *a* white	39	97.5	109	90.1	14	93.3	143	97.9	.33	.27
(other)	1	2.5	11	9.1	1	6.7	3	2.1		
Education	14.4	1.9	14.3	2.0	13.2	2.2	14.5	2.0	.74	**<.04**
Marital Status *b*Y	30	75	86	71.1	12	80	82	56.2	.80	.12
Parity	.9	1.0	.78	1.0	1.9	1.3	1.43	1.3	.69	.20
Hormones Y	5	12.5	20	16.5	0	0	25	17.1	.60	.08
Smoking Y	11	27.5	26	21.5	3	20	48	28.1	.43	.50

Values are the mean (SD) or number (percentage)
*MS= Metabolic Syndrome
**between cases with and without MS
***between controls with and without MS
Missing:
a=1
b=10

Table 7-1 Continued

	PCOS Cases		Controls		
MS	n= 148		n=151		p value
Deleted/missing	13		10		
Variable	M	±SD	M	±SD	
Age	35.2	7.2	36.5	7.9	.163
Race *a* white	136	91.9	146	97.4	**<.029**
(other)	11	7.9	4	2.6	
Education	14.3	2.0	14.4	2.1	.608
Marital Status Y *b*	113	71.5	93	58.1	<.**030**
Parity	.8	1.0	1.5	1.4	**<.001**
Hormones Y *c*	25	15.5	25	16.6	.190
Smoking Y	34	23.0	40	26.5	**.**483

Values are the mean (SD) or number (percentage)
*MS= Metabolic Syndrome
**between cases with and without MS
***between controls with and without MS
Missing: *a*=1
b=10
c=2

Table 7-2 Distribution of MS Components among PCOS Cases and Controls

MS risk factors	**PCOS**	**Controls**
	(n=148)	(n=151)
MS absent (≤ 2 risk factors) †	108 73.0%	136 90.1.0%
None	42	72
One	35	40
Two	31	24
MS present (3+ risk factors)	**40 27.0%**	**15*** 9.9%**
Three	17	10
Four	14	5
Five	9	0

*3 cases deleted with 1 missing risk factor that could have changed MS status to present
** 1 control deleted with missing risk factor that could have changed MS status to present
*** 1 control had risk factors =3 even with 1 missing risk factor, added to sample
† if subject had missing risk factor or factors but remained <3, left in sample

Table 7-3 Psychological Variables in PCOS Cases and Controls at Baseline by MS Status (1993-1994)

	Cases				Controls					
MS	Y	n=40	N	n=108	Y	n=15	N	n=136	P***	P****
Variable	M±SD		M ±SD		M ±SD		M ±SD			
BDI *a*	9.1	7.4	7.5	7.1	6.6	4.3	5.6	5.2	.254	.501
Anger *b*	9.3	4.4	9.1	4.2	9.1	4.4	8.2	3.6	.744	.379
Anxiety *c*	9.5	5.4	9.3	4.4	9.0	5.4	8.9	5.3	.653	.926
Host/cyn* *d*	6.8	2.9	7.5	3.0	8.0	2.9	8.0	2.6	.176	.873
Sat. w/l** *e*	23.0	6.6	24.2	7.1	26.5	5.7	24.0	6.3	.351	.134

Mean and SD
*Hostility/Cynicism
**Satisfaction with life
***between cases with and without MS
****between controls with and without MS
Missing:
a=21
b=22
c=25
d=20
e=13

Table 7-3 Continued Psychological Variables in Total PCOS Cases and Controls at Baseline (1993-1994)

	Total Cases	Total Controls	
	n=188	n=136	P***
Variable	M ±SD	M ±SD	
BDI *a*	8.0 7.2	5.8 5.1	**<.003**
Anger *b*	9.1 4.2	8.2 3.7	.103
Anxiety *c*	9.6 5.5	8.8 5.3	.249
Host/cyn**d*	7.3 2.9	8.0 2.6	.056
Sat. w/l***e*	23.8 7.0	24.2 6.3	.606

Mean and SD
*Hostility/Cynicism
**Satisfaction with life
***between cases with and without MS
****between controls with and without MS
Missing:
a=21
b=22
c=25
d=20
e=13

Table 7-4 Logistic Regression Models of MS (yes/no) and Selected Sociodemographic and Psychological Risk Factors for Cases and Controls with MS

	n	β	SE	OR	95% CI for OR	p value
BDI	278	.043	.022	1.044	(.999,1.090)	.053
PCOS	299	1.211	.329	3.358	(1.762,6.400)	**<.001**
BDI	278	.030	.023	1.030	(.986,1.077)	.187
PCOS		1.068	.338	2.910	(1.501,5.640)	**<.002**
BDI *	278	.035	.024	1.036	(.989,1.084)	.139
PCOS		1.252	.355	3.496	(1.743,7.014)	**<.001**
Age		.096	.025	1.101	(1.049,1.156)	**<.001**
BDI	278	.036	.024	1.037	(.990,1.087)	.128
PCOS		1.231	.359	3.425	(1.695,6.922)	**<.001**
Age		.094	.026	1.099	(1.045,1.155)	**<.001**
MARS**		-.154	.396	.857	(.394,1.864)	.697
BDI	278	.037	.024	1.037	(.990,1.087)	.120
PCOS		1.175	.372	3.238	(1.562,6.712)	**<.002**
Age		.101	.026	1.106	(1.051,1.163)	**<.001**
Parity		-.099	.152	.905	(.672,1.220)	.514
BDI	278	.031	.024	1.032	(.984,1.081)	.195
PCOS		1.266	.357	3.547	(1.762,7.141)	**<.001**
Age		.096	.025	1.101	(1.048,1.156)	**<.001**
Education		-.069	.081	.933	(.796,1.094)	.393

*Final Model
** **MARS= Marital Status**

Table 7-5 Logistic Regression Models of MS (yes/no) and Selected Sociodemographic and Psychological Risk Factors for >30 BMI

	n	β	SE	OR	CI for OR	p value
BDI	101	-.009	.026	.991	(.941,1.044)	.742
PCOS	108	.640	.429	1.896	(.817,4.398)	.136
BDI	101	-.018	.027	.982	(931,1.036)	.505
PCOS		.720	.449	2.055	(.852,4.958)	.109
BDI	101	-.007	.029	.993	(.938,1.051)	.812
PCOS		.841	.475	2.319	(.915,5.881)	.076
Age		.098	.034	1.103	(1.031,1.180)	**<.004**
BDI	101	-.003	.030	.997	(.941,1.057)	.920
PCOS		.797	.483	2.219	(.862,5.714)	.099
Age		.094	.035	1.099	(1.025,1.178)	**<.008**
MARS*		-.778	.473	.459	(.182,1.160)	.100
BDI	101	-.006	.029	.994	(.939,1.052)	.838
PCOS		.784	.492	2.190	(.834,5.750)	.111
Age		.101	.035	1.106	(1.032,1.185)	**<.004**
Parity		-.087	.201	.916	(.618,1.359)	.664
BDI	101	-.012	.030	.988	(.932,1.048)	.697
PCOS		.873	.479	2.393	(.937,6.116)	.068
Age		.106	.036	1.112	(1.036,1.193)	**<.003**
Education		-.102	.106	.903	(.734, 1.110)	.332

***MARS= Marital Status**

8.0 DISCUSSION

The present investigation evaluated the prevalence of Metabolic Syndrome among women with PCOS and controls of similar age and the association between MS and certain psychological factors.

Previous studies have reported on the prevalence of MS in PCOS (10, 40-42). Studies have reported that the prevalence of the Metabolic Syndrome in premenopausal women with PCOS ranges from 33% to 47% (42). In our study, 27% of the PCOS cases had MS according to the ATP III criteria. As can be seen, the prevalence in PCOS women is concerning. In a previous study by Talbott and colleagues (10), 15.3% met the same ATP IIII criteria for MS even when subjects were limited to those with a BMI of <35. The literature supports the fact that MS is common in PCOS and notably in women with the highest BMI and insulin and androgen levels (43).

No studies have reported specifically on the MS syndrome in PCOS and its relationship to psychological factors. Only one investigation, related to MS (44), did a pilot study which investigated the rate of depression among women with PCOS and with clinical and biochemical markers of PCOS. Others have found that there is a significant relationship between depression and anger and the number of risk factors comprising the Metabolic Syndrome (23). Similarly, others have supported the finding of increased depressive symptoms in studies with MS in other

populations (14, 23, 24). In this study, we also found that women exhibited high levels of depression at baseline as in a previous study by Cipkala-Gaffin et al. 2009 (45).

In our study, we found that increased depressive symptoms were borderline significant in its association with MS on univariate analyses. However, it did not remain at this level of significance when other factors entered the models.

Age was a significant predictor of MS in PCOS and this finding has been consistent in the investigation of age and MS in PCOS. In a case control study, it was found that patients with a BMI>25 and who were 30 years of age or older had a higher prevalence of MS (46). Age, PCOS, and MS have been proven to have associations overall. The prevalence of MS increases with age (47) and likewise the prevalence of PCOS increases with age(48).

There are limitations to our study. The sample consisted mostly of Caucasians, limiting the generalization of the findings for other ethnic groups. Also, the matching was not retained throughout the analyses as the sample size would have been greatly reduced. Further, this study was cross-sectional which limited the ability to identify the depressive symptoms in subjects. The BDI, although reliable and valid, is a screening measure for increased depressive symptoms and does not provide diagnostic information.

In conclusion, there is a high prevalence of MS in PCOS women compared to controls, a threefold increase. Depressive symptoms and age are associated with MS in PCOS women and as the number of MS risk factors increase, so does age and the severity of depressive symptoms. Moreover, parity, marital status, and education all appeared to have no significant impact on these risk estimates. The presence of MS and depressive symptoms in PCOS has clinical implications in screening for depression and also for evaluating women at intervals as they age so as to prevent the progression of MS. Early identification and treatment of depression in

PCOS women could possibly reduce the prevalence of MS as well as other features of MS, such as obesity and diabetes.

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9.0 POLYCYSTIC OVARY DISEASE, (PCOS), PSYCHOLOGICAL FACTORS, AND INTIMA-MEDIA THICKNESS (IMT)

Objective: Earlier work has shown that women with PCOS have increased subclinical atherosclerosis as measured by IMT in addition to increased depression. The aim of this study is to investigate whether psychological factors, independent of baseline cardiovascular risk factors, are a risk factor for IMT in women with PCOS

Methods: A longitudinal study was done. The sample originated from 161 cases and controls matched on age, race, and neighborhood that participated in the baseline psychological assessment arm of our original study. In turn, these subjects were part of the original Cardiovascular Health and Risk Measurement (CHARM) study by Talbott et al. conducted in 1993-4 to investigate coronary heart disease risk factors in women with PCOS. Psychological characteristics of the women were collected at baseline using the Beck Depression Inventory I (BDI I), the Spielberger Trait Anger and Anxiety Scales, the Cook-Medley Scale (Hostility/Cynicism), and the Diener Satisfaction with Life Scale. Cardiovascular risk factors were also measured at baseline. Four years later (l997-1998), subjects aged 30 years and older returned for follow-up and underwent B-mode ultrasonography of the carotid arteries for the evaluation of carotid intima-media thickness (IMT). There were 196 subjects that had both psychological and IMT data which formed the basis for these analyses.

Results: Overall, PCOS remained a significant risk factor for carotid IMT independent of age, BMI, and systolic blood pressure in cases compared to controls (for the total group). In the group < 45 years of age, systolic blood pressure was a significant predictor of IMT. There were no significant effects from any of the psychological factors (depression, state anger and anxiety, hostility/cynicism, and satisfaction with life), independent of baseline cardiovascular risk factors, on IMT.

Conclusions: There was no independent relationship between the psychological variables and IMT measurements (either for the total group or when the groups were divided by age at follow-up after adjusting for age and selected risk factors). Psychological variables do not appear to be independently related to IMT. Further research to explore the association between psychological traits and IMT, independent of cardiovascular risk factors, is indicated.

Public Health Significance: It is well known that there is an association between subclinical cardiovascular disease and negative emotional states (depression, state anger and anxiety, and hostility/cynicism) which warrants psychological evaluations in PCOS women in order to prevent the incidence of psychiatric disorders in this population.

10.0 INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine condition, manifesting in puberty, with a prevalence rate between 6-10% among women of reproductive age (1). Features of PCOS, a heterogeneous disorder, include chronic anovulation, hyperandrogenism, obesity, and insulin resistance (2-6). There is concern that PCOS women may be at risk for cardiovascular disease (CVD) given the characteristics of PCOS which include dyslipidemia, hypertension, obesity, metabolic cardiovascular syndrome (MCS) (7), abnormalities in coagulation, and fibrinolytic pathways. Other studies have supported these findings in younger women with PCOS (8-10). Orio et al. (8) studied women with a mean age of 22.2 years and Carmina and colleagues (10) investigated women with a mean age of 25.2 years. These studies concluded that the diagnosis of PCOS was associated with carotid intima-medial wall thickness (IMT) independent of insulin resistance or visceral fat distribution. In a large study by Talbott (3), women ≥45 years of age had significantly greater IMT readings than controls. Intima-media wall thickness (IMT) has been highlighted and researched as a marker of subclinical CVD particularly because of its association with an adverse cardiovascular risk profile such as elevated LDLc and triglycerides, higher systolic blood pressure, increased abdominal adiposity, and hyperinsulinemia (3, 11). Research has substantiated that this risk profile is equivalent to the risk factors in PCOS (12, 13). Carotid IMT determined by B-mode ultrasound has been shown to be directly associated with an increased risk of myocardial

infarction and stroke in older adults without a previous history of cardiovascular disease (14). Similarly, B-mode ultrasonography has been proven to be a reliable measure of generalized atherosclerosis (15) and has been associated with adverse cardiac events (16, 17).

Evidence for the association between PCOS and premature carotid atherosclerosis was reported in middle-aged women (ages ranged from 30-44 and ≥ 45 years of age) by measuring carotid IMT (3). In a follow-up study by Talbott et al. (3), 125 white PCOS cases and 142 controls ≥ 30 years of age, matched on age, were investigated by B-mode ultrasound. In the total group (30-60 years of age), no difference was found. However, when the group was stratified between 30-44 years and ≥ 45 years, the PCOS women ≥ 45 years had significantly greater mean IMT than controls (0.78 vs 0.70 mm, p= 0.005). This was independent of age and BMI. The results suggests that lifelong exposure to an adverse cardiovascular profile in women with PCOS may lead to premature atherosclerosis (3). The difference between the 2 groups remained significant even after controlling for BMI (p<.005). The results suggest that the association between PCOS and IMT was mediated by central adiposity (7).

In addition to the medical consequences of PCOS, often there are also psychological difficulties such as depression, anxiety, anger, hostility, and dissatisfaction with life (16). These psychological complications may increase the risk of cardiovascular disease in this population. Cipkala–Gaffin et al. 2009 (18) noted that compared to a control group, **w**omen with PCOS had a higher prevalence of depression (BDI scores > 9): 31% vs. 17% in controls, P<.016: OR 1.9 (CI 1.55-2.16). The literature has focused on depression as the most evident psychological insult (19-22). Hollinrake and colleagues (2007) found that women with PCOS were at an increased risk for depressive disorders (new cases) compared with controls (21% vs 3%; odds ratio 5.11 [95% (CI) 1.26-20.69]; P<.03) (22). Additionally, the overall risk of depressive disorders in

women with PCOS was 4.23 (95% CI 1.49-11.98; P<.01) independent of obesity and infertility. Compared with the nondepressed PCOS subjects, the depressed PCOS subjects had a higher body mass index (BMI) and evidence of insulin resistance (P<.02).

Over the past 20 years, the literature is replete on the relationship of CVD and negative emotional states such as depression, anxiety, anger, and hostility (23). Agista et al. 2005 reported on the association of coronary and aortic calcification in women with a history of major depression in the Study of Women's Health Across the Nation (SWAN). After adjusting for cardiovascular risk factors and sociodemographic characteristics in a sample of 58 African American and 152 healthy white women, it was found that when comparing a history of recurrent major depression with a single episode or no history that the Odds Ratio (OR) was 2.46 for any coronary calcification, 2.71 for high coronary calcification, and 3.39 for high aortic calcification (24). Depression and coronary heart disease have been associated in many studies independent of standard cardiovascular risk factors (24-26). Rozanski et al. (25), reported that patients with coronary heart disease compared to the 1 month prevalence of major depressive episodes in community samples (approximately 5%) yielded results that were nearly 3 fold greater among patients with coronary heart disease. The Pittsburgh Healthy Heart Project (26), an ongoing prospective cohort study of healthy, older men and women from the general community, examined depressive symptoms, anxiety symptoms, and hostility/anger in predicting subclinical atherosclerotic progression over a 3 year period by measuring IMT. Regression analyses indicated that higher depressive symptoms at baseline were associated with greater 3 year change in carotid IMT (ΔR^2=0.026, P=.002) even when accounting for demographic factors, cardiovascular risk factors, medication use, medical conditions, and other correlated negative emotions. Anxiety, hostility, and anger were unrelated to IMT. Stewart et al. (27) have

measured IMT to determine the relationship between hostility and carotid atherosclerosis and found that there was a significant relationship between hostility and greater subclinical atherosclerosis not explained by traditional risk factors in middle-aged women. Evenson-Rose et al. (28) also reported on the relationship between cynical hostility and carotid atherosclerosis in American, white women from the SWAN Heart Study. They found that hostility is related to small but significantly greater subclinical athersoclersosis in middle-age women. Even after adjusting for race, education, body mass index, resting systolic blood pressure, and smoking, the association remained significant at a $P \leq .01$. Others studies support that men and women who were high on hostile attitudes had increased IMT readings (29, 30). Matthews et al. in 1998 (29) reported that women who held their anger in as opposed to expressing it in an outward fashion were more likely to have increased IMT and carotid plaque. Lastly, Paterniti et al. (31) reported that men and women who had persistent anxiety with elevated anxiety scores had a greater increase in IMT across 4 years.

Thus far, there has been little attention paid to investigating the psychological risk factors as predictors of cardiovascular disease (measuring IMT) in women with PCOS. This study seeks to examine psychological factors as predictors of IMT over a 5 year follow-up. The aim of this study is to examine whether the psychological factors (depression, state anger and anxiety, hostility/cynicism, and satisfaction with life) act as a risk factor for IMT independent of baseline cardiovascular risk factors.

11.0 METHODS

11.1.1 Subjects

Women with PCOS were originally identified from the practice records of physicians in the Division of Reproductive Endocrinology at Magee-Women's Hospital between 1970 and 1990. A clinical diagnosis of PCOS was made if there was: (1) a history of chronic anovulation in association with (2) clinical evidence of androgen excess (hirsutism) or biochemical evidence of an elevated total testosterone concentration (>2.0 nmol/L), or with (3) a ratio of luteinizing hormone to follicle-stimulating hormone of > 2.0. A total of 244 cases and 244 controls from the Cardiovascular Health and Risk Measurement (CHARM I) study by Talbott et al. (32) agreed to a clinical assessment of their hormonal and cardiovascular status. Voter registration tapes and household directories were used to identify the 244 age-matched control women. Detailed data collection and laboratory methodologies have been previously published (32). In the second phase of the CHARM study, Talbott et al. investigated whether the increase in cardiovascular risk factors noted four years earlier would now manifest in increased subclinical carotid atherosclerosis measures in carotid IMT (CHARM II). PCOS cases and controls who were ≥30 years were eligible for CHARM II. A total of 335 subjects,, cases (n=175) and controls (n=160), participated (75% of eligible). Of the 335, a total of 196 had both baseline data (including psychological data) and subsequent IMT measurement on follow-up (1996-1999) (3).

11.1.2 Covariates

Covariates considered included age and race. These variables were used for matching in the original study. Body composition variables were BMI and average waist measurements. BMI was chosen to represent weight. History of hormone use and smoking history were included. Systolic blood pressure and the following lab values were evaluated: LDL, Hdl, Insulin, Testosterone, Triglycerides, Cholesterol, and Glucose. Details of the blood analyte, blood pressure, and anthropometrics have been published elsewhere (3). Psychological variables were depression, anger, anxiety, hostility, and satisfaction with life

11.1.3 Carotid Ultrasound Protocol

A detailed description of the carotid ultrasound protocol for measuring intima–media thickness has been published (2000). A Toshiba SSA-270A scanner equipped with a 5-MHz linear array imaging probe was used. Sonographers scanned the right and left common carotid artery, carotid bulb, and the first 1.5 cm of the internal and external carotid arteries. For each location, the sonographer imaged the vessel in multiple planes and then focused on the interfaces required to measure IMT and also on any areas of focal plaque. The best images were digitized for later scoring. Trained readers measured the thickness of the intima and medial layers of the vessel wall across 1-cm segments of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and the internal carotid artery on both right and left sides. Measures from each location were then averaged to produce an overall measure of carotid IMT. A computerized reading program developed for the Cardiovascular Health Study and modified in Pittsburgh was used. Sonographers also scored the ultrasound images for plaque in the common

carotid, carotid bulb, internal carotid, and external carotid. Plaque was defined as a distinct area protruding into the vessel lumen with at least 50% greater thickness than the surrounding areas. Reproducibility of carotid IMT was assessed in 5 women who underwent 2 ultrasound examinations within 1 week. Two separate sonographers scanned these women; 2 readers also scored each scan. When accounting for sonographer and reader variation, the intraclass correlation was 0.86 for IMT.

11.1.4 Standardized Psychological Measures

Depression Assessment: The Beck Depression Inventory I (BDI I) (33) is a self-report inventory measuring characteristic attitudes and symptoms of depression. It contains 21 questions with a cutoff of >9 (total score) to identify potential clinically significant symptoms of depression. The psychometric properties of the BDI have been reported as high with internal consistency ranging from .73 to .92 with a mean of .86. The split-half reliability coefficient reported was .93. Concurrent validity was determined by correlations with clinician ratings of depression using the revised BDI and ranged from .62 to .66.(34). The BDI was previously tested on the PCOS population (35, 36) and in other research studies on women with obesity that may be applicable to the PCOS population, being that obesity is a central feature of PCOS.

Anxiety and Anger Assessments: The Spielberger Trait Anger/Anxiety Scales are components of the State-Trait Personality Inventory by Spielberger (37) (2 of 6 subscales). For reliability testing, alpha coefficients ranged from .80 to .87 and provide evidence for internal consistency of the six STPI scales (38). Overall reliability testing was also done to determine an internal consistency (alpha coefficient = .81-.87) (39). Cronbach alphas were .82-.85 and..80-.85 for anger and anxiety.

Hostility/Cynicism Assessment: This 13 item scale derived from the Cook-Medley Hostility Scale (40) and measures cynical attitudes and hostile feelings and behaviors rather than overt expressions of anger and aggression. Higher scores indicate greater hostility (range 9-13). Cronbach's alpha for the scale was .79 indicating good internal consistency.

Diener Satisfaction With Life Scale: This scale(41) measures the judgmental component of subjective well-being. It is comprised of 2 major components: the emotional or affective component and the judgmental or cognitive component. The scale consist of 5 questions with a 7 point likert scale ranging from strongly disagree to strongly agree.

A higher score reflects a greater satisfaction with life. Test-retest reliability was .84 (41). While brief, this instrument offers as high or higher predictive validity than several longer measures of life satisfaction.

11.1.5 Statistical Analysis

Statistical analyses were performed by using SPSS (version 15.0). The baseline risk factors were collected during the 1993 to 1994 clinic visit to represent CVD risk status at that time point. Demographic, hormonal, and all laboratory and psychological data were available for analysis from the original sample previously described (32).

Results are presented for 196 women with IMT measurements and psychological data. Descriptive statistics inclusive of measurement of central tendency and dispersion were computed for PCOS cases and controls. The t test for independent samples (for continuous data) or chi square tests (for categorical data) were used to detect differences in means (± SD) or proportions, respectively, between cases and controls.

Linear regression modeling was used to identify the independent baseline psychological factors that predicted IMT, the dependent continuous variable. Baseline cardiovascular risk variables were used as covariates to represent cardiovascular disease. They included age, race, BMI, Hdl, systolic blood pressure, triglycerides, glucose, and insulin. Carotid IMT levels were stratified by age and BMI to better assess the confounding effects of age and BMI on IMT. Psychological predictors of IMT in these analyses included depression, anger, anxiety, hostility/cynicism, and satisfaction with life and were assessed with individual linear regression models. All regression analyses were conducted by the linear regression module in SPSS. BDI was forced into the model as it was the main psychological predictor of interest. The regression models were constructed for the total population and for subgroups stratified by age, <45 and ≥ 45 years.

12.0 RESULTS

A total of 196 subjects, 93 PCOS cases and 103 controls, underwent carotid ultrasound scanning. The baseline sociodemographic factors in PCOS cases and controls obtained during the initial clinic visit (1992-1994) are presented in **Table 12-1**. Cases and controls were similar in most characteristics, except for age, parity, and marital status. Controls were slightly older than cases (38.5 versus 36.4 years, respectively), which may have been a result of the unmatching of the groups from the initial study. As well, not all of the original cases and controls had IMT measurements. Cases had fewer pregnancies as often seen in PCOS cases due to infertility issues. No difference was found in menopausal status, as a result of the small numbers of women who experienced natural or surgical menopause.

Baseline psychological characteristics are shown in **Table 12-2**. Consistent with recent findings (Cipkala-Gaffin et al. 2009) (18) by earlier analyses on 161 cases and 161 controls from the same population, BDI ratings differed between groups, P<.014. When comparing the categories for symptoms of depression, PCOS cases rated higher in all categories than controls: Mild, 26% versus 11.7%; Moderate, 5.4% versus 2.9%; Severe, 1.1% versus 0, respectively, P<.038. The remaining psychological characteristics were similar between cases and controls.

