Investigation of the biochemical and clinical phenotype in women with polycystic ovary syndrome

By

Punith Kempegowda

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Institute of Metabolism and Systems Research

College of Medical and Dental Sciences

The University of Birmingham

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Abstract

Objectives

- Establish the distinct androgen signature in a healthy population
- Investigate whether people with PCOS have a high prevalence of anxiety, depression, and body dysmorphia
- Take steps to include people with PCOS in designing and delivering education regarding the condition can help us reduce the gaps in knowledge, attitude, and practice of PCOS.

Methods

The objectives were addressed in four parts:

- Morning serum and saliva samples were collected from 290 and 83 healthy volunteers respectively. Serum and salivary steroids were quantified by liquid chromatography-tandem mass spectrometry profiling assays (Healthy volunteer study).
- 1006 women completed an online survey which included validated questionnaires on four domains: Emotional wellbeing (anxiety and depression), body image, weight-related stigma, and sexual function (Blue Morpho study).
- 43 women aged 18-60 years were invited to complete an online survey about their lived experiences at the onset of the symptoms of PCOS, their journey during diagnosis, an explanation of PCOS to their younger self, and any advice for their younger self (PCOS pearls study).
- HCP and people with PCOS underwent simulation-based and workshop-based learning respectively on four PCOS case scenarios. Data regarding confidence

and expectations regarding PCOS were collected pre- and post-simulation. Wilcoxon Signed-Rank test was used to compare change in confidence levels. Thematic induction was used to identify areas of gaps between expectation and delivery of care (SIMBA-PCOS study).

Results

Healthy volunteer blood samples confirmed that 11-oxygenated androgens form a stable circulating pool of androgens during adulthood, while classic androgens decline with age and are subject to menstrual cycle-dependent variation. In Blue morpho study, we found women of non-white ethnicity (611/1003) reported a higher depression (OR 1.96 [95% CI 1.41-2.73]) and lower BDD (OR 0.57 [95% CI 0.41-0.79]) rates, than white ethnic women (392/1003). In PCOS Pearls, we found that people with PCOS were impacted significantly by their symptoms and many women feel dissatisfied with the support they receive from healthcare professionals. In SIMBA PCOS, HCPs reported increased confidence to manage PCOS cases (simulated: +41.0%, $p<0.001$; non-simulated: +40.0%, $p<0.001$; all: +40.5%, $p<0.001$). There was 6.25% ($p=0.0141$) and 17.7% ($p=0.0002$) increase in PPI participants' confidence in HCPs to diagnose and manage PCOS-related issues respectively.

Conclusions

A combination of classic and 11-oxygenated androgens can be used to understand the impact of androgen excess in PCOS. There is a need for tailored, multidisciplinary approach to the management of people with PCOS in the community and improving awareness amongst primary healthcare to improve patient care.

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My heartfelt gratitude to my family who continue to stand by me throughout all the ups and downs of this journey. Coming from a large family, I will probably need a chapter if I were to name and thank them individually. However, I would like to make special mentions to my appa- Thyloor Chikkakullegowda Kempegowda, amma- Jayalakshmi Kempegowda, akka- Anitha Kempegowda, thamma- Manith Kempegowda, naadini- Asha Manith and the newest addition to our family, nam kulaputra- Jaivik Manas Gowda, for unconditional support so I can focus on my PhD.

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List of abbreviations

17OH-Preg: 17 hydroxy progesterone

ACC: Adrenocortical carcinoma

ACGME: Accreditation Council for Graduate Medical Education

ACTH: Adrenocorticotropic Hormone

AE-PCOS: The Androgen Excess and PCOS Society

AKR: Aldo-keto reductase

AMP: Adenosine Monophosphate

aOR: Adjusted Odds Ratio

AR: androgen receptor

ATP: Adenosine Triphosphate

BAOP: Beliefs About Obese Persons

BAT: Brown Adipose Tissue

BDD: Body dysmorphic Disorder

BICI: Body Image Concern Inventory

BMI: Body Mass index

BMNAH- Bilateral Macronodular Adrenal Hyperplasia

CAH: Congenital adrenal hyperplasia

CI: confidence interval

CoMICs: Concise Medical Information Cines

COVID: Coronavirus disease

CYP: cytochrome P450

DHEA: dehydroepiandrosterone

DHEAS: dehydroepiandrosterone sulfate

DHT: Dihydrotestosterone

DNA: deoxyribonucleic acid

ESHRE/ ASRM: European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine

FDA: Food and Drug Administration

FSFI: Female Sexual Function Index

FSH: Follicle-stimulating hormone

GC: Gas Chromatography

GCSE: General Certificate of Secondary Education

GDPR: General Data Protection Regulation

HADS: Hospital Anxiety and Depression Scale

HDL: High Density Lipoprotein

HSD17B3: 17-beta hydroxysteroid dehydrogenase 3

HSD3B2: Hydroxy-Delta-5-Steroid Dehydrogenase

IQR: Inter Quartile Range

IRS- Insulin receptor substrate

LBL: Lecture-based learning

LC: Liquid Chromatography

LCMS-MS: Liquid Chromatography with tandem mass spectrometry

LDL: Low Density Lipoprotein

LH- Luteinising Hormone

LLOQ: Lower Limit of Quantification

MCQ: Multiple-choice questions

MDT: Multidisciplinary team

MS: Mass Spectrometry

NAD: Nicotinamide adenine dinucleotide

NAFLD: Non-Alcoholic Fatty Liver Disease

NICE: National Institute for Health and Care Excellence

NIH- National Institutes of Health

OR-odds ratio

PCOS: Polycystic Ovary Syndrome

PCOSQ: Polycystic Ovary Syndrome Questionnaire

PCOSQOL: Polycystic Ovary Syndrome Quality of Life

PPI: Patient and Public Involvement

PRO: Patient reported outcome

PROM: Patient reported Outcome Measures

QOL: Quality of Life

SBL- Simulation based learning

SBL: Simulation-based learning

SC- subcutaneous

SD: Standard Deviation

SHBG: Sex hormone-binding globulin

SIMBA: Simulation via Instant Messaging- Birmingham Advance

SIMBA-HCP: Simulation via Instant Messaging- Birmingham Advance-Healthcare Professionals

SIMBA-PCOS: Simulation via Instant Messaging- Birmingham Advance-Polycystic Ovary Syndrome

T2DM- type 2 diabetes mellitus

TNF-α: Tumour Necrosis Factor alpha

UHPSFC: ultrahigh performance supercritical fluid chromatography

UK: United Kingdom

USA: United States of America

VLDL: Very Low Density Lipoprotein

WAT- White Adipose Tissue

WHOQOL: World Health Organisation Quality of Life

1 Chapter 1: Introduction

Parts of this chapter have been published as:

Kempegowda, Punith, Eka Melson, Konstantinos N Manolopoulos, Wiebke Arlt, and Michael W O'Reilly. 2020. "Implicating Androgen Excess in Propagating Metabolic Disease in Polycystic Ovary Syndrome." Therapeutic Advances in Endocrinology and Metabolism 11 (January): 2042018820934319. https://doi.org/10.1177/2042018820934319.

Melson, Eka, Wentin Chen, Dengyi Zhou, Emma Ooi, Nia Evans, Dwi Delson, Meri Davitadze, and Punith Kempegowda. 2021. "Adaptation and Use of Media in an Innovative Simulation-Based Clinician Training Programme." BMJ Simulation and Technology Enhanced Learning 0 (June): bmjstel-2020-000808. https://doi.org/10.1136/bmjstel-2020-000808.

1.1 An introduction to polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is one of the most common endocrine conditions, affecting approximately 10% of all women across the globe (Marina A Skiba et al. 2018). Women with PCOS commonly present with menstrual irregularities, infertility and signs and symptoms of androgen excess. PCOS has been traditionally perceived as a predominantly benign reproductive disorder, with minimal focus on long-term metabolic complications. However, recent studies have shown that PCOS is associated with significant health consequences in affected women (Teede, Misso, Costello, Dokras, Laven, Yildiz, et al. 2018), representing a lifelong metabolic disorder.

1.1.1 Diagnostic criteria and differential diagnoses

There are several groups which have attempted to define the various criteria to diagnose PCOS. The two most quoted criteria are the National Institute of Health Criteria, Rotterdam criteria and the Androgen Excess Society criteria

In 1990, a group of scientists and clinicians were brought together for a National Institutes of Health (NIH) sponsored meeting where a consensus was reached based on a questionnaire amongst the group. They defined PCOS as presence of hyperandrogenism or hyperandrogenaemia with reduced or no menstruation, when all other possible endocrinopathies have been excluded (Zawadzki et al. 1992). However, controversies persisted regarding the diagnostic criteria. So, Homburg's proposal was put forward in 2002 to bridge the gap. In this criterion, women presenting with either menstrual irregularities or anovulatory infertility or acne or hirsutism would undergo an ultrasound scan of their ovaries. A presence of polycystic ovarian morphology would yield a diagnosis of PCOS. Presumably, related disorders are excluded. In the absence of such a radiological feature, these women undergo additional biochemical

test and a diagnosis of PCOS was given if there was an elevated testosterone and/or elevated androgen index and/or elevated LH levels and/or a subnormal glucose: insulin ratio (<4.5). In 2003, a group of American and European clinicians arrived at a closed session consensus and agreed androgen excess remains a fundamental biological and diagnostic feature of the disorder (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004; Azziz et al. 2009b). This was called the Rotterdam criteria and was defined as presence of two of three following criteria after excluding other endocrine conditions: Clinical or biochemical hyperandrogenism and/or Oligo-anovulation and/or Polycystic appearances of the ovaries at ultrasound. Following this, the Androgen Excess Society recommended hyperandrogenism as a mandatory criterion for the diagnosis of PCOS, further highlighting PCOS as a disorder of androgen excess (Azziz, Carmina, Dewailly, Diamanti-Kandarakis, Escobar-Morreale, Futterweit, Janssen, Legro, Norman, Taylor, and Witchel 2006; Azziz, Carmina, Dewailly, Diamanti-Kandarakis, Escobar-Morreale, Futterweit, Janssen, Legro, Norman, Taylