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ON IDENTIFYING POLYCYSTIC OVARY SYNDROME IN THE CLINICAL DATA WAREHOUSE AT BOSTON MEDICAL CENTER

by

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ABSTRACT

Introduction

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenemia, oligo-anovulation, and numerous ovarian cysts. Although the most common cause of female factor infertility, its characteristics and metabolic risks are difficult to study due to its heterogeneity. Additionally, ethnic-specific data is scarce. Hospital electronic medical records and the diverse patient population at Boston Medical Center (BMC) may provide an avenue for investigating the longitudinal nature of PCOS and its race-specific characteristics.

Objectives

1. Describe the Clinical Data Warehouse (CDW) dataset available for studying PCOS.

2. Develop an automated method for extracting ovarian features from written ultrasound reports.

3. Identify PCOS patients from their record of the three cardinal PCOS features.

Methods

Patients evaluated on at least one of the three cardinal PCOS features, between October 1, 2003 and September 30, 2015 were queried from the BMC CDW. This thesis describes methods for cleaning the data, as well as the development of an ultrasound classifier based on natural language processing techniques.

Results

On a validation set of 1000 random ultrasounds, the automatic ultrasound classifier had a recall and precision for the presence of PCOM, 99.0% and 94.2%, respectively. Overall, 2421 cases of PCOS were identified, with 1010 not receiving a diagnosis. Black patients had twice the odds of being underdiagnosed compared to White patients (OR: 2.09; 95% CI: 1.69–2.59).

Conclusions

Ascertaining PCOS through the medical record offers advantages over self-reported PCOS, including documentation of disease and recorded measurements. In the future, this PCOS dataset can be used in conjunction with cardiovascular and metabolic outcomes for developing a predictive model.

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List of Abbreviations

5α-RA	5α-reductase
AE-PCOS	Androgen Excess and PCOS Society
AMH	anti-Müllerian hormone
BMC	Boston Medical Center
CDW	Clinical Data Warehouse
DHT	dihydrotestosterone
EMR	electronic medical record
FAI	free androgen index
IGF-1	insulin-like growth factor 1
LOD	limit of detection
MBS	metabolic syndrome
mFG	modified Ferriman-Gallwey
PCOM	polycystic ovary morphology
PCOS	polycystic ovary syndrome
SHBG	sex hormone-binding globulin
WHO	World Health Organization

Chapter 1

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous metabolic and reproductive disorder that affects between 5% and 15% of reproductive-aged women [15]. It is characterized by hyperandrogenism, oligo-anovulation, and enlarged, polycystic ovaries. Women who suffer from PCOS are at an increased risk of insulin resistance, obesity, dysfunctional uterine bleeding, and cardiovascular disease [126]. PCOS is currently a leading cause of female factor infertility, yet the difficulty in its diagnosis and maintenance of long-term follow up for its longitudinal health risks make it challenging to study [101]. As a result, the disease etiology is unknown, although some investigators have proposed that the primary defect is increased androgen production in ovarian theca cells [12, 111, 112].

The syndrome is difficult to study in part because the it requires diagnosis through blood tests, ultrasound tests, and high quality menstrual data. Additionally, it is a disease of exclusion, meaning that other endocrinopathies must be ruled out of consideration first before a diagnosis can be made [15, 126]. Further complicating its study, retrospective identification seems to be of limited use: Clark et al. found in 2016 that specificity of self-reported concern for PCOS features was rather low; among 126 women who believed they had outward features of PCOS, only 53% of the women met the NIH criteria, 70% met the Rotterdam criteria, and 62% met the AE-PCOS criteria [31]. Blood and laboratory tests require a large commitment from participants, and self-reported (retrospectively

obtained) menstrual cycle data is often inaccurate [134]. As a result, previous prevalence studies, which often recruit subjects from infertility clinics, are based on subgroups not necessarily representative of the general population [104].

Little is known about race-specific PCOS characteristics, since most previous studies of metabolic syndrome (MBS) in PCOS have study populations composed of over 90% white women. As a result, race- and ethnic-specific cutoffs for the diagnostic criteria have not yet been proposed. Furthermore, medically underserved women and those of low socioeconomic status may not have access to the resources for treating PCOS, since the disease traditionally falls under the domain of a reproductive endocrinologist/infertility specialist, whose services the women may not be able to afford [1, 70, 95, 106, 141]. The diverse patient population serviced by Boston Medical Center (BMC) may provide insight into the race-specific characteristics of the disease.

On the other hand, hospital-based electronic medical records (EMRs) provide an avenue for investigating the longitudinal nature of PCOS [75]. Due to their inherent origin in natural clinical process, the cost of collecting the data is lower than large-scale epidemiological studies. The trade-off is that they are a convenience sample[1], and care must be taken in generalizing results to the general population. Still, depending on how the data is queried from the database, they may be representative of the clinical population at that hospital and may offer insights into clinical practice at that location.

This thesis project concerns the mining of the BMC Clinical Data Warehouse (CDW) for insights into PCOS. It is situated within a larger research program of

[1]Convenience sampling is a form of non-probability sampling based on data that is readily obtainable. Because it is nonrandom, a particular process (usually not fully understood) accounts for how the observations are generated.

developing a robust model of PCOS phenotype prediction and characterization of metabolic disease risk.

In particular, this project aims to accomplish the following objectives:

1. Demonstrate how a large dataset generated by natural clinical encounters can be mined for useful epidemiological insights.

2. Develop a set of tools for preprocessing ultrasound notes and automatic classification of polycystic ovary morphology (PCOM).

3. Document the characteristics underdiagnosed PCOS patients.

1.1 Brief PCOS history

PCOS was first published on by Irving Stein and Michael Leventhal in 1935 from observations in seven women complaining about long periods of amenorrhea, sterility, and hirsutism. The two physicians consistently found enlarged ovaries in these patients. Upon bilateral wedge resection of the ovaries, they also found numerous small cysts in the ovarian cortex as well as an absence of corpora lutea [137]. Since then, the literature on PCOS has grown, with the terms ”polycystic ovary” and ”Stein and Leventhal Syndrome” appearing in over 38,000 publications [14].

1.2 Diagnostic criteria

As is the case with other diseases, the definition of PCOS has been refined over time. Since the beginning, it has always been a disease of exclusion [58]. Clinical diagnosis of PCOS relies on excluding pregnancy and other endocrinopathies which may cause amenorrhea or androgen excess, including nonclassical adrenal

hyperplasia, Cushings syndrome, androgen-producing tumors, drug-induced androgen excess, thyroid disorders, and hyperprolactinemia [12].

Between 1990 and 2005, the three modern diagnostic criteria most widely used today were developed: the 1990 NIH criteria, the 2003 Rotterdam criteria, and the 2006 Androgen Excess and PCOS Society (AE-PCOS) criteria. In 1990, a group of investigators attending a National Institutes of Health (NIH) conference defined PCOS on the basis of a consensus questionnaire to be the combined presence of hyperandrogenism with oligo-anovulation, and exclusion of other endocrinopathies that cause anovulatory infertility.

Before proceeding, it is important here to draw a clear distinction between the terms "polycystic ovarian morphology" (PCOM) and "polycystic ovary syndrome (PCOS)." Polycystic ovary morphology (PCOM) is the abnormal appearance of the ovaries under ultrasound imaging. This abnormality is characterized by enlarged ovarian stroma and numerous follicles often oriented peripherally. On the other hand, polycystic ovary syndrome (PCOS) is the heterogeneous disorder as a whole. Although PCOM was noticed by Stein and Leventhal in their original study, there is not necessarily a one-to-one correspondence between the two; PCOM may not be specific to the disease and not all PCOS women have PCOM [137]. In fact, under the 1990 NIH criteria, polycystic ovary morphology under ultrasound was merely considered to be suggestive of PCOS, not necessarily diagnostic, and a woman unaffected by PCOS could have the appearance of normal ovaries under ultrasound.

In 2003, the Rotterdam consensus criteria expanded the diagnostic criteria to be at least 2 of the following:

1. clinical or biochemical hyperandrogenism

2. oligo-anovulation

3. polycystic ovary morphology PCOM,

with exclusion of other endocrinopathies [126]. The key change from the 1990 NIH criteria is that hyperandrogenism and oligo-anovulation are no longer both required for a diagnosis, as long as the patient also has PCOM (Table 1.1). Thus, the Rotterdam criteria add 2 new phenotypes: the ovulatory phenotype with hyperandrogenism and PCOM but no oligo-anovulation, and the normoandrogenic phenotype with oligo-anovulation and PCOM but no hyperandrogenism.

In recent years, the symptoms which constitute the syndrome have been contested. Most of the controversy surrounds the question of whether or not the appearance of polycystic ovaries are required and whether or not its presence can replace either hyperandrogenism of oligo-anovulation. Criticism of the Rotterdam criteria mostly focuses on its expansion of phenotypic variability of PCOS and that some authors feel that PCOM is not a specific enough for PCOS [13, 120]. In their view, extending the criteria results in a uniformity of treatment between groups women whose metabolic risk may warrant differential approaches.

Some preliminary evidence shows that women with the ovulatory PCOS phenotype are less insulin resistant than anovulatory PCOS women [3, 24, 122] and the normoandrogenic PCOS phenotype are not insulin resistant [20]. The classical forms of PCOS (those acceptable under the NIH critera) are found to be at the highest risk of metabolic disturbances [9, 130]. Still, the criteria have also been described as better representing the spectrum of the syndrome and the phenotypic variability [20, 53].

In light of this evidence, the Androgen Excess and PCOS Society convened in 2006 and developed a new set of diagnostic criteria. This new definition pushed for contracting the previous Rotterdam criteria so that hyperandrogenism was considered a necessary component. As a result, the normoandrogenic phenotype

Table 1.1. Comparison of PCOS phenotypes accepted under different diagnostic criteria

Diagnostic criteria	Frank PCOS	Non-PCO PCOS	Ovulatory PCOS	Normoandrogenic PCOS
Hyperandrogenism (HA)	+	+	+	-
Oligo-anovulation (IM)	+	+	-	+
Polycystic ovary morphology (PCOM)	+	-	+	+
Included in 1990 NIH criteria	Yes	Yes	No	No
Included in 2003 Rotterdam criteria	Yes	Yes	Yes	Yes
Included in 2006 AE-PCOS criteria	Yes	Yes	Yes	No

Note. — A similar comparison chart was first published in [13]

no longer appears in this new definition. Still, the Rotterdam criteria are the most commonly used and because they are inclusive of the other criteria, they will serve as the baseline criteria used in this study.

1.3 Treatment for PCOS

Over time, treatment for PCOS has evolved. In the early stages of its discovery, treatment for PCOS was primarily surgical and there was a resistance to using endocrine therapy [136]. Modern treatment regimens involve various treatments for the different characteristics of PCOS: treatments for weight loss; insulin resistance; acne and hirsutism; and ovulation.

Obesity increases the risk and severity of all downstream metabolic and reproductive issues in PCOS women. In 2012, a meta-analysis of 30 studies on obesity in PCOS found that obesity was associated with decreased sex hormone-binding globulin (SHBG), increased androgens, hirsutism, fasting glucose, fasting insulin, and a worse lipid profile [98]. Furthermore, the most effective form of treatment for endocrine and reproductive function seems to be permanent weight loss: Kiddy et al. found that even moderate weight loss from long-term calorie

restriction shows a return of the ability to conceive in most women [84]. Thus, dietary intervention and weight management is usually a clinical goal; however, at this time, there are no particular programs that are clearly superior. A meta-analysis of 10 lifestyle intervention programs in overweight and obese infertile women found that the median dropout rate was 24% [110]. For patients in whom dietary intervention is unsuccessful, bariatric surgery represents another option [26]. Lastly, metformin is used as an insulin sensitizer and it is also associated with moderate weight reduction [67, 88, 142, 159].

For managing the symptoms of hirsutism, treatments such as electrolysis, plucking, shaving, waxing, and laser hair removal may be effective in the short term [39, 131, 149]. Pharmacologic treatments for acne and hirsutism aim to lower serum androgen levels by lowering androgen production, altering the binding to plasma proteins, and blocking androgen action [44]. Combined oral contraceptives are often used to suppress androgen production and enhance to production of SHBG [118, 167]. Antiandrogen treatments such as spironolactone (in large doses) and finasteride are used to inhibit the binding of dihydrotestosterone (DHT) to 5α-reductase (5α-RA) [83, 133].

Weight loss and improving insulin sensitivity usually improve ovulation and menstruation, but if fertility does not return after weight loss, clomiphene citrate or letrozole may be used for ovulation induction [109, 113, 127, 143]. If this treatment fails, the second line of treatment is administration of gonadotropins, such as human menopausal gonadotropin (hMG) or recombinant follicle-stimulating hormone (r FSH) [151].

1.4 Metabolic syndrome in PCOS and race/ethnic considerations

The downstream risk of metabolic syndrome is difficult to study in PCOS patients, mostly because the chronic nature of the disease warrants long-term follow-up, which may be costly. Indeed, current estimates of MBS prevalence in PCOS vary widely by study (Table 1.2), even when restricting to a particular diagnostic criteria.

The race- and ethnic-specific risk adds an additional layer of complexity to consider. Most studies of PCOS have been in White subjects of continental European descent, although there have been some prevalence studies in other groups as well. These studies are summarized in Table 1.3. In brief, PCOS prevalence seems to be higher in South Asians and Hispanics than other ethnic groups.

Other authors have also noted ethnic and racial variations in the expression of PCOS symptoms, including hirsutism, biochemical hyperandrogenism, PCOM, and insulin resistance, although the number of studies directly comparing ethnic profiles are limited. Tables 1.4, 1.5, 1.6, 1.7, and 1.8 summarize of PCOS characteristics by ethnicity. The few studies directly comparing different ethnic groups are flagged by a superscript and corresponding table note.

The key findings from these studies are that compared to White women with PCOS, South Asian and Middle Eastern women with PCOS may have more severe hirsutism and insulin resistance even at a lower BMI and testosterone level. Southeast Asians and Hispanics with PCOS have a higher prevalence of abnormal glucose tolerance and metabolic syndrome than Whites, and Pacific Islanders have the highest levels of obesity, hirsutism, and testosterone. Black women seem to be as hirsute as White women, and are more likely to have hypertension, although the total number in PCOS studies is low.

Table 1.2. Metabolic syndrome prevalence in PCOS

Study	Race (White)	Study design	PCOS definition	Result
Legro, Kunselman, et al.(1999) JCEM [93]	74.4%	Prospective	1990 NIH*	31.1% (79/254)
Glueck, Papanna, et al. (2003) Met Clin Exp [57]	100%	Prospective	1990 NIH	46% (64/138)[1]
Chang, Knochenhauer, et al. (2005) FNS [25]	86.4%	Prospective	1990 NIH	78.2% (247/316)[3]
Dokras, Bochner, et al. (2005) Obstet Gynecol [40]	unknown	Retrospective	1990 NIH	47.3% (61/129)[2]
Apridonidze, Essah, et al. (2005) JCEM [9]	unknown	Retrospective	1990 NIH	43.4% (46/106)[2]
Vrbikova, Vondra, et al. (2005) Hum Rep [146]	100%	Case-control	1990 NIH	1.6% (1/64)[1]
Ehrmann, Liljenquist, et al. (2006) JCEM [45]	unknown	Prospective	1990 NIH	33.4% (123/368)[1]
Attaoua, Mkadem, et al. (2008) [11]	100%	Case-control	2003 Rotterdam	36.2% (75/207)[1]
Echiburu, Perez-Bravo, et al. (2008) [43]	unknown (Chilean)	Case-control	1990 NIH	10.6% (17/159)[4]
Goverde, Koert, et al. (2009) [60]	100%	Cross-sectional	2003 Rotterdam	15.9% (25/157)[1]
Yildiz, Bozdag, et al. (2012) Hum Rep [162]	100%	Prospective	2003 Rotterdam	10.3% (8/78)[1]

*This was never stated explicitly, but it is most likely due to the study date.

[1]This study used the ATPIII guidelines.

[2]This study used a modified version of the ATPIII guidelines.

[3]This study used HOMA-IR, (fasting serum insulin (μU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5), as a surrogate for MBS.

[4]This study used an oral glucose tolerance test as a surrogate for MBS.

Table 1.3. PCOS prevalence in ethnic groups

Ethnic group and location	Prevalence and diagnostic criteria	Study
White; Lesbos, Greece	6.77% (13 of 192)[1]	[38]
White; Madrid, Spain	6.5% (10 of 154)[1]	[10]
White; Oxford, UK	8% (18 of 224)[1]	[107]
White and Black; southeastern USA	4.7% (6 of 129) in Whites[1] 3.4% (5 of 148) in Blacks[1]	[87]
White and Black; Birmingham, AL	4.8% (8/166) in Whites[1] 8.1% (18/223) in Blacks[1]	[17]
Mexican-Americans; Los Angeles, CA	13% (20 of 156)[1]	[59]
White; Adelaide, Australia	8.7% (63 of 728)[1] 11.9% (87 of 728)[2] 10.2% (74 of 728)[3]	[104]
East Asian; Guangzhou, China	2.2% (20 of 915)[1]	[30]
Southeast Asian; Chiang Mai, Thailand	5.7% (62 of 1095)[2]	[148]
South Asian; Gampaha, Sri Lanka	6.3%,(183 of 2915)[2]	[89]
Arab; 4 provinces representative of Iran	7.1% (66 of 929)[1] 14.6% (136 of 929)[2] 11.7% (109 of 929)[3]	[140]

[1] 1990 NIH Criteria

[2] 2003 Rotterdam Criteria

[3] 2006 AE-PCOS Society Criteria

1.5 Significance of the study

The race- and ethnic-specific diagnostic criteria are important to consider, because a diagnosis may mean life-long treatment and management of the disease. Indeed, what is the difference between 9.99 and 10.01? Should disease management depend on such numbers? As the authors of the AE-PCOS guidelines have written,

> "Clinically, diagnosing a woman as having PCOS implies an increased risk for infertility, dysfunctional bleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, and possibly cardiovascular disease... Furthermore, it has important familial implications, principally, but not exclusively, for her sisters and daughters. Finally, a diagnosis of PCOS may mandate life-long treatments, e.g. the use of insulin sensitizers, and may negatively affect her ability to access health care coverage, principally in capitalistic markets. Consequently, the diagnosis of PCOS should not be assigned lightly, and diagnostic criteria should be based on robust data." [15]

Table 1.4. PCOS characteristics in South Asian populations

Ethnic group	Study population	Findings	Reference
South Asian and White in UK[1]	47 South Asian, 40 White	Although South Asian PCOS women were younger and less obese, they were more hirsute, more prevalent acanthosis nigricans, and had higher fasting insulin.	[154]
Sri Lankan	469 PCOS, 231 BMI-matched controls	PCOS women had more central obesity and higher insulin resistance than non PCOS. More prevalent acanthosis nigricans compared to other studies.	[155]
South Indian	40 PCOS, 40 weight-matched control	PCOS women had higher fasting insulin, lower insulin sensitivity, and greater intima-media thickness, a marker for atherosclerosis.	[138]
North Indian	37 PCOS, 21 non weight-matched controls	Total and subcutaneous fat volumes were linked to insulin resistance.	[79]

[1]This study compared different racial groups.

Table 1.5. PCOS characteristics in Southeast Asian populations

Ethnic group	Study population	Findings	Reference
Thai	531 reproductive-aged women from the general population	97.8% had mFG scores <3. Their recommended cut-off value of mFG in Thai women is 3	[28]
Thai	121 PCOS	The prevalence of abnormal glucose tolerance was 42.9%; acanthosis nigricans was an important predictor for abnormal glucose tolerance	[27]
Thai	170 PCOS	The prevalence of MBS was 35.3%	[150]

Table 1.6. PCOS characteristics in East Asian populations

Ethnic group	Study population	Findings	Reference
South Chinese	102 PCOS, mean BMI of 21.7	22.4% of Chinese women with PCOS have abnormal glucose tolerance. The prevalence of impaired glucose tolerance was 20.5% and diabetes was 1.9%.	[29]
South Chinese	719 PCOS	After comparing Rotterdam phenotypes, metabolic syndrome is most prevalent in the Frank and Non-PCO phenotypes (28.5% and 25.5%)	[164]
South Chinese	883 PCOS, (˜20% with BMI >25); 717 controls	Total and subcutaneous fat volumes were linked to family history of type 2 Diabetes.	[166]
South Chinese	273 PCOS, mean BMI 22.2	Hirsutism in 34%, acne in 45%; the prevalence of hyperandrogenism, obesity and IR were lower than in women from other races with PCOS	[62]
South Chinese	915 PCOS women, mean age 30 years	Prevalence of PCOS was 2.2%; low rates of hirsutism, FG score low (13); 7.5% were overweight, 1.3% were obese; hyperandrogenism was age and BMI dependent	[96]
South Chinese	2988 reproductive-aged women from the general population	Cluster analysis identifies mFG score of 5 as cutoff. This was observed in 10%. Incidence of PCOS symptoms increased among hirsute women.	[165]
Chinese	10120 reproductive-aged women from the general population	95.5% had an mF-G score <5, mF-G scoring >4 can be used to diagnose hirsutism	[97]
Hong Kong Chinese	197 PCOS, mean BMI of 26	Hyperandrogenic phenotypes were more insulin resistant and had higher fasting insulin levels.	[91]
Taiwan Chinese	47 PCOS, mean BMI 28; 45 controls	Acanthosis nigricans in 31.9% compared to 0% and abnormal glucose tolerance in 46.8% compared to 6.25%	[99]
Japanese	46 PCOS	Prevalence of hirsutism was only 10%. Total testosterone had a poor area under the ROC curve.	[73]
Korean	166 PCOS, 277 controls	After sorting into Rotterdam phenotypes, there were very few ovulatory PCOS phenotype compared to other studies (n=4). Hyperandrogenic phenotypes had the worst insulin resistance and fasting insulin levels.	[23]

Table 1.7. PCOS characteristics in New World populations

Ethnic group	Study population	Findings	Reference
Chilean[2] and Argentinian[2]	206 PCOS Argentinians, 220 PCOS Chilean	After dividing into Rotterdam phenotypes, BMI (all phenotypes), triglyceride (Frank, Non-PCO), LDL-C (Frank, Non-PCO, Ovulatory), and prevalence of MBS (all phenotypes) were higher in Chileans compared to Argentinians.	[34]
White, Black, Asian, Hispanic and Others, Northern California[1]	11,035 PCOS	Compared with Whites, Blacks and Hispanics were more likely and Asians less likely to be obese; Asians and Hispanics were more likely to have diabetes; and Blacks were more likely and Hispanics less likely to have hypertension.	[100]
White and Black, Alabama[1]	283 White 350 and Black, both unselected to represent the general population	The 95%ile for mFG was 7.7. With an mFG cut-off of 8, 5.4% (15) White and 4.3% (15) Black were considered hirsute. Overall, prevalence and scores were similar.	[35]
Mexican American, California	20 PCOS and 136 controls determined from screening subjects in a cardiovascular study	Prevalence (13%) of PCOS in Mexican American women.	[59]
Mexican American and White, Texas[1]	37 Mexican American PCOS and 65 White PCOS[3]	Mexican Americans had higher IR and BMI; insulin resistance was 73% in Mexican American PCOS women versus 44% in White PCOS women	[82]
Mexican American and White, Texas[1]	50 Mexican American PCOS and 111 White PCOS[3]	Mexican American women had higher IR than white women but lower DHEAS; similar testosterone levels between groups	[81]
White, African-Americans and Asian, Pennsylvania[1]	435 White, 109 Black, 17 Asian, 72 Native American, average BMI of 35.2	Compared to Whites, fasting insulin was slightly higher in Blacks and lower in Whites. PCOM was present in over 90% of the subjects. Asians tended to have testosterone lower than Whites and African-Americans	[94]

Note. — New World = Western Hemisphere; Americas

[1]This study compared different racial groups.

[2]The ethnic subdivision of the Argentinian population is 87% of European, predominantly Italian, descent; 10% Hispanic-Amerindian mixture; and 3% other ethnicities while the Chilean PCOS population used is 90% Hispanic-Amerindian mixture, 7% Amerindian, and 3% other races.

[3]These two study populations may overlap.

Table 1.8. PCOS characteristics in European, Middle Eastern, and other populations

Ethnic group	Study population	Findings	Reference
Muslim Immigrants and Austrians, Austria[1]	35 Austrian PCOS, 14 Muslim PCOS	Of the laboratory tests conducted, only SHBG was markedly different (52.2 nmol/l in Austrians and 19.0 in Muslim immigrants)	[132]
Turkish	43 PCOS, 43 controls	PCOS levels of total testosterone was 94.4ng/dl, FG score was 13.4, and fasting insulin was 22 μIU/ml. PCOS women had greater carotid intima-media thickness.	[147]
White and Middle Eastern, Denmark[1]	784 White, 190 Middle Eastern women who were hirsuite or had PCOS	Middle East were more hirsute (mean FG 16), but had lower testosterone levels, BMI, and waist circumference compared to White women.	[56]
European, Maori, Pacific Islander[1]	162 women with at least one symptom of PCOS	European and Maori women were more hirsute; Maori and Pacific Island women were more obese and insulin resistant. Maori women had the highest testosterone.	[157]
White in Iceland and Boston; Caucasian, African-American, Hispanic, and Asian women in Boston[1]	367 PCOS patients, 262 Boston women and 105 Icelandic women	Androstenedione was higher and testosterone and mFG score were lower in Caucasian Icelandic compared with Boston women with PCOS; PCO was demonstrated in 93-100% of women with PCOS in all ethnic groups	[152]

[1] This study compared different racial groups.

Chapter 2

Study Population

2.1 Inclusion and exclusion criteria

The data used in this study was queried from the Boston Medical Center (BMC) Clinical Data Warehouse (CDW), a repository for historical clinical data. The data was pulled starting from the date October 1, 2003, when BMC started using its SDK registration system, until September 30, 2015, the last day BMC used the 9th version of International Statistical Classification of Diseases and Related Health Problems (ICD-9). ICD codes are maintained by the World Health Organization (WHO), and they provide a global standard for coding diseases [6]. After September 30, 2015, BMC switched to the newer ICD-10 codes, but these were not considered for the present study because of the additional variance they introduce.

The inclusion criteria for this study require that the subjects be female, be of reproductive age (between 18 and 45), and have records at BMC for at least one of the following: androgen blood tests, menstrual regularity, and pelvic ultrasound. In particular, Table 2.1 describes the specific CDW queries for these inclusion criteria. These inclusion criteria allow us to include both women who are considered normal and women who considered abnormal on each of the three polycystic ovary syndrome (PCOS) axes to be included, with the limitation that those who are administered an androgen lab or a pelvic ultrasound are more likely to have abnormalities. In essence, this dataset captures all women appearing at BMC who have the potential to be diagnosed with PCOS. Women who were younger

Table 2.1. CDW inclusion queries

Inclusion criteria	ICD-9 code, lab, or procedure
Evaluation of androgens	704.1 - hirsutism Total testosterone lab Free testosterone lab Bioavailable testosterone lab
Evaluation of menstrual regularity	626.0 - absence of menstruation 626.1 - scanty or infrequent menstruation 626.4 - irregular menstrual cycle
Evaluation of pelvic ultrasound	Pelvic ultrasound

than 18 at any point in this study and those who were older than 45 at any point in this study had their data left-censored and right-censored respectively at those ages. Similarly, those given a specific diagnosis of menopause had their data right-censored at that time. This resulted in a study population of 37,959 women.

Table 2.2 gives the endocrinopathies for exclusion. This list of ICD-9 codes was generated by examining all possible ICD-9 codes and retaining the ones that may cause oligo-amenorrhea, hyperandrogenism, or infertility. Thus, it spans the set of all endocrinopathies considered by the WHO. Any woman with one of these ICD codes had her data completely excluded from the study. Overall, there were 1679 women excluded by the presence of a disorder appearing on this list.

2.2 Study population characteristics

Our dataset is the most diverse for PCOS. About 43% of the women are Black/African-American, 26% are White, 17% are Hispanic/Latino, and 4.4% are

Table 2.2. CDW exclusion queries

Endocrinopathy	ICD-9 code
Malignant neoplasm of corpus uteri, except isthmus	182.0
Goiter, specified as simple	240.0
Goiter, unspecified	240.9
Nontoxic uninodular goiter	241.0
Nontoxic multinodular goiter	241.1
Thyrotoxicosis with or without goiter	242
Congenital hypothyroidism	243
Acquired hypothyroidism	244
Thyroiditis	245
Other disorders of thyroid	246
Cushings syndrome	255.0
Hyperaldosteronism	255.1
Adrenogenital disorders	255.2
Other corticoadrenal overactivity	255.3
Corticoadrenal insufficiency	255.4
Other adrenal hypofunction	255.5
Medulloadrenal hyperfunction	255.6
Other specified disorders of adrenal glands	255.8
Unspecified disorder of adrenal glands	255.9
Other ovarian dysfunction	256.8

Asian. American Indian/Native American, Middle Eastern, and Native Hawaiian/Pacific Islander categories accounted for less than 2% of the dataset. About a quarter did not attend or complete secondary school and another quarter either finished or received a GED. Almost 15% had some kind of higher education and under 20% graduated college.

In the future, it would be better to develop more refined race/ethnicity categories. For example, South Asians and East Asians are all coded as Asian within this study, but PCOS characteristics may be dependent on the race and ethnicity to an even finer degree [161]. For example, Wijeyaratne et al. found that hirsutism was more prevalent and severe among PCOS patients of South Asian ancestry than

those of European White ancestry [154]. On the other hand, at the same androgen level, East Asian subjects have lesser degree of hirsutism than White subjects [49]. As a result, grouping South Asians and East Asians together results in information loss about some race-specific nuances.

Along the same vein, Boston has a significant Cape Verdean and Haitian population, which are usually coded as "African-American" or "Other" within the CDW dataset, yet these recent immigrant populations have cultural practices and diets distinct from Black Americans whose families trace their history within the country for a few generations. Future studies that aim to understand the influence of lifestyle characteristics and genetics on PCOS should take care to distinguish between these people groups.

Table 2.3. Study population characteristics

Characteristic (n = 37959)	% (n) or mean ± SD
Age	
Age on 2015/9/30	36.7 (8.9) years
Race	
American Indian/Native American	0.5638% (214)
Asian	4.415% (1676)
Black/African American	43.49% (16510)
Hispanic/Latino	17.15% (6509)
Middle Eastern	0.9879% (375)
Native Hawaiian/Pacific Islander	0.08957% (34)
Non-Hispanic White	26.03% (9880)
Other/Multiracial	4.418% (1677)
Declined/Not Available	2.856% (1084)
Anthropometrics	
Height (cm) (n = 27325)	162.4 ± 7.1
Weight (kg) (n= 31889)	76.2 ± 20.5
BMI (n = 28371)	
Underweight <18.5	1.6% (450)
Normal weight 18.5-24.9	32.1% (9115)
Overweight 25-29.9	28.9% (8198)
Obese Class I 30-35	18.8% (5344)
Obese Class II 35-40	10.1% (2855)
Obese Class III >40	8.5% (2409)
Blood pressure (n = 32560)	
Systolic blood pressure (mmHg)	118.0 ± 11.6
Diastolic blood pressure (mmHg)	75.1 ± 7.5
Socioeconomic status	
Education	
Did not attend school	4.536% (1722)
8th grade or less	4.268% (1620)
Some high school	19.84% (7532)
Graduated high school or GED	24.32% (9232)
Some college/vocational school/technical school	14.21% (5394)
Graduated college/postgrad.	19.74% (7496)
Other Education	0.7034% (267)
Declined/Not Available	12.37% (4696)

Table 2.3 (cont'd)

Characteristic (n = 37959)	% (n) or mean ± SD
Reproductive	
Age at Menarche (n = 273)	12.7 ± 2.0

Note. — For repeated measurements, a within-woman average was calculated first. Then these are used to calculate the measures of central tendency and dispersion.

2.3 Characteristics of the Clinical Data Warehouse dataset

Because the dataset was generated by natural clinical processes and was not originally collected for research purposes, many variables in the data needed to be cleaned before they were suitable for analysis. For example, before cleaning, many nonsensical BMI values appeared in the dataset (Figure 2.1).

There are so many large outliers that the interquartile range looks like a line at this resolution! For comparison, the heaviest recorded weight for an adult man is 635 kg, and he stood 1.85 meters tall, which puts his BMI at 185.5 [61]. Clearly BMI values several orders of magnitude greater than that are absurd. The goal in this part of the analysis was to salvage as much usable data as possible for the purposes of characterizing the study population and also later development into a predictive model involving metabolic characteristics. The following subsections describe the preprocessing of the race, anthropometrics, socioeconomic status (SES), and reproductive data characterizing the population.

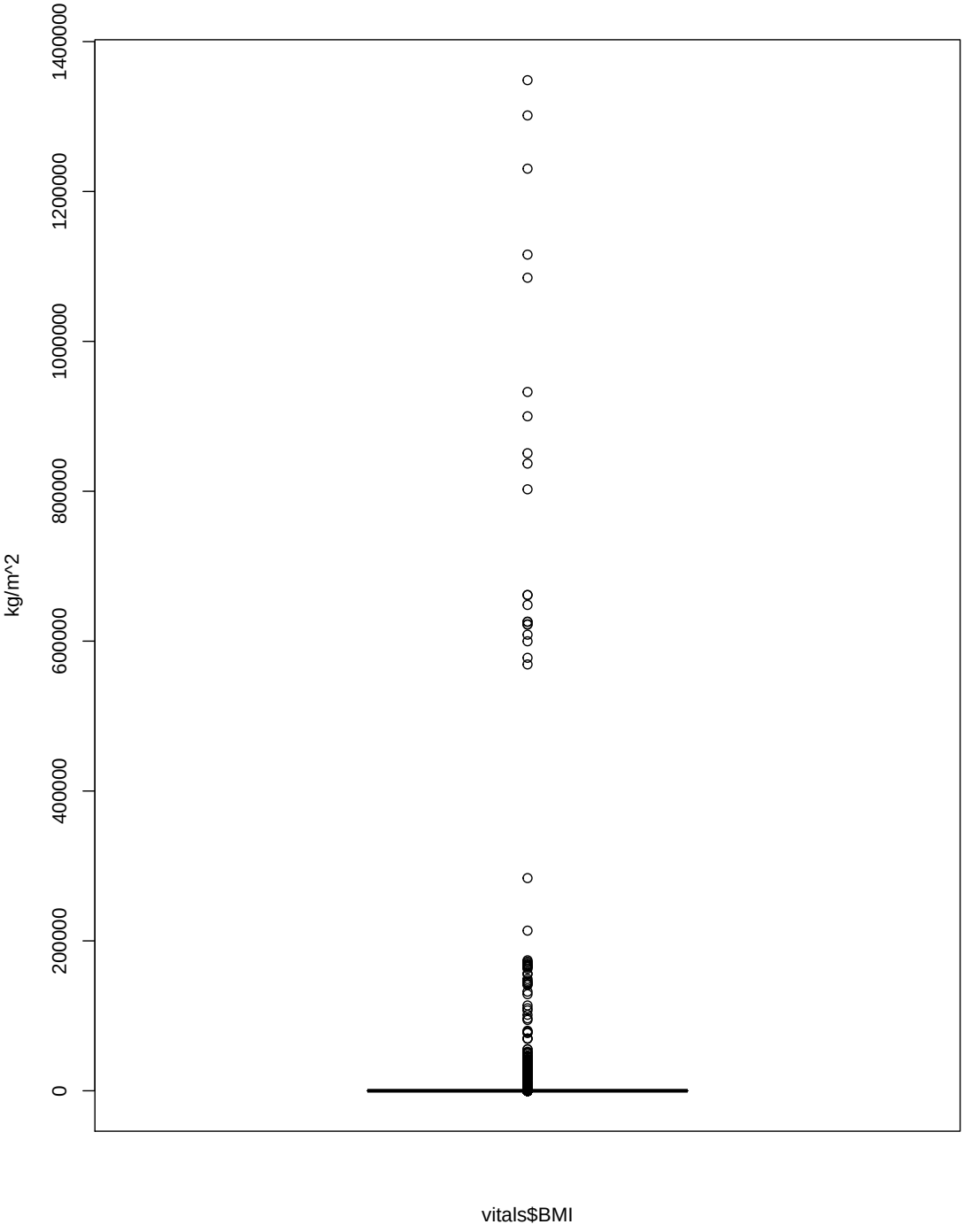

Fig. 2.1 Boxplot of crude BMI data in the CDW dataset

Table 2.4. The same ratio between true and given BMI values within a cluster

ID	BMI	Height (m)	Weight (kg)	New BMI	Ratio
4558	78548.42	1.18	70.5	50.6	1552.36
6617	29090.91	1.97	72.7	18.7	1552.36
10151	80068.71	1.18	71.8	51.6	1552.36
16693	38363.64	1.97	95.9	24.7	1552.36
17788[1]	35818.18	1.97	89.5	23.1	1552.36
17788[1]	39841.82	1.97	99.6	25.7	1552.36

Note. — The first BMI column (BMI) contains the given values and the second BMI column (New BMI) contains the recalculated values.

[1]These entries represent the same patient on different hospital visits.

2.3.1 Anthropometric data

Visual inspection of the boxplot of crude BMI in Figure 2.1 reveals that there seem to be clusters between 100 and 40,000; 40,000 and 70,000; 70,000 and 100,000; and over 100,000. Since BMI is computed in practice from clinically measured weight and height – that is, BMI is not measured directly, but instead calculated from directly measured values – this suggests that the BMI computations may be the least trustworthy among height, weight, and BMI values in the dataset. Within each of these outlying clusters, a similar systematic error may pervade the measurements and indeed, a preliminary analysis revealed that within a cluster, when a "true BMI" was calculated from seemingly reliable weight and height data, the true BMI falls within normal ranges of human experience. Even more striking is that the ratio between the given "false BMI" and calculated BMI are similar between data points. Table 2.4 shows a sample calculation for some data points between 35,000 and 80,000 that fit this description.

Table 2.5. Examples of mixed units for height in the dataset

Meters	Inches	Centimeters	Feet & inches	Ambiguous
1.97	64	166	5.2	17.717

To preserve as much BMI information as possible for analysis, an intermediate step of cleaning the height and weight data was necessary, as some observations did not have a recorded BMI but did have measurements for height and weight. Of height and weight, the height data was cleaned first and similar to the BMI data, there were clusters of points along its range. Manual inspection of the height data revealed that it seemed to be recorded in a variety of measurement units, e.g. "1.97," "64," "166," "5.2," and "17.717" (Table 2.5). It is clear that measurements of the first type refers to meters, the second to inches, and the third to centimeters, but the fourth type is unclear. Does it mean 5 feet and 2 inches or 5.2 feet? As elaborated later, a nuance within measurements in this category allowed a well-defined ascertainment. Measurements of the fifth type were completely incomprehensible and were counted as missing. This category included the extremely large values for which no explanation could be mustered, e.g. "0.39," "2007.00," "26444.00." Thus, to clean the heights, the data was first sorted into five categories: "meters," "inches," "centimeters," "feet & inches," and "mark as missing."

Further inspection of the "feet & inches" category revealed some nuances in how it was recorded. For example, there were entries for 5.10 and 5.11, but never 5.12 (or 5.13, 5.14, etc.). There also seemed to be a difference between 5.10 and 5.1, with the latter group tending to have lower weights. Thus, the height data in this category was interpreted such that the digits to the right of the decimal place

referred to the number of inches and the digit to the left referred to the number of feet.

During this process, some of the heights and weights seemed as if they should be switched. For example, an observation with a weight entry of 60 and height entry of 300 probably represent a woman who is 60 inches tall and who weighs 300 pounds, rather than a 25 foot tall woman weighing 60 pounds. As a rule of thumb and barring extreme observations, it seemed safe to assume that weight in pounds would always exceed height in inches, so outliers with heights in line with normal weight ranges (100–300) and weights in normal height ranges (40–80) were flipped. There were 16 such cases and their median "height" was 137.5 (range 107–372) and median "weight" was 64 (range 50–68). In 11 cases, the patients other entries in BMI, weight, or height from separate occasions confirmed that this type of error occurred and that the swap was warranted.

According to the CDCs *Anthropometric Reference Data for Children and Adults: United States, 2007-2010*, a 5 standard deviation range in height covers 50 inches to 77 inches (127–196 cm) [54]. Thus, the final criterion for marking as missing (fifth category) was the value of height falling in one of the following intervals: between 7 and 49 (values too small to be inches), between 78 and 126 (values too large to be inches and too small to be centimeters) or above 197 (values too large to be centimeters). After exclusion, the data were standardized to inches, which was the most common measurement, using the conversion ratio of $1 : 0.393701$ centimeters to inches. This resulted in 81,101 complete height measurements in 27,325 unique patients.

The weight data exhibited the best general behavior of the three. There was a scattering of large values above 600 and small values, but otherwise the histogram between 0 and 600 is rather good (Figures 2.2 & 2.3).

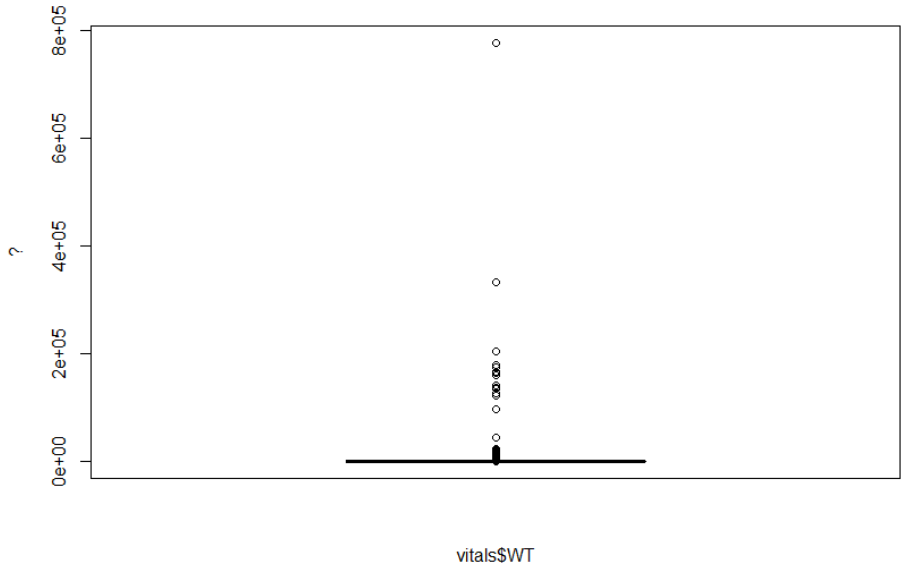

Fig. 2.2 Boxplot of crude weight data in the CDW dataset

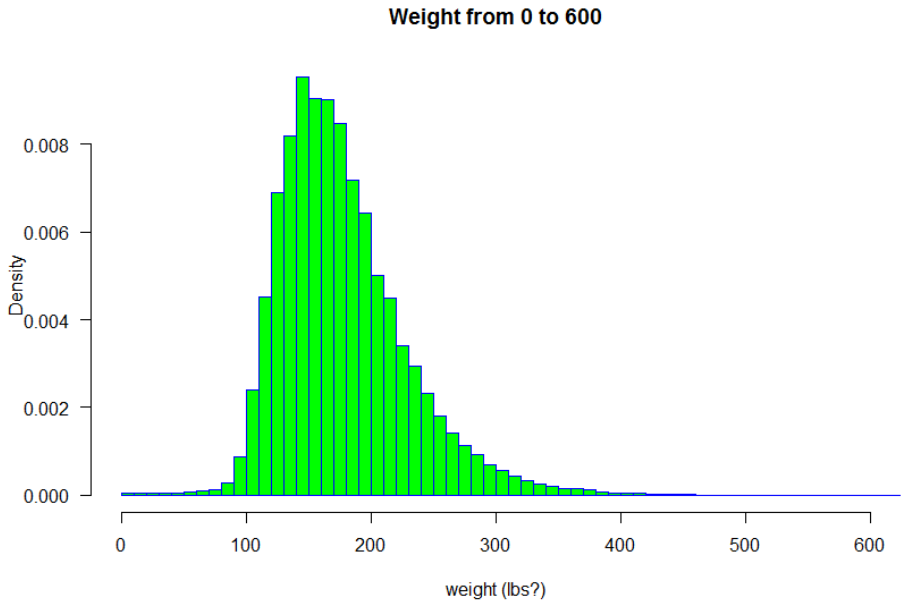

Fig. 2.3 Histogram of crude weight data between values 0 to 600

The weight data were also presumed to span different units, but here the same trick used for the height data was not able to be applied because the numeric value of weight for imperial and metric units overlaps between categories even at 3 standard deviations of human experience: 87–297 pounds and 40–136 kg [54]. Thus, values between 87 and 136 were ambiguous due to this issue. Furthermore, weights below 40 kg and weights above 297 were credulous, since BMC's service population does not preclude those with extremely low or high bodyweight, a reflection of the large homeless and poor population it serves.

To determine the right unit for each observation, a combination of BMI, height, and historical data was used. Before that, the values for BMI below the limit of human female starvation, 11, were removed [66]. Next weights below 17 were removed, since 17 kg would correspond to the weight of the shortest woman in this data set at a BMI of 11. Weights with entries between 17 and 40 would be in kilograms presumably, if it all possible, and these were only kept if they harmonized with a matching BMI and height measurement as well as previous measurements; those missing either BMI, height, or other records confirming this measurement were changed to missing. To summarize this step, values that represent an impossible physical reality were removed and those that corresponded to starvation were only kept if they were confirmed by all other measurements.

In the final and most time-intensive step, all weights in the dataset were double-checked for correctness of units by comparing its numeric value with previous and future hospital visits. Table 2.6 demonstrates an example of this process. When a unit conversion was more in line with the patient's history, the converted version was preferred.

Table 2.6. Comparison of weight with the patient's history

ID	Clinical date	BMI	Height	Weight	SBP	DBP
509	8/29/2007	33.42		180	110	90
509	9/17/2007			178	125	80
509	12/13/2007	34.72		187	120	80
509	6/4/2008	37.32		201	100	90
509	**5/19/2009**			**93.9**[1]	**130**	**88**
509	6/29/2009	39		212	126	90
509	1/13/2010	38.62		208	130	88
509	4/21/2010	39.17		211	114	76
509	5/5/2010	40	61.8	215	147	87

[1]Instead of believing the patient could gain over 100 lbs in a month, 93.9 (kg) was converted to 207 (pounds), which is more in line with the patient's history.

2.3.2 Reproductive data

The data for age at menarche also needed refining. The main issue was that the range of values in the dataset did not line up with clinical experience. Sometimes this was because it was not formatted similarly; these entries were usually recorded as years, e.g. 14 or 14y, and occasionally as dates, which could then help triangulate the age at menarche in conjunction with the subjects current age. However, there were others with integers that were much larger, such as 28 and 28d. Interestingly, for many of these cases, the patients had other age at menarche entries within a reasonable range. Due to the d and the prevalence of 28, these are considered estimates of the patients cycle length mistakenly entered into this form. All records with age at menarche greater than 19 were hand-checked, and those greater than age 22 were determined to be errors due to the presence of d

Table 2.7. Summary of menarche outliers

Summary measure	Value
Min.	23.0
1st Quartile	25.5
Median	28.0
Mean	43.1
3rd Quartile	41.0
Max.	114.0

or being greater than 40. There were 12 such observations. The following table presents the characteristics of these outliers.

There were likewise many small values that were considered errors. It is less certain what the mistake was. Here, the mode of these values was 1. All values less than 8 were handchecked, and those equal to 3 or smaller were considered errors. There were 6 such observations. A boxplot of the processed data is displayed in Figure 2.4.

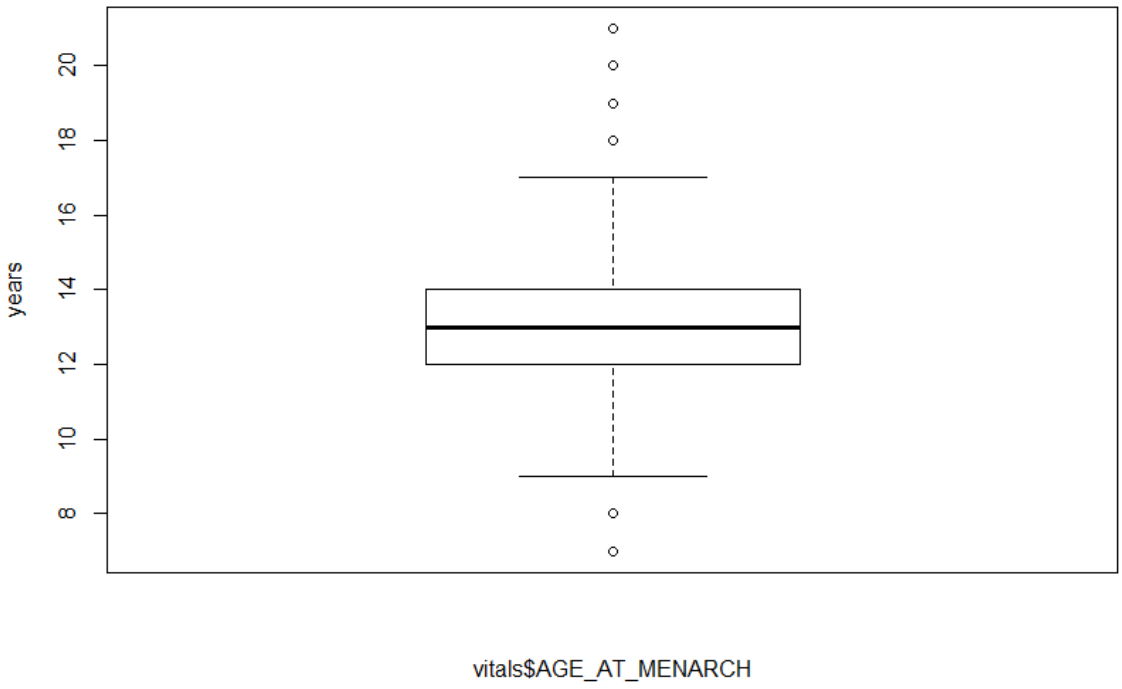

Fig. 2.4 Boxplot age at menarche data after processing

Chapter 3

Hyperandrogenism

3.1 Background

3.1.1 Clinical vs biochemical hyperandrogenism

Clinical hyperandrogenism, or hirsutism, is the presence of excess body and terminal hair growth in females in a male-like pattern [161]. It is the most recognizable feature of polycystic ovary syndrome (PCOS) and conversely, it has great sensitivity; Adams et al. found in 1986 that 92% of women with regular menstrual cycles and hirsutism also presented with polycystic ovary morphology (PCOM) under ultrasound [2].

When surveyed, hirsute women display a greater measures of social fear and anxiety [135]. Other quality of life surveys comparing PCOS women to controls found that PCOS women were less satisfied with their sex life, found themselves less sexually attractive, and believed their partners were less satisfied [47, 63]. Surveyed women believed to a greater extent that their excessive body hair negatively affected their sexuality and ability to form social contacts.

On the other hand, biochemical hyperandrogenism is defined as elevated serum androgens. Testosterone is the chief male sex hormone responsible for development of male sex characteristics and spermatogenesis. In women, it is produced in the ovaries in a smaller amount, and both sexes produce it in the adrenal cortex. Around 60% of testosterone is specifically bound to sex hormone-

binding globulin (SHBG) and another 38% is nonspecifically bound to albumin [85, 145]. The remaining 2% is in an unbound state, called free testosterone [41, 125]. The physiologically important levels of testosterone are the nonspecifically bound and free testosterone and as a result, an increase of SHBG decreases the bioavailability of testosterone, even if the total testosterone levels remain the same. To be more explicit, if nonspecifically bound testosterone (albumin-bound) is represented as AT and free testosterone will be represented as FT, the following relationship holds:

$$\mathrm{BT} = \mathrm{FT} + \mathrm{AT}, \tag{3.1}$$

where BT is bioavailable testosterone.

3.1.2 Biological mechanism

Terminal (coarse) hairs are distinct from vellus hairs, which are short, fine, and non-pigmented. An excess of vellus hairs is not hirsutism, and instead referred to as hypertrichosis, which may be caused by corticosteroid or prostaglandin administration [65, 76, 77]. However, some hair follicles can ”terminalize” vellus hairs, converting them into terminal hairs under the influence of androgens [42, 55].

Virilization in mammals is accomplished by both testosterone and its metabolite dihydrotestosterone, with the latter being the more potent [128]. The enzyme responsible for reducing testosterone to dihydrotestosterone (DHT) is 5α-reductase (5α-RA). The relation to PCOS is that in human and rat scrotal fibroblasts, addition of a monoclonal antibody against insulin-like growth factor 1 (IGF-1) reduces the effect of dihydrotestosterone [69]. In 2005, Cappel et al. noted that in women with clinical acne, IGF-1 correlated with DHT, and there was an interaction effect between IGF-1 and DHT on acne lesion counts [102]. Other studies

have noted the elevated IGF-1 levels in hyperandrogenic disorders and idiopathic hirsutism [4, 48].

3.1.3 Evaluation of clinical hyperandrogenism

The most common[1] method of evaluating hirsutism is the modified Ferriman-Gallwey (mFG) score, a modified version of the method originally described by David Ferriman and John Gallwey in 1961 [52, 64]. The original version called for the evaluation of 11 regions of the body: lip, chin, chest, upper back, sacro-iliac region, upper abdomen, lower abdomen, arm, posterior forearm, thigh, and leg. Since hair growth on the lower leg and forearm were found to be independent of the hair on the other 9 regions, the modified version of the does not include them. In both the original and modified version of the scoring system, each region is assigned a score of 0-4, with 0 representing the absence of terminal hairs, 1 representing minimally evident terminal hair growth, and 4 representing extensive hair growth comparable to that in males. These scores are then summed and the aggregate score is then used to determine the presence of absence of hirsutism [10, 52, 64, 129].

There is still room for improvement on the front of assessing hirsutism: the metric (of summing the regional scores to find a total) used alongside the popular mFG system does not match conventional intuition about severity of hirsutism. As a simple counterexample, one could consider two hypothetical white female patients: the first patient scoring "1" (minimally evident terminal hair growth) in each body part would receive a total mFG score of "9," and a second patient scoring "3" only in the chin and the upper lip would receive a total mFG score of "6." Most mFG cutoffs in white women vacillate between 8 and 9 (Table 3.1),

[1] The pervasiveness is still largely restricted to research studies, as patients and practitioners often consider a full body examination too invasive for the added marginal benefit [86].

Table 3.1. Determinations of mFG cutoffs in unselected White women

Location	Study population size	mFG cutoff	Study
Spain	154	8	[10]
USA	283	8	[35]

and so the first patient would technically be classified as hirsute while the second would be classified as normal.

The inherent issue is common to any problem regarding comparisons with multivariate objects (e.g. college rankings) and essentially, the summation over all body regions results in two difficulties: first, equating the change from "0" to "1" and "1" to "2" within a region (assuming equal intervals for an ordinal variable) and second, equating the change from "0" to "1" between two regions (assuming equal units).

This issue has also come to the attention of other investigators, as well as the issue of inter-observer variation, which increases with an increasing number of dimensions (body part regions) to measure [8, 156]. In particular, Cook et al. proposed in 2011 a simplified scoring system using only the sum of scores from the upper abdomen, lower abdomen and chin, but their proposal has not gained widespread acceptance [32].

3.1.4 Evaluation of biochemical hyperandrogenism

Since bioavailable testosterone is the physiologically meaningful quantity, any measure of hyperandrogenism at least indirectly measures the bioavailable testosterone. Based on the law of mass action, the equilibrium equation for albumin binding to testosterone is $AT = K_a \cdot C_a \cdot FT$, where AT and FT are the concen-

trations of albumin-bound testosterone and free testosterone, respectively, K_a is the association constant of albumin for testosterone and C_a is the concentration of albumin, so AT is linearly proportional to FT at constant concentrations of albumin. Thus, several methods measure free testosterone and the concentration of albumin in order to calculate albumin-bound testosterone and bioavailable testosterone. One drawback to these methods is that reliable direct measurement of free testosterone remains elusive, because the procedures available are time-consuming and the amount of free testosterone is a tiny proportion of total testosterone [33, 115, 139, 145]. The lack of sensitivity and accuracy of measuring free testosterone is especially apparent in women, who have naturally lower levels [124].

Another option is to use the free androgen index (FAI), defined as

$$\text{FAI} = 100\frac{\text{Total testosterone}}{\text{SHBG}}, \tag{3.2}$$

but opinion in the current literature is mixed. Vermeulen et al. found that FAI does not correlate well, but other studies have found correlation coefficients ranging between $r = 0.86$ and $r = 0.93$ in adult females [80, 108, 145]

Once androgens are quantified, it is necessary to delineate the boundary between normal and hyperandrogenemia. The diagnostic criteria do not explicitly give cutoffs for biochemical hyperandrogenism, but in practice, a common cutoff used is 2 standard deviations above the mean within ovulatory, nonhirsute women. This value will vary between studies and labs due to variability in measuring testosterone at the levels present in adult women [124].

3.2 Methods

3.2.1 Evaluation of hyperandrogenism within the study

Within the study, hirsutism was ascertained through the ICD-9 code 704.1. Acne was briefly considered for the study, since a third of younger PCOS women present with acne [15]. However, it is a nonspecific finding and there is no information about its severity within this dataset. Furthermore, due to its pervasiveness in adolescents and young adults in general, it is that unknown whether someone without an ICD diagnosis for acne is actually acne free and whether someone with an ICD diagnosis actually has a clinically severe case.

The cutoff points for biochemical hyperandrogenism was determined by finding the 95th percentile of free testosterone, bioavailable testosterone, and total testosterone within the study population, after excluding those with irregular menstrual cycles, hirsutism, and PCOM (Chapter 4). These empirical cutoffs were 12 pg/mL, 23.3 ng/dL, and 63 ng/dL, respectively.

3.2.2 Limit of detection

Prior to preprocessing, some entries in the free testosterone, total testosterone, and bioavailable testosterone data below the limit of detection (LOD). These were usually indicated by an entry that looks like "< LOD." These nondetects were assigned the value

$$\frac{\text{LOD}}{\sqrt{2}}. \tag{3.3}$$

Since the limit of detection was so far below cutoff points, nondetects did not affect the classification of those patients. Additionally, using $\frac{\text{LOD}}{\sqrt{2}}$ preserves the mean in normally distributed data.

Table 3.2. Summary of testosterone labs

Summary measure	Total testosterone	Bioavailable testosterone	Free testosterone
Min.	0.7	0.1	0.1
1st Quartile	20.0	3.4	1.8
Median	32.0	6.8	3.4
Mean	56.7	13.3	6.5
3rd Quartile	50.0	13.2	6.7
Max.	3784	3201	1408

3.3 Results

904 women had the code for hirsutism and 626 women had androgen levels above the cutoffs determined previously. Altogether, 1444 unique women had hyperandrogenemia. Table 3.2 gives the summary measures for total testosterone, bioavailable testosterone, and free testosterone.

3.4 Limitations

The total testosterone and bioavauilable testosterone cutoffs were comparable to those found in other studies, but the free testosterone cutoff measured here was over 30% greater than other estimates [5, 16, 82, 104]. The large difference is probably due to a bias toward abnormal values for women who are evaluated at a hospital. The following quantile-quantile plots comparing the distribution of the lab values to normality confirm that this is likely the case (Figure 3.1). Therefore, because the cutoffs are skewed higher, there are likely other women in the dataset who would be considered hyperandrogenic if cutoffs derived from an unselected population had been used instead.

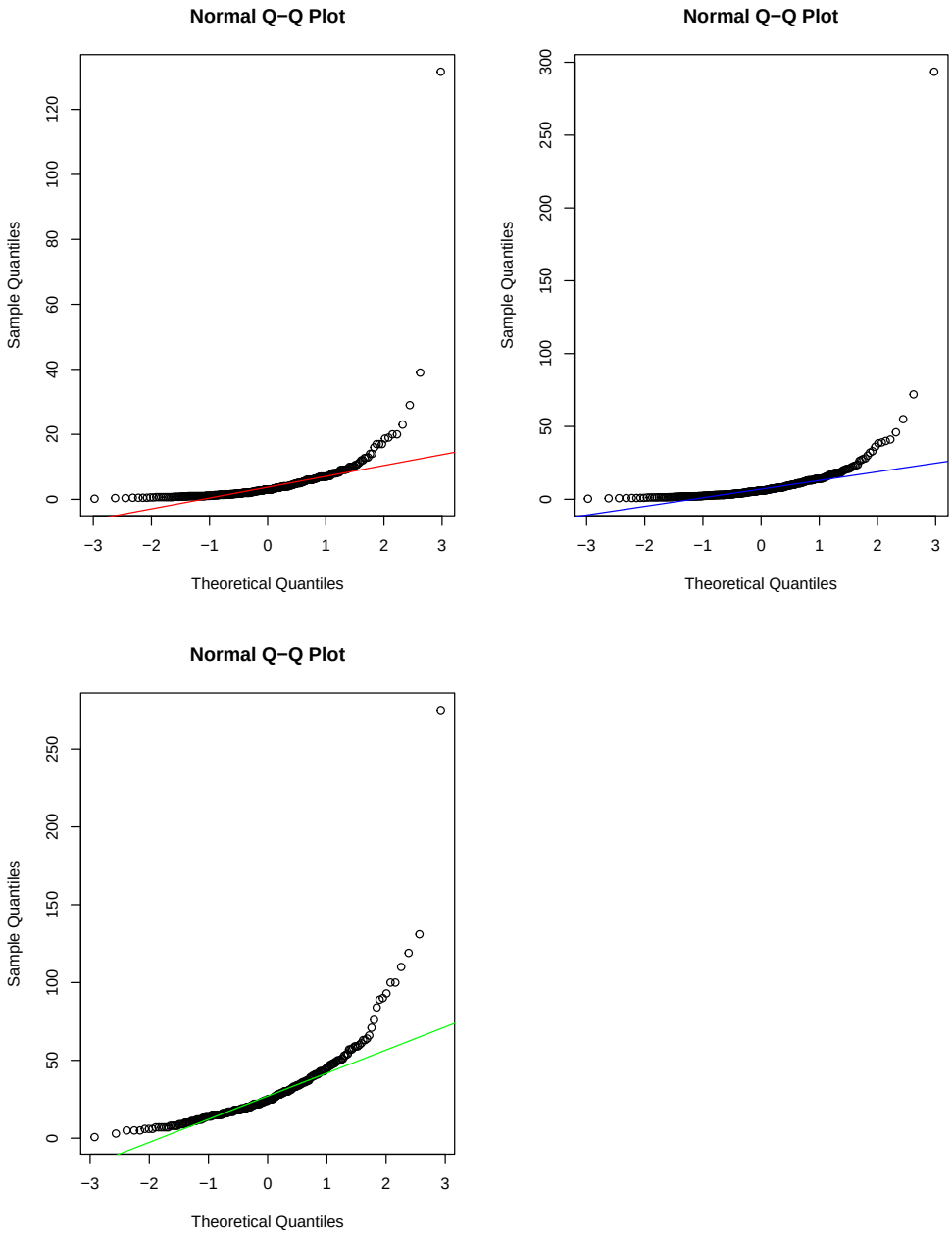

Fig. 3.1 Quantile-quantile plot of testosterone labs. The top left is free testosterone, top right is bioavailable testosterone, and bottom left is total testosterone. The data exhibit right-skewness, heavy-tailedness, and possible bimodality.

Chapter 4

Oligo-anovulation/oligo-amenorrhea

4.1 Background

Oligo-ovulation is infrequent or irregular ovulation and anovulation is the absence of ovulation [92]. Most polycystic ovary syndrome (PCOS) patients are diagnosed in an infertility clinic, first presenting with oligo- or anovulation [22]. For most patients, ovulation can be restored, but some studies have demonstrated that oligoovulatory PCOS women have milder symptoms than anovulatory women, and that they respond better to ovulation induction treatments and have higher live birth rates after fertility treatment [22, 71, 72].

4.1.1 Biological mechanism

The etiology of oligo-anovulation in PCOS is not fully understood and nearly 12% of PCOS patients who present with oligo- or amenorrhea still show signs of spontaneous ovulation [22]. As mentioned in the discussion of treatments in Section 1.3, weight loss and insulin sensitization often returns ovulation to PCOS women. Willis et al. found that granulosa cells from anovulatory PCOS women were more responsive to luteinizing hormone (LH) than granulosa cells from ovulatory PCOS women and suggest that insulin acts to sensitize granulosa cells to LH and leads to premature maturation of these cells [158]. In animal models, Wu et al. found that mice with diet-induced obesity were infertile and hyperandrogenic, while obese

mice with a disrupted insulin receptor gene on theca-interstitial cells in the ovary exhibited improved fertility and testosterone levels similar to lean mice [160].

4.1.2 Evaluation of oligo-anovulation and oligo-amenorrhea

The gold standard for detecting ovulation is ultrasound visualization, but methods involving the measurement of hormones in blood or urine have also been validated [7, 18, 116]. Currently, two main hormone markers are used to detect ovulation [74, 123]. The most common markers used are elevated serum progesterone and elevated urinary prenanediol 3-glucuronide [62, 90, 109, 114]. In practice, oligo-anovulation may be substituted by oligo-amenorrhea, defined as menstrual cycles longer than 35 days, and anovulation is usually diagnosed clinically as amenorrhea, defined as less than 10 menstruations per year [121].

4.2 Methods

4.2.1 Evaluation of oligo-anovulation within the study

Within the study, oligo-anovulation/oligo-amenorrhea was ascertained by the presence of ICD-9 codes 626.0, absence of menstruation; 626.1, scanty or infrequent menstruation; and 626.4, irregular menstrual cycle. One assumption here is that women who have irregular cycles will report it to their caregiver such that those without these ICD-9 codes will have fairly regular menstrual cycles. However, this may not necessarily be the case and it is almost certain that some women with irregular menstrual cycles were not detected. Some of the diagnoses appeared after documentation of menopause, so these were censored.

Table 4.1. Summary of age at diagnosis of irregular menstrual cycles

Summary measure	Value
Min.	24.0
1st Quartile	36.6
Median	40.2
Mean	39.6
3rd Quartile	42.9
Max.	45.0

4.3 Results

Using the ICD-9 codes, a total of 7088 premenopausal women were identified as having irregular menstrual cycles. Table 4.1 summarizes the age at diagnosis.

4.4 Limitations

One limitation of this method is that the women represented by this diagnostic code may include menopausal women. Even after excluding those given an ICD-9 code diagnosis, there remained subjects that received the diagnosis at age 45 (Table 4.1). The selection of 45 was arbitrary, and 44 or 43 could have just as easily been chosen. Thus, a minority of those identified may have had irregular menses due to an earlier menopause, rather than PCOS.

Chapter 5

Polycystic ovarian morphology

5.1 Background

The 2003 Rotterdam Consensus criteria that define polycystic ovary morphology (PCOM) as the "Presence of 12 or more follicles in each ovary measuring 29 mm in diameter, and/or increased ovarian volume (10 mL)," are based off of Pache et al., 1992; van Santbrink et al., 1997; and Jonard et al., 2003 [78, 117, 144], which were the available literature at the time. Since then, there is evidence that the improved resolution of newer ultrasound technology increases the number of observable follicles, and thus inflates the number of PCOM that is diagnosed [36]. For this reason, some authors have proposed changing the cutoff from 12 follicles to 20 or abandoning ultrasound altogether in favor of other biomarkers, such as serum anti-Müllerian hormone (AMH) [37, 46]. Current open questions about PCOM include characterizing the variability of ovarian volume measurements and understanding its physiology.

5.2 Methods

5.2.1 Description of the problem

Although the images themselves were not used in this analysis, the great majority of ultrasounds included 3-dimensional measurements of ovarian size and details about ovarian morphology, including the counts, echogenicity, and sizes of folli-

cles and other ovarian abnormalities. This enabled calculation of ovarian volume to compare with the cutoff of 10 ml given by the Rotterdam Criteria in the absence of a dominant follicle, "According to the available literature, the criteria fulfilling sufficient specificity and sensitivity to define PCO are the following: 'presence of 12 or more follicles in each ovary measuring 29 mm in diameter, and/or increased ovarian volume (>10 ml)'. The subjective appearance of PCO should not be substituted for this definition" [126].

Of the three PCOS diagnostic criteria, evaluating for polycystic ovary morphology from radiology notes was the most challenging. Physician notes were pulled from the Clinical Data Warehouse (CDW) about the indication, findings, and impression for each pelvic ultrasound. There were 39,093 ultrasounds in the database for 25,535 unique patients and in total, this corpus consisted of 3,707,837 words, with each observation containing 94.84657 words on average. As a comparison for understanding the magnitude of this dataset, Herman Melville's *Moby-Dick* is 209,117 words long. Here is what a typical observation might look like:[1]

> **ID:** 10469
>
> **Clinical date:** 5/7/2007
>
> **History:** 38-year-old female with right lower quadrant cystic lesion identified on CT scan of April 30; 2007. Patient dictaphone tb with April 16; 2007.
>
> **Findings:** Transvaginal pelvic ultrasound was performed for optimum visualization of the uterus and the adnexa. Transabdominal pelvic ultrasound was performed for evaluation of the remainder of the pelvic contents. Uterus measures 6.7x5.0x5.4 cm. . Endometrial stripe measures 8 mm. Myometrium appears heterogeneous with areas of shadowing and subtle cystic areas within the my-

[1] All patient identifiers were stripped before analysis. Shown below is a randomized study ID.

ometrium. The appearance suggests adenomyosis. No discrete submucosal fibroid identified. Right ovary measures 6.5x6.3x5.7 cm. There is a cyst measuring approximately 6 cm in size located centrally within the right ovary with a thin rim of peripheral tissue. Cyst is hemorrhagic with low-level internal echoes. No solid component a mural nodule. The cyst is avascular. Taking into account differences in imaging technique; the cyst appears to have increased in size compared to the CT scan. Would recommend followup ultrasound in approximately 2 or 3 menstrual cycles. If cyst persists; would recommend MRI for further evaluation. Left ovary measures 2.9x1.7x2.16. Left ovary is normal. No free pelvic fluid. Limited evaluation of the right and left kidneys demonstrates no obstruction.

Impression: Approximate 6 cm hemorrhagic appearing cyst in the right ovary which appears to have enlarged compared to a prior CT scan; as described . Would recommend followup ultrasound in approximate 2 or 3 menstrual cycles. If cyst persists; would recommend MRI for further evaluation. Evidence for adenomyosis of the uterus. MRI can be used to confirm suspected adenomyosis if clinically indicated.

From this type of data, it was necessary to extract measurements of each ovary, assign the measurement to the proper side, "avoid" notes about other organs, and identify important morphological features.

5.2.2 Approach to the problem

The general strategy was to make use of the pervasive ovarian volume measurements and compare them to the threshold provided by the diagnostic criteria. Since ovarian volume changes along the menstrual cycle, using the volume cut-off for PCOM requires that ovarian volume is caused by stromal expansion seen in polycystic ovary syndrome (PCOS) and is not confounded by the volume of a

dominant follicle. Thus to make full use of this volume cutoff, those that had enlarged ovaries but also some "volume confounder"[2] that contributed to this increased volume had to be noted and marked as "unidentifiable in the current examination," as per the 2006 AE-PCOS task force guideline, "Evidence of a dominant follicle or a corpus luteum necessitates examination during the next cycle and presence of an abnormal cyst or ovarian asymmetry further investigation" [15]. Thus, following the criteria guidelines, an ultrasound classifier should sort pelvic ultrasouds into PCOM-present, PCOM-absent, and unidentifiable.[3]

If ovaries were larger than the cutoff and there were no volume confounders, they were considered to have PCOM. If volume confounders were present, then they were marked as unidentifiable. If the ovaries were smaller than the cutoff, then they were marked as free from PCOM.

Many ultrasounds also included sentences with language similar to the following: numerous follicles arranged in a peripheral distribution indicative of PCOS, and although fewer also explicitly gave counts for the amount of follicles, those that included both found greater than 10 follicles. Therefore, ultrasounds including phrases equivalent to numerous peripheral follicles also were recognized as having PCOM.

Algorithm 1 summarizes the strategy and it is equivalent to the coding schema outlined in Table 5.1:

[2] A more precise definition of this term will be given in section 5.2.4

[3] "Unidentifiable" is an actual category and is not the same as missing data, as this is what a trained human ultrasonographer should declare the ovaries to be with regards to PCOM status.

Algorithm 1 Ultrasound classifier pseudocode

```
1:  procedure Calculate ovarian volumes
2:      for all ovaries do
3:          extract ovarian measurements with regular expressions
4:  procedure Determine presence of volume confounders
5:                                              ▷ details given in section 5.2.4
6:  procedure Determine presence of numerous peripheral follicles
7:                                              ▷ details given in section 5.2.4
8:  procedure Classifying each ovary
9:      for all ovaries do
10:         if this ovary has "numerous peripheral follicles" then
11:             mark it as PCOM-present
12:         else if this ovary is larger than 10 ml then
13:             check for the presence of a volume confounder.
14:             if a "volume confounder" is present in this ovary then
15:                 mark the ovary as "undiscernible in this ultrasound"
16:             else
17:                 mark the ovary as PCOM-present
18:         else if this ovary is smaller than 10 ml then
19:             mark the ovary as PCOM-absent
20:         else if this ovary is not visualized then
21:             mark the ovary as "undiscernible in this ultrasound"
22: procedure Classifying patient status
23:     for all patients do
24:         if either ovary is PCOM-present then
25:             the subject has PCOM
26:         else if both ovaries are PCOM-absent then
27:             the subject does not have PCOM
28:         else if one ovary is PCOM-absent and the other is undiscernible then
29:             the subject does not have PCOM
30:         else if both ovaries are undiscernible then
31:             the subject is undiscernible in this evaluation
```

Table 5.1: Coding table for patient status based on the 6 extracted features

Ovarian vol. (L) mL	Numer. per. folls. (L) yes/no	Vol. confounder (L) yes/no	Ovarian vol. (R) mL	Numer. per. folls. (L) yes/no	Vol. confounder (L) yes/no	PCOM status[1]
>10	1	0	>10	1	0	1
>10	0	1	>10	1	0	1
>10	0	0	>10	1	0	1
<10	1	0	>10	1	0	1
<10	0	1	>10	1	0	1
<10	0	0	>10	1	0	1
NA	1	0	>10	1	0	1
NA	0	1	>10	1	0	1
NA	0	0	>10	1	0	1
>10	1	0	>10	0	1	1
>10	0	1	>10	0	1	0
>10	0	0	>10	0	1	1
<10	1	0	>10	0	1	1
<10	0	1	>10	0	1	0
<10	0	0	>10	0	1	0
NA	1	0	>10	0	1	1
NA	0	1	>10	0	1	0
NA	0	0	>10	0	1	0
>10	1	0	>10	0	0	1
>10	0	1	>10	0	0	1
>10	0	0	>10	0	0	1
<10	1	0	>10	0	0	1
<10	0	1	>10	0	0	1
<10	0	0	>10	0	0	1
NA	1	0	>10	0	0	1
NA	0	1	>10	0	0	1
NA	0	0	>10	0	0	1
>10	1	0	<10	1	0	1

Table 5.1 – Continued

Ovarian vol. (L) mL	Numer. per. folls. (L) yes/no	Vol. confounder (L) yes/no	Ovarian vol. (R) mL	Numer. per. folls. (L) yes/no	Vol. confounder (L) yes/no	PCOM status[1]
>10	0	1	<10	1	0	1
>10	0	0	<10	1	0	1
<10	1	0	<10	1	0	1
<10	0	1	<10	1	0	1
<10	0	0	<10	1	0	1
NA	1	0	<10	1	0	1
NA	0	1	<10	1	0	1
NA	0	0	<10	1	0	1
>10	1	0	<10	0	1	1
>10	0	1	<10	0	1	0
>10	0	0	<10	0	1	1
<10	1	0	<10	0	1	1
<10	0	1	<10	0	1	-1
<10	0	0	<10	0	1	-1
NA	1	0	<10	0	1	1
NA	0	1	<10	0	1	-1
NA	0	0	<10	0	1	-1
>10	1	0	<10	0	0	1
>10	0	1	<10	0	0	0
>10	0	0	<10	0	0	1
<10	1	0	<10	0	0	1
<10	0	1	<10	0	0	-1
<10	0	0	<10	0	0	-1
NA	1	0	<10	0	0	1
NA	0	1	<10	0	0	-1
NA	0	0	<10	0	0	-1
>10	1	0	NA	1	0	1
>10	0	1	NA	1	0	1
>10	0	0	NA	1	0	1
<10	1	0	NA	1	0	1

Table 5.1 – Continued

Ovarian vol. (L) mL	Numer. per. folls. (L) yes/no	Vol. confounder (L) yes/no	Ovarian vol. (R) mL	Numer. per. folls. (L) yes/no	Vol. confounder (L) yes/no	PCOM status[1]
<10	0	1	NA	1	0	1
<10	0	0	NA	1	0	1
NA	1	0	NA	1	0	1
NA	0	1	NA	1	0	1
NA	0	0	NA	1	0	1
>10	1	0	NA	0	1	1
>10	0	1	NA	0	1	0
>10	0	0	NA	0	1	1
<10	1	0	NA	0	1	1
<10	0	1	NA	0	1	-1
<10	0	0	NA	0	1	-1
NA	1	0	NA	0	1	1
NA	0	1	NA	0	1	0
NA	0	0	NA	0	1	0
>10	1	0	NA	0	0	1
>10	0	1	NA	0	0	0
>10	0	0	NA	0	0	1
<10	1	0	NA	0	0	1
<10	0	1	NA	0	0	-1
<10	0	0	NA	0	0	-1
NA	1	0	NA	0	0	1
NA	0	1	NA	0	0	0
NA	0	0	NA	0	0	0

[1] An asterisk (*) denotes IRDCs with more than one detected velocity component.

5.2.3 Evaluation of ovarian volumes

The ovarian measurements were fairly regular. Most tended to be in the form "#.# × #.# × #.#cm" and variations tended to occur in spacing, use of centimeters vs millimeters, and the number of significant digits. Units were converted and variation in spacing and number of digits was taken care of by using regular expressions in the *stringr* package in R by Hadley Wickham [153]. The one used here was:

$$[[:digit:]]+[.]*[[:digit:]]*[x][[:digit:]]+[.]*[[:digit:]]*[x][[:digit:]]+[.]*[[:digit:]]*. \tag{5.1}$$

Another pitfall was that sometimes ultrasounds included 3 dimensional measurements of other organs, such as kidneys and the uterus. In this case, sentences mentioning these other organs were removed from each observation before extracting measurements. To calculate the volume, the formula

$$length \times width \times height \times \pi/6 \tag{5.2}$$

as recommended in Balen et al. (2003) [19] is used.

5.2.4 Determining presence of volume confounders and numerous peripheral follicles

In order to accurately distinguish between enlarged ovaries due to increased stromal volume and enlarged ovaries due to recruitment of a dominant follicle or due to presence of abnormal pathology, a comprehensive list of reasons that could confound the representation of stromal volume through total ovarian volume needed to be determined.

This list was constructed empirically with natural language processing techniques, by using the ultrasound text. The general idea is to find words and n-

grams (phrases) correlated with a large ovarian volume, calculated previously. This approach offered two distinct advantages: firstly, this ensured that all possible reasons in the dataset are accounted for once the full list of reasons is generated and secondly, this implicitly accounts for the natural language of the data, or the multitude of ways radiologists could write about these volume confounders. Typically these two problems are impossible to solve *a priori*. To do accomplish this goal, two R packages were relied on extensively: the *tm* package by Ingo Feinerer was used as a text mining framework and the *SnowballC* package by Milan Bouchet-Valat was used for its text stemming capabilities [21, 50, 51].

The first step was to create a *Corpus*, an abstract representation of the collection of documents, in this case, the collection of ultrasound notes. Each unique ultrasound then becomes a document in this *Corpus* object. The next step was cleaning the documents in the *Corpus* so that the natural language processing tools from *tm* package could be applied. First, extra whitespace was stripped from each document and punctuation removed. Since the actual way the word is expressed is not as important as identifying similar concepts together, this allows "play" and "play," to be considered the same term. Next, all letters were converted to lower case (R is case-sensitive), then numbers and English stopwords (a, the, for, etc.) were removed, since they are not as informative and increase dimensionality greatly. Here is how a typical document appears after this process:[4]

> **id**
>
> **clinical date**
>
> **history** yearold female right lower quadrant cystic lesion identified ct scan april
>
> patient dictaphone tb april
>
> **findings** transvaginal pelvic ultrasound performed optimum visualization uterus

[4]Bolding and linebreaks are added for emphasis and legibility.

adnexa transabdominal pelvic ultrasound performed evaluation remainder pelvic contents uterus measures xx cm endometrial stripe measures mm myometrium appears heterogeneous areas shadowing subtle cystic areas within myometrium the appearance suggests adenomyosis no discrete submucosal fibroid identified right ovary measures xx cm there cyst measuring approximately cm size located centrally within right ovary thin rim peripheral tissue cyst hemorrhagic lowlevel internal echoes no solid component mural nodule the cyst avascular taking account differences imaging technique cyst appears increased size compared ct scan would recommend followup ultrasound approximately menstrual cycles if cyst persists recommend mri evaluation left ovary measures xx left ovary normal no free pelvic fluid limited evaluation right left kidneys demonstrates obstruction **impression** approximate cm hemorrhagic appearing cyst right ovary appears enlarged compared prior ct scan described would recommend followup ultrasound approximate menstrual cycles if cyst persists recommend mri evaluation evidence adenomyosis uterus mri can used confirm suspected adenomyosis clinically indicated

After this point, the text is still relatively comprehensible. The final step of preprocessing was a process called "stemming." Stemming represents all words with the same root as the same entity. For example "measures" and "measuring" both become considered the same term, "measur." After stemming, the text begins to look more like a sequence of words. Here is how a typical ultrasound looks after this process:

id

clinic date

histori yearold femal right lower quadrant cystic lesion identifi ct scan april patient dictaphon tb april

find transvagin pelvic ultrasound perform optimum visual uterus adnexa transabdomin pelvic ultrasound perform evalu remaind pelvic content uterus **measur** xx cm endometri stripe measur mm myometrium appear heterogen area shadow subtl cystic area within myometrium the appear suggest adenomyosi no discret submucos fibroid identifi right ovari measur xx cm there cyst **measur** approxim cm size locat central within right ovari thin rim peripher tissu cyst hemorrhag lowlevel intern echo no solid compon mural nodul the cyst avascular take account differ imag techniqu cyst appear increas size compar ct scan would recommend followup ultrasound approxim menstrual cycl if cyst persist recommend mri evalu left ovari measur xx left ovari normal no free pelvic fluid limit evalu right left kidney demonstr obstruct

impress approxim cm hemorrhag appear cyst right ovari appear enlarg compar prior ct scan describ would recommend followup ultrasound approxim menstrual cycl if cyst persist recommend mri evalu evid adenomyosi uterus mri can use confirm suspect adenomyosi clinic indic

After preprocessing, a document term matrix was constructed from the *Corpus*. In a document term matrix (or term document matrix), each row represents a document and each column represents a term. The number of rows corresponds to the number of documents in the *Corpus*, and the number of rows corresponds to the number of unique words in the entire *Corpus* (after stemming and exclusion of stopwords). The document term matrix thus represents a table of frequency counts with cells corresponding to the number of times each word appears in each document (Table 5.2.4).

Since the goal is to find terms that represent structures that confound the identification of large stromal volume, the next step was to use the ovarian volumes calculated in Section 5.2.3 and crudely classify the ultrasound documents

Table 5.2 Example document term matrix with m documents and n unique terms

	Term 1	Term 2	Term 3	...	Term n
Document 1	3	1	4	...	1
Document 2	5	9	2	...	6
Document 3	5	3	5	...	8
...	...	...	...	...	...
Document m	9	7	9	...	3

Note. — For $0 \leq i \leq m$ and $0 \leq j \leq n$, the $\{i,j\}$ cell indicates frequency count for the number of times term j appears in document i.

into those with large (>10 ml) and small (<10ml) ovaries. Next, the terms were sorted into the order of their correlation with being either associated with either large or small ovaries. Lastly, the top terms that represented a condition or structure that confounds the stromal volume were chosen manually [15]. Table 5.3 gives the list of volume confounders that were included as features after variable selection. The ultrasounds reports that included these terms within the context of describing the ovaries were marked as having volume confounders.

The process for identifying phrases that indicated the physician positively identified PCOM was similar. Ultrasound reports that described ovaries as having "numerous" or "peripheral" follicles or a "PCOS-like distribution" of follicles indicated PCOM.

5.3 Results

Of the 39,093 observations, there were 8,439 observations classified as having PCOM, 18,606 observations classified as not having PCOM, and 12,048 observations as unidentifiable. Among the 8439 observations of polycystic ovarian morphology, there were 7104 unique patients.

Table 5.3. Terms representing presence of volume confounders

Term	Indicates presence of
Anechoic	a region that is solid or fluid-filled
Corpus luteum	a single dominant follicle
Cyst (singular)	a single dominant follicle
Decreased	a structure noted on a previous examination that is still present
Dermoid	an ovarian cyst containing hair, bone, fluid, skin, or teeth
Dominant	a single dominant follicle
Endometrioma	a cystic mass, formed from endometrial tissue in the ovary containing brown, tar-like fluid [103]
Follicle (singular)	a single dominant follicle
Hemorrhagic	a cyst formed from bleeding into a follicular or corpus luteal cyst [163]
Heterogeneity	abnormal tissue within the ovary
Hypoechoic region	a region that is solid or fluid-filled
Interval resolution	a structure noted on a previous examination that is still present
Large	an internal structure
Lesion	an internal structure
Nodule	an internal structure
Simple	dominant follicles
Single	an internal structure
Structure	an internal structure
Two	multiple internal structures

5.4 Validation of methods

At the test time, a random sample of 1000 out of 39,093 were hand-checked for accuracy. This was done blinded to the results of the automatic classification program. The results are summarized in Table 5.4. Out of 1000 test cases, only 16 were incorrectly classified. Thus, the classification accuracy was 98.4%. Of these 16, further examination of examined why the model classified PCOM status incorrectly found that 7 errors were typographical errors very difficult for a program to parse and 9 were errors due to the classifier.

Of the 7 typographical errors, 6 cases were due to a typo by the radiologist in recording the measurements of ovaries; in one instance, the lack of a decimal point (2.7x25x2.7 cm vs 2.7x2.5x2.7 cm) led to an absurdly high value. In another case, a multiplication sign instead of a decimal point also led to a large value (2x9x2.3x1.9 cm vs 2.9x2.3x1.9 cm). Sometimes errors appeared due to dictation software (2.7x2.6 six3.7 vs 2.7x2.6x3.7 cm) led to the string of text not being recognized as a valid measurement text. The other case, "the left ovary" was incorrectly written as "the left kidney" in a context that would be relatively easy for a human with domain knowledge to recognize the mistake, but the program reads the sentences too literally: "The right ovary measures 3.5x2.3x3.2cm and the left kidney measures 2.6x3.2x3.3cm. Both ovaries are normal in size; shape and echogenicity." A human trained would be able to recognize these errors and correct them, so these were still counted as errors of automatic classification.

The other 9 errors are attributed to the shortcomings classification method itself, and they are all errors of not being able to incorporate relevant information in a second sentence with a pronoun. For example, these sentences about the right ovary were not understood to indicate that there is a volume confounder present: "The right ovary is normal in size and echotexture and measures 2.5x3x2.3 cm.

Table 5.4. Summary of error rates

Variable	Error rate
Overall PCOM status	1.6% (16/1000)
Ovarian measurements	0.8% (16/2000)
Presence of numerous peripheral cysts	0.0% (0/2000)
Presence of volume confounder	1.2% (23/2000)

It contains a simple cyst measuring 2.4x2.1 cm." More powerful natural language processing methods such as object identification and part of speech tagging could deal with the issues arising from information contained in second sentences with pronouns. The program does not identify the "It" in the second sentence as the same object as the right ovary mentioned in the first sentence. Still, an overall error rate of 1.6% achieved with only shallow statistical learning methods is quite impressive.

In addition to the overall PCOM status, each test case is associated with six other variables: the ovarian volume, presence of numerous peripheral follicles in the ovary and presence of a volume confounder in the ovary, on each side. Thus, the program evaluates $6 \cdot 1000 = 6000$ other variables, and there were 40 variables marked incorrectly. Here, the accuracy was 99.33%. Only 38 test cases contained any errors, including the 16 whose overall PCOM status was classified incorrectly. Thus, 22 others contained minor errors in secondary variables, but these did not affect their overall classification. Notably, the error rate for identifying numerous follicles in a peripheral orientation was perfect. Here, the reasons for the errors were similar. Table 5.3 summarizes the errors.

Here is the multi-class confusion matrix 5.5 and the recall and precision for the labels 5.6.

Table 5.5 Multi-class confusion matrix for actual (A) vs predicted (P) ultrasound classification labels

	Absent (A)	Unidentifiable (A)	Present (A)	
Absent (P)	474	1	0	475
Unidentifiable (P)	1	316	2	319
Present (P)	2	10	194	206
	477	327	196	Totals

Table 5.6. Recall and precision for classification labels

Label	Recall	Precision
Absent	99.4% (474/477)	99.8% (474/475)
Unidentifiable	96.6% (316/327)	99.1% (316/319)
Present	99.0% (194/196)	94.2% (194/206)

5.5 Limitations

It is not guaranteed that this method would work well on similar ultrasound report datasets generated throughout the Anglosphere. The major limitations of this protocol are its indifference to pronouns and recognition of past vs. present. Thus, a team of radiologists whose writing styles use these elements of language more often than average would generate a more stubborn dataset.

Chapter 6

Evaluation of PCOS in the study

6.1 Identifying PCOS

As mentioned in Section 2.1, the inclusion criteria of the study was record of at least one aspect of the Rotterdam diagnostic criteria. Table 6.1 summarizes the definition of the phenotypes ascertained in this study and Table 6.2 summarizes the frequency counts for each of the phenotypes. In total, 2421 women were identified as having polycystic ovary syndrome (PCOS). Of the Rotterdam phenotypes, the Non-PCO phenotype was the most commonly identified. Its frequency relative to the other phenotypes should not be understood as representing the proportion within the general population population, since far more women (25,535) were evaluated for a pelvic ultrasound than testosterone lab (5254). In order to draw population level estimates, poststratification would be first be necessary [68].

6.2 Race-specific PCOS and undiagnosed PCOS

A recent study investigating PCOS prevalence have suggested that as many as 60% of PCOS cases may be undiagnosed [104]. The same study found that in their sample, 30-50% of PCOS women were previously determined as being PCOS-free.

There exists an ICD-9 code for PCOS diagnoses 256.4 and throughout the analysis, some patients were identified as having PCOS (by means of their lab,

Table 6.1. Phenotype definitions

Phenotype	HA	IM	PCOM
Frank PCOS	+	+	+
Non-PCO PCOS	+	+	-
Ovulatory PCOS	+	-	+
Normoandrogenic PCOS	-	+	+
Underdetermined PCOS[1]			
1990 NIH PCOS	+	+	Any
Andro-agnostic PCOS	Any	+	+
Single cardinal feature			
Only HA	+	-	-
Only IM	-	+	-
Only PCOM	-	-	+

[1]The Any in the underdetermined subtypes can take on all values. E.g. the Frank PCOS and Non-PCO PCOS phenotypes are subsets of the 1990 NIH PCOS.

ultrasound, and menstrual data), but never having an ICD diagnosis. It is unclear how many of these actually represent undiagnosed cases – perhaps some physicians will take note of the patients PCOS in other ways and not through the ICD-9 code. In practice, a relatively extensive workup is required for a diagnosis of PCOS, and a positive determination will usually be recorded with an ICD-9 code. Thus, it can said with fair certainty that those without ICD-9 codes are not diagnosed with PCOS. Overall, 2421 patients were identified as having PCOS, and of those, 1010 did not have an ICD-9 code indicating the presence of PCOS. An apt question is then, what does this group of undiagnosed PCOS women "look" like? In other words, what is the composition of this group?

Table 6.2. Phenotype frequency

Phenotype	Frequency
Study population	37959
All identifiable PCOS	2421
ICD identified PCOS	1411
No ICD PCOS	1010
Rotterdam phenotypes	
Frank PCOS	124
Non-PCO PCOS	57
Ovulatory PCOS	140
Normoandrogenic PCOS	250
Underdetermined PCOS	
1990 NIH PCOS	482
Andro-agnostic PCOS	876
Single cardinal feature	
Only HA	111
Only IM	238
Only PCOM	310

Using a logistic regression model, odds ratio were calculated with race as a predictor. Then compared to the White PCOS women, Black PCOS women have 2.09 times the odds of being undiagnosed. There also seems to be some moderate disparity between non-Hispanic Whites and Hispanic patients, with the logistic regression giving an odds ratio of 1.19. Given that a diagnosis of These results are concerning especially in the light of evidence that shows that Hispanics and Blacks are at greater risk for diabetes and cardiovascular disease [105, 119].

Table 6.3. Race-specific comparisons

Race	All PCOS (n=2421) % (n)	ICD PCOS (n=1411) % (n)	No ICD PCOS (n=1010) % (n)	No ICD rate % (n/n)
American Indian/Native American	0.5% (13)	0.5% (7)	0.6% (6)	46.2% (6/13)
Asian	3.4% (81)	3.9% (55)	2.6% (26)	32.1% (26/81)
Black/African American	50.0% (1210)	43.2% (609)	59.5% (601)	49.7% (601/1210)
Hispanic/Latino	14.7% (356)	16.2% (228)	12.7% (128)	36.0% (128/356)
Middle Eastern	1.5% (37)	1.1% (15)	2.2% (22)	59.5% (22/37)
Native Hawaiian/Pacific Islander	<0.1% (1)	<0.1% (1)	0% (0)	0.00% (0/1)
White	22.4% (542)	26.1% (368)	17.2% (174)	32.1% (174/542)
Other/Multiracial	4.7% (113)	5.2% (74)	3.6% (39)	34.5% (39/113)

Table 6.4. Odds of being undiagnosed

Race[1]	OR (95% CI)
Asian	1.00 (0.60, 1.63)
Black/African-American	2.09 (1.69, 2.59)
Hispanic/Latino	1.19 (0.90, 1.57)
Other/Multiracial	1.11 (0.72, 1.70)

[1]The referent group is Non-Hispanic White women.

6.3 Conclusion

This thesis endeavored to lay the groundwork for a PCOS study based off the Boston Medical Center (BMC) Clinical Data Warehouse (CDW) data. Chapter 1 gave an introduction to PCOS, Chapter 2 described the general characteristics about the study population and aspects of cleaning the data, and Chapters 3, 4, and 5 described the cardinal features of PCOS in this dataset.

Examination of error sources suggest there may be diminished returns in pursuing performance gains through more computationally intensive techniques like word vectors and part of speech tagging. Future research in PCOS ultrasound feature extraction should be directed towards methods for the raw ultrasound images themselves. Ascertaining PCOS through the medical record offers advantages over self-reported PCOS, including confirmation of disease and existence of recorded measurements. This preliminary evidence indicates that Black PCOS women may be at a greater risk of being undiagnosed. In the future, this work could be used in conjunction with data on patients' cardiovascular and metabolic outcomes for studying the longitudinal health risks of PCOS.

List of Journal Abbreviations

Acta Obstet Gynecol Scand	Acta Obstetricia et Gynecologica Scandinavica
Am J Obstet Gynecol	American Journal of Obstetrics & Gynecology
Am J Ophthalmol	American Journal of Ophthalmology
Ann Epidemiol	Annals of Epidemiology
Annu Rev Biochem	Annual Review of Biochemistry
Arch Dermatol	Archives of Dermatology
Arch Gynecol Obstet	Archives of Gynecology & Obstetrics
Arch Intern Med	Archives of Internal Medicine
Arch Sex Behav	Archives of Sexual Behavior
Aust Nz J Obstet Gyn	Australian & New Zealand Journal of Obstetrics & Gynaecology
Best Pract Res Cl En	Best Practice & Research Clinical Endocrinology & Metabolism
Biochem Biophys Res Commun	Biochemical & Biophysical Research Communications
Bjog-int J Obstet Gy	BJOG: an International Journal of Obstetrics & Gynaecology
Bmc Med Genet	BMC Medical Genetics
Brit Med J	British Medical Journal
Clin Chem	Clinical Chemistry
Clin Endocrinol	Clinical Endocrinology
Clin Endocrinol Meta	Clinics in Endocrinology & Metabolism
Cochrane Db Syst Rev	Cochrane Database of Systematic Reviews
Endocr J	Endocrine Journal
Eur J Contracep Repr	European Journal of Contraception & Reproductive Health Care
Eur J Endocrinol	European Journal of Endocrinology

Eur J Obstet Gyn R B	European Journal of Obstetrics & Gynecology & Reproductive Biology
Expert Opin Inv Drug	Expert Opinion On Investigational Drugs
Fertil Res Pract	Fertility Research and Practice
Fertil Steril	Fertility & Sterility
Gynecol Endocrinol	Gynecological Endocrinology
Hum Biol	Human Biology
Hum Reprod	Human Reproduction
Hum Reprod Update	Human Reproduction Update
Int J Gynecol Obstet	International Journal of Gynecology & Obstetrics
J Am Acad Dermatol	Journal of The American Academy of Dermatology
J Clin Endocr Metab	Journal of Clinical Endocrinology & Metabolism
J Gen Intern Med	Journal of General Internal Medicine
J Med Assoc Thailand	Journal of The Medical Association of Thailand
J Obstet Gynaecol Can	Journal of Obstetrics & Gynaecology Canada
J Obstet Gynaecol Re	Journal of Obstetrics & Gynaecology Research
J R Stat Soc Ser A-g	Journal of The Royal Statistical Society Series A (General)
J Sex Med	Journal of Sexual Medicine
J Stat Softw	Journal of Statistical Software
J Steroid Biochem	Journal of Steroid Biochemistry & Molecular Biology
J Steroid Biochemist	Journal of Steroid Biochemistry
J Ultras Med	Journal of Ultrasound in Medicine
Metab Syndr Relat D	Metabolic Syndrome & Related Disorders
Metabolis	Metabolism
Mol Endocrinol	Molecular Endocrinology
Nat Rev Genet	Nature Reviews Genetics
Nestle Nutr Works Se	Nestle Nutrition Workshop Series

New Engl J Med	New England Journal of Medicine
Obes Rev	Obesity Reviews
Obstet Gynecol	Obstetrics & Gynecology
Oman Med J	Oman Medical Journal
Postgrad Med J	Postgraduate Medical Journal
Reprod Biol Endicrinol	Reproductive Biology & Endocrinology
Reprod Biomed Online	Reproductive Biomedicine Online
Semin Cutan Med Surg	Seminars in Cutaneous Medicine & Surgery
Surv Ophthalmol	Survey of Ophthalmology
Trends Endocrin Met	Trends in Endocrinology & Metabolism
Turk J Med Sci	Turkish Journal of Medical Sciences
Women Health	Women & Health
Yonsei Med J	Yonsei Medical Journal

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