Selected cardiovascular risk factors are seen in **Table 12-3**. Similar to previous findings, significant differences (P<.001) were noted in several baseline characteristics including BMI, waist measurement, HDLt, Insulin, triglycerides, and total testosterone. Systolic blood pressure

and glucose was marginally significant (P<.081 and P<.071, respectively). Diastolic blood pressure, cholesterol, and LDLc were not significant. Results were similar for the original cohort study of 244 cases and controls (Talbott et al., 1995) (32) and for the subsequent study of 125 PCOS cases and 142 controls ≥ 30 years of age (Talbott et al., 2000) (3).

To control for possible confounding, age and BMI adjusted analyses were performed. The mean adjusted values for each of the biochemical parameters are reported. Again, the results were similar, except that waist measurement was no longer significantly different between the cases and controls.

Overall, no significant differences in carotid IMT were noted between cases and controls for the total group (P=.261). (**Table 12-4**) However, subgroup analyses by age revealed different results. The mean BMI for PCOS cases and controls was significantly different, P<.001, with cases having higher BMI (30.3±8.7 versus 26.8±6.4 respectively). Among cases, those ≥ 45 years of age had a BMI of 32.9±9.6 versus 29.0±8.0 in the <45 group, P <.044. Therefore, IMT was adjusted for age and BMI. Adjusted IMT means for cases and controls < 45 years of age were not significantly different for BMI <26 (P=.629) and BMI ≥ 26 (P=.694). In the age group <45, no significant differences were noted. However, in the older women ≥45 years, PCOS cases had significantly greater IMT readings than did controls (.790±.196 versus.708±.084mm, respectively, P <.042). These findings were consistent with the overall study of 335 cases and controls and reflects the overall reasonable representation of this smaller subgroup of 196.

For the older age group, ≥ 45 years of age, again there were no differences between cases and controls for those with BMI <26 (P=.996). However, for the women ≥ 45 with a BMI ≥ 26,

there was a borderline significant difference between cases and controls, P=0.54. This may be explained in part due to the greater BMI within cases, as is usually seen in PCOS women.

Univariate analyses were performed in order to select significant variables. (**Tables 12-5, 12-6)** Multiple linear regression models (**Table 12-7**) were carried out to assess the independent effect of the psychological variables on IMT, adjusted for age, BMI, and cardiovascular risk factors found to be associated with IMT in the univariate analyses (HDL, systolic blood pressure, triglycerides, glucose, and insulin). BDI was forced into the model as it was significantly different between cases and controls.

The cardiovascular risk factors, age, BMI, and systolic blood pressure showed themselves to also be consistent significant predictors of IMT in most models for the total sample. However, when the sample was stratified by age groups, age and systolic remained consistently significant, but BMI did not for the group <45. For the ≥ group age was the only consistent predictor.

In the final model for the total sample, PCOS, age, and BMI were both significant in predicting IMT, (P<..005; P<.001; P< .023 respectively). Systolic blood pressure was borderline significant p=.073 whereas BDI was not significant. There was an interaction between PCOS and age, P< .003.

In the final model for the age group < 45 years of age, only age and systolic blood pressure were significant predictors for IMT, P<.002 and P<.042 respectively. In the final model for the age group ≥ 45, only age was a significant predictor of IMT, P<.004.

Even though PCOS and BDI were not significant in the final models for the total group and for the 2 stratified age groups, age was consistently a significant predictor of IMT. Further, the cardiovascular risk factors, BMI, and systolic blood pressure showed themselves to also be significant predictors of IMT in the three different models.

Table 12-1 Baseline Sociodemographic Factors in PCOS Cases and Controls

Variables	PCOS (n= 93)	Controls (n=103)	P
Age	36.4 ± 6.4	38.5 ± 6.9	< .018
Race			
White	94.6%	99.0%	.776
Other	5.4%	1.0%	
Education	14.3 ± 1.9	14.6 ± 2.0	.441
Married y	82.8%	65.0%	<.006
Current Smoking % y	23.7%	17.5%	.284
OC % y	21.5%	22.3%	.776
Hormones % y	14.0%	14.6%	.907
Parity	1.0 ± 1.1	1.6 ± 1.3	<.000
Reported no periods % y	(10)10.8%	(11)10.7%	.987
Age when stopped periods	32.0 ± 8.8	37.4 ± 8.4	.177
Menopausal status			
Natural	1 (1.1%)	1(1.0%)	.303
Surgical*	6 (6.5%)	9 (8.7%)	

Values are means and ± SD or percentages
OC = Oral Contraceptive
Menopausal status, y = still having periods
** surgical menopause = total hysterectomy and bilateral oophorectomy (questionnaire states surgical, uterus and/or ovaries removed)

Table 12-2 Baseline Psychological Characteristics in PCOS Cases and Controls

Variables	PCOS (n= 93)	Controls (n=103)	P
BDI Ratings	7.6 ± 6.8	5.4 ± 5.0	<.014
Missing	4.3%	4.9%	
Normal	62.4%	80.6%	<.038
Mild	26.9%	11.7%	
Moderate	5.4%	2.9%	
Severe	1.1%	0	
Anger *	8.5 ± 4.0	8.1 ± 3.5	.468
Anxiety *	9.6 ± 5.8	8.5 ± 5.1	.167
Hostility/Cynicism **	7.9 ± 2.9	8.5 ± 2.5	.167
Satisfaction with Life †	24.2 ± 6.7	24.3 ± 6.3	.875

Values are means and ± SD or percentages
* missing = 10
** missing =11
† missing = 4

Table 12-3 Selected Risk Factors in PCOS Cases and Controls of Similar Age 1992-1994 Adjusted for Age and BMI

	Cases (n= 93)		Controls (n=103)		
		Adjusted		Adjusted	Unadjusted
Variables	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	P
BMI	30.3±8.7	NA	26.8±6.4	NA **	<.001
Waist cm	91.7±20.0	88.4±1.3	81.8±18.9	85.0±1.2	<.001
SBP,mm Hg	114.6±14.9	113.2±1.2	111.0±13.0	112.3±1.7	.081
DBP,mm Hg	72.8±11.2	71.8±0.9	70.8±8.4	71.7±0.9	.162
CHOL, mg/dl	192.5±26.8	191.9±3.4	186.3±35.9	186.8±3.2	.184
LDLc, mg/dl	117.5±27.8	116.5±3.2	113.8±32.7	114.4±3.1	.399
HDLt,mg/dl	49.85±14.65	51.0±1.5	56.58±14.14	55.7±1.4 †	<.001
Insulin,µU/ml	25.5 ± 23.6	23.2±1.8	14.2±10.0	16.3±1.7*	<.001
TRI. Mg/dl	125.5± 80.1	122.3±6.3	79.7±39.1	83.3±6.0 **	<.001
Total T, nmol/dl	1.7±1.2	1.7±0.1	1.1±.5	1.1±0.1**	<.001
Glucose	97.1±27.3	96.0±3.0	89.7±29.4	90.9±2.8	<.071

Adjusted for age and BMI
**Adjusted P<0.001;* P<.05;† P<.026;
Missing
1= CHOL; LDLc; HDLt; TRI; Glucose
2=BMI; Total T;
3= SBP; DBP;
7=Waist cm
21=Insulin

Table 12-4 IMT Results in PCOS Cases and Controls

Variables	n	PCOS (n= 93)	Controls (n=103)	P
IMT total	196	.697 ± .142	.678 ± .088	.261
<45*	125	(n= 63) .655 ± .083	(n=62) .659 ± .006	.779
≥45y	70	(n=29) .790 ±.196	(n=41) .708 ± .084	<.042

Values are means and ± SD
* 1 case missing

Table 12-5 Univariate Linear Regression Results of IMT and Baseline CHD Risk Factors

	Total				Age<45				Age≥45			
	n	β	SE	P	n	β	SE	P	n	β	SE	P
PCOS	196	-.019	.016	.247	125	.004	.013	.779	70	-.082	.034	.020
Age	196	.007	.001	.000	125	.006	.001	.000	70	.007	.005	.132
Race	196	-.012	.030	.684	125	-.010	.023	.659	70	.009	.074	.901
BMI	194	.005	.001	.000	123	.003	.001	.002	70	.006	.002	.003
Hormone	196	.006	.023	.793	125	.016	.018	.381	70	-.061	.058	.293
Smoking	196	.003	.010	.723	125	-.004	.008	.580	70	.013	.020	.530
LDL	195	.000	.000	.091	125	.000	.000	.135	69	.001	.001	.256
HDL	196	-.003	.001	.035	119	-.001	.001	.238	66	-.004	.002	.127
SBP	193	.003	.001	.000	122	.002	.000	.000	70	.003	.001	.005
DBP	193	.003	.001	.000	122	.002	.001	.001	70	.003	.002	.060
Insulin	175	.001	.000	.035	110	.001	.000	.087	64	.002	.001	.081
Waist	189	.002	.000	.000	120	.001	.000	.000	68	.002	.001	.015
Testosterone	194	-.002	.009	.818	123	.006	.007	.377	70	-.007	.018	.725
Trig	195	.000	.000	.002	125	.000	.000	.255	69	.001	.000	.016
Chol	195	.001	.000	.030	125	.000	.000	.192	69	.001	.001	.114
Glu	195	.001	.000	.018	125	-3.50	.000	.892	69	.001	.001	.152

IMT was measured in 1995-1997 and baseline risk factors were measured in 1992-1994

Table 12-6 Univariate Linear Regression Results of IMT and Baseline Psychological Variables

	Total				Age<45				Age≥45			
Depression	187	.002	.001	.148	121	.001	.001	.174	65	.003	.003	.331
Anger	186	.002	.002	.363	119	.003	.002	.106	66	.003	.006	.617
Anxiety	186	.002	.002	.259	118	.001	.001	.305	67	.003	.003	.416
Hostility	185	-.001	.003	.744	117	.001	.003	.783	67	-.002	.006	.793
Satis w life	192	-.002	.001	.054	123	-.002	.001	.025	68	-.002	.003	.572

IMT was measured in 1995-1997 and baseline risk factors were measured in 1992-1994

Table 12-7 Multiple Linear Regression Models of Effect of PCOS on IMT Adjusted for Age and Selected Risk Factors

	TOTAL				<45y				≥ 45y			
	n	β	SE	P	n	β	SE	P	n	β	SE	P
PCOS	187	0.001	0.017	0.516	121	-0.010	0.013	0.432	65	0.076	0.038	.052*
BDI		0.002	0.001	0.193		0.002	0.001	0.146		0.001	0.003	0.467
PCOS	195	0.030	0.015	0.041	125	-0.003	0.013	0.828	70	0.098	0.034	0.005
Age		0.007	0.001	0.001		0.005	0.001	0.001		0.012	0.005	0.014
PCOS	193	0.016	0.014	0.281	123	-0.009	0.012	0.473	70	0.063	0.034	0.072
Age		0.007	0.001	0.001		0.006	0.001	0.001		0.014	0.005	0.004
BMI		0.004	0.001	0.001		0.003	0.001	0.001		0.006	0.002	0.007
PCOS	192	0.014	0.014	0.321	122	-0.011	0.012	0.378	70	0.062	0.035	0.079
Age		0.007	0.001	0.001		0.005	0.001	0.001		0.013	0.005	0.010
BMI		0.003	0.001	0.015		0.001	0.001	0.164		0.005	0.003	0.062
SYS BP		0.001	0.001	0.020		0.001	0.001	0.008		0.001	0.001	0.430
PCOS	173	0.017	0.016	0.278	109	-0.008	0.013	0.535	64	0.057	0.039	0.152
Age		0.007	0.001	0.001		0.006	0.001	0.001		0.013	0.005	0.015
BMI		0.003	0.001	0.037		0.001	0.001	0.338		0.005	0.003	0.113
SYS BP		0.002	0.001	0.018		0.002	0.001	0.001		0.001	0.002	0.351
Insulin		0.001	0.001	0.777		4.98	0.001	0.9		-9.58	0.001	0.943
PCOS	191	0.014	0.015	0.332	122	-0.011	0.012	0.376	69	0.006	0.037	0.078
Age		0.007	0.001	0.001		0.005	0.001	0.001		0.014	0.005	0.008
BMI		0.003	0.001	0.037		0.001	0.001	0.209		0.004	0.003	0.150
SYS BP		0.002	0.001	0.017		0.001	0.001	0.008		0.001	0.001	0.332
HDI		0.001	0.001	0.782		-5.87	0.001	0.903		0.001	0.001	0.724
PCOS	191	0.011	0.015	0.459	109	-0.010	0.013	0.446	69	0.058	0.039	0.141
Age		0.007	0.001	0.001		0.005	0.001	0.001		0.013	0.005	0.010
BMI		0.002	0.001	0.034		0.156	0.001	0.001		0.004	0.003	0.155
SYS BP		0.001	0.001	0.026		0.002	0.001	0.008		0.001	0.001	0.360
TRI		9.49E	0.001	0.434		-3.53	0.001	0.749		0.001	0.001	0.504
PCOS	183	0.001	0.015	0.454	118	-0.015	0.012	0.212	65	0.065	0.038	0.090
Age		0.007	0.001	0.001		0.005	0.001	0.001		0.013	0.005	0.016
BMI		0.003	0.001	0.026		0.001	0.001	0.263		0.005	0.003	.058*
SYS BP		0.001	0.001	0.056	*	0.001	0.001	0.034		0.001	0.001	0.497
BDI		0.001	0.001	0.388		0.001	0.001	0.248		0.001	0.003	0.964
PCOS	183	-0.254	0.090	**0.005**	118	-0.047	0.098	0.635	65	-0.771	0.496	0.125
Age		0.010	0.002	**0.001**		0.005	0.002	**0.002**		0.022	0.007	**0.004**
BMI		0.003	0.001	**0.023**		0.001	0.001	0.250		0.005	0.003	**.064***
SYS BP		0.001	0.001	**0.073**	*	0.001	0.001	**0.042**		0.001	0.001	0.462
PCOS*Age		-0.006	0.002	**0.003**		0.001	0.003	0.747		-0.017	0.010	0.096
BDI		0.001	0.001	0.424		0.001	0.001	0.253		0.001	0.003	0.886

*borderline

13.0 DISCUSSION

This study was the first reported to examine whether psychological factors, independent of cardiovascular risk factors, predict IMT in women with PCOS. Although in this sample of women with PCOS, none of the psychological variables measured (depression, anger, anxiety, hostility/cynicism, and satisfaction with life) predicted IMT independent of traditional CVD risk factors, there were some noteworthy findings. First, depression at baseline for PCOS cases was significantly different compared to controls (P<.014). In particular, for the group ≥45 years of age (P<.039) with PCOS, cases scored higher on this dimension. The findings are consistent with previous studies (18, 21, 22, 36, 42) that were done reporting that PCOS women have an increased risk of depressive disorders. Hollinrake in 2007 (22) found that women with PCOS were at an increased rate for newly diagnosed depression compared with controls (OR 5.11). A longitudinal study by Kerchner 2008 (42) investigating the risk of depression over time found that over 1-2 years the prevalence rate for depression increased from 40% to 56% in PCOS cases.

An explanation for the lack of relationship between baseline depression scores and IMT can be due to the possibility that the PCOS cases may have adapted over time to their diagnosis of PCOS or could have been treated for depression with medications or psychotherapy. Additionally, IMT was only measured once on follow-up several years later and was represented at baseline by cardiovascular risk factors. Finally, depression was not measured at the follow-up time with IMT.

Depression has been associated with subclinical atherosclerosis in various studies (24, 43, 44). Post hoc analyses (44) investigating negative emotions in the 3 year progression of

subclinical atherosclerosis reported that the somatic-vegetative symptoms of depression (P<.002) were positively associated with intima-media thickness. In another study (44) measuring lifetime history of major depression, subclinical atherosclerosis, and IMT in middle-aged women, it was found that women with recurrent major depressive episodes were more than twice as likely to have plaque on carotid ultrasonography than women with no history of major depression. Moreover, a single major depressive episode or current depressive symptoms were not associated with an increased risk of plaque. These findings are relative to the null findings in the present study, as depression was only measured (screened with the BDI) at baseline, and it was not determined whether patients had recurrent depressive episodes or how severe the clinical depression was.

Other negative emotions, state anger and anxiety and hostility/cynicism, were explored and found not to be predictive of IMT readings independent of the cardiovascular factors. These results are similar to what was reported by Stewart et. al (44) in women ages 50-70 years of age. Except for depression, anxiety, anger and hostility were not predictors of atherosclerotic progression over a 3 year period. Yet, over the past 20 years, the literature supports the fact that hostility is an independent risk factor for CHD and all-cause mortality (45). Others investigated hostility scores and high trait anger associated with subclinical atherosclerosis. In a 10 year follow up study by Matthews in 1998 (46), with a sample of 200 postmenopausal women, high hostility scores and high trait anger and anger-in were associated with the extent and severity of carotid atherosclerosis. In this same study, baseline levels of trait anxiety were not related to mean levels of carotid IMT. More recently, in the Study of Women's Health Across the Nation (SWAN) Heart Study, Everson-Rose and colleagues (28) found that in age and site adjusted models that each 1 point increment in hostility score predicted a significant 0.0057-mm higher

mean IMT (P<.0001) and 0.0081-mm higher maximum IMT (P<.0001), effects that were identical in magnitude to each 1 year increment in age. In this study, the one time measurement of state anxiety and anger may not have been an adequate representation of the psychosocial variables and certainly over the follow-up time period of approximately 4 years these 2 characteristics could have changed, thus affecting their association with IMT. Similarly, the hostility/cynicism ratings could have been biased by when the subjects were diagnosed with PCOS, as they may have gone through various coping stages and adapted to their disease process.

The null findings for satisfaction with life as a predictor of IMT are not surprising given the nature of the measure. The Diener Scale is a global measurement of satisfaction with life. Further, this instrument was not tested on the PCOS population. Since the development of this tool, other measures that are specific to the measurement of quality of life for the PCOS population have been reported, such as The Polycystic Ovary Syndrome Health-Related Quality of Life (PCOSQ) (47). Using population tested measures would most likely yield more accurate results. Further, it was surprising that there were no differences exhibited by the other psychological variables. This could be explained by the fact that the original study was not designed to measure the relationship between psychological variables and IMT.

The regression analyses, intended to explain whether the psychological variables, independent of cardiovascular risk factors, predicted IMT, resulted in all negative findings. Depression, measured by the BDI, was the major focus given the baseline findings showing significant differences between cases and controls (P<.014), with cases having higher depression ratings. In all of the models, BDI did not show to be a significant predictor of IMT, independent of the selected cardiovascular risk factors.

In the final model including PCOS, age (at IMT reading), BMI, systolic blood pressure, PCOS*age and BDI forced into the model, the variables, age, BMI, systolic blood pressure and the interaction between PCOS and age were significant predictors of IMT for the total sample. In previous studies (14, 250), BMI has been associated with increased subclinical atherosclerosis. In a study by Talbott et al. 2000 (14), IMT was greater in thin and heavy women with PCOS compared with controls of similar size.

In the group aged < 45 years, age and systolic blood pressure were significant predictors of IMT in the final model, whereas BMI was not. Because age and blood pressure were significant, there are clinical implications for the younger group. PCOS women at a younger age and with elevated blood pressure readings may be at higher risk for subclinical cardiovascular disease as previously supported by Talbott et al. (14).

The older aged group, ≥ 45 years, consistently showed age as a predictor for IMT in all models, which would be expected as IMT would increase over time. For the final model, only age was significant whereas BMI was borderline significant as a predictor of IMT. The findings for BMI are surprising as one would think that BMI would increase with age in this population. On the other hand, the mean age for cases and controls were 36.4 ± 6.4 and 38.5 ± 6.9, respectively, indicating that they were early in the menopausal transition and thus may not have had weight increases.

There are many strengths to this study despite the null findings. The original sample from which this cohort was obtained was from random digit dialing chosen and matched on age, race, and neighborhood. A reliable technique for assessing subclinical cardiovascular disease, B-mode ultrasonography was utilized. All of the psychological measures were reliable and valid and the BDI was previously used in other studies with PCOS women (18, 19).

Limitations of the study included the need to unpair the PCOS cases and controls in order to preserve the greatest number of subjects who had IMT ratings and psychological data. Because the original study was not intended to measure the relationship between the psychological variables as predictors of IMT, follow up (repeated measures of the psychological characteristics) was not included in the design. Lastly, a baseline measurement of IMT would have been useful instead of utilizing the cardiovascular risk factors in its place.

There are significant research and clinical implications from this study. First, it is evident that PCOS women are at risk for a multitude of reasons ranging from infertility to obesity, diabetes, changes in body image, metabolic syndrome, hormone disturbances, diabetes, and cardiovascular disease. These comorbid factors tend to aggravate depression. Further research to identify women who are depressed is essential, beginning at diagnosis and through repeated measures during their course of treatment. Diagnostic research tools such as the Primary Care Evaluation of Mental Disorders (PRIME-MD) (49) and the Patient Health Questionnaire (PRIME-MD PHQ), which is a four-page self administered version of the PRIME-MD, was validated for use in gynecology outpatients (49). The PRIME-MD PHQ and other screening measures such as the BDI are time efficient and useful in identification and the prevention of depression. Utilizing these assessment measures could decrease the progression of depressive symptoms into a clinical depression. In all, additional research is needed, incorporating the psychological variables, depression, anxiety, anger, hostility/cynicism, and satisfaction with life, to further determine whether there is an association to subclincial cardiovascular disease in this vulnerable PCOS population.

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14.0 GENERAL DISCUSSION

14.1 SUMMARY OF FINDINGS

The objective of this dissertation was to evaluate the psychosocial and socio-demographic factors associated with Metabolic Syndrome and cardiovascular risk in Polycystic Ovary Syndrome cases and controls (women without PCOS).

Research Paper 1: Women with PCOS had a higher prevalence of depression, 31% versus 17%, than controls at a mild level of depression. The difference between cases and controls for the BDI scale was statistically significant. Within cases, BMI, education, and parity were statistically significant predictors of depression ($p<.05$). The odds of being depressed, of at least a mild severity, increased by 6% for each unit increase of BMI, the odds of being depressed decreased by 20% for each year of education and increased by 44% for parity (*per live birth*). The odds of having PCOS (for the entire sample) increased with each unit of BDI score by 1.06 times, when adjusting for marital status, BMI, smoking, and education. These results have clinical implications in the comprehensive treatment of PCOS patients. Psychological evaluations of patients at diagnosis and repeated throughout their lifetime are indicated to prevent, identify, and provide treatment for those women who present with depressive symptoms.

Research Paper 2: Twenty-seven percent of the cases and 9.9% of the controls had MS. Age was statistically significant between cases and controls. Additionally, differences between controls, with and without MS, for education were statistically significant.

Although on univariate analyses, BDI was borderline associated with MS, only PCOS and age were significant predictors for MS when BDI was forced into the model. The odds of having MS increased by 10% for each year increment of age and threefold for PCOS cases. Within the subjects who had a BMI>30, the odds of having MS increased by 3% for each year increment of age. These results highlight the need to target individuals with PCOS, increased BMI > 30, and MS to receive psychological evaluations to screen for possible mental health problems.

Research Paper 3: *Research Paper 3*: there was no significant effect of any of the psychological factors (depression, state anger and anxiety, hostility/cynicism, and satisfaction with life), independent of baseline cardiovascular risk factors, on IMT. Age was a consistent predictor of IMT in regression analyses. For the total group PCOS, age, BMI, and PCOS* age were predictors of IMT. Systolic blood pressure was a borderline significant predictor. For the group ≥ 45, age and BMI (borderline) were predictors of IMT. Age and systolic blood pressure were significant predictors in women <45 of IMT. Even though there were null findings from this study, clinical implications are still apparent. It is well known that there is an association between subclinical cardiovascular disease and negative emotional states (depression, state anger and anxiety, and hostility/cynicism) which warrants psychological evaluations in PCOS women in order to prevent the incidence of psychiatric disorders in this population.

PSYCHOLOGICAL FACTORS AND PCOS

It is clear that the psychological ramifications of PCOS are problematic for the women who are diagnosed with the condition and throughout their life. There is a myriad of stressors with PCOS that can lead to possible mental health problems including chronic anovulation, hursutism, acne, obesity, infertility, baldness, DiabetesII, and cardiovascular disease. Only recently, are the psychological issues in PCOS being addressed. The area of depression seems to be the most reported consequence of the stress of PCOS. It is implicit that the plan of medical care for women with PCOS include a psychological component to ensure that excellent comprehensive care is available to women with PCOS.

PUBLIC HEALTH SIGNIFICANCE

Women are twice as likely than men in the general population to be diagnosed with depression. Thus, women with PCOS become even more susceptible to depression. Women with PCOS should be screened on diagnosis and monitored closely for depression, a major public health problem, which can affect their level of functioning and increase their overall burden of disease.

Metabolic syndrome has been related to premature coronary heart disease. PCOS women have three times the prevalence of MS and should be monitored for a reduction in CHD risk factors as well as for lifestyle modification. Early identification of depressive symptoms could possibly decrease the prevalence of characteristics of MS such as obesity, which is epidemic.

PCOS women should be monitored for weight and encouraged to make lifestyle changes i.e. nutrition and exercise**.**

This research has shown that women with PCOS, aged ≥ 45 years, had significantly greater mean IMT than did controls. Prevention and screening for subclinical cardiovascular disease is important to decrease the risk of cardiovascular disease in all PCOS women.

FUTURE RESEARCH

Further research to identify women with PCOS who are depressed is essential, beginning at diagnosis and through repeated measures during their course of treatment. Appropriate diagnostic research tools such as the Primary Care Evaluation of Mental Disorders (PRIME-MD) and the Patient Health Questionnaire (PRIME-MD PHQ) should be considered when screening for mental health disorders. The PRIME-MD PHQ and other screening measures such as the BDI are time efficient and useful in identification and the prevention of depression in PCOS women as has been shown in previous research studies.. Utilizing these assessment measures could possibly decrease the progression of depressive symptoms into a clinical depression. In all, additional research is needed, incorporating the psychological variables, depression, anxiety, anger, hostility/cynicism, and satisfaction with life, to further determine whether there is an association to metabolic syndrome and subclinical cardiovascular disease in this vulnerable PCOS population.

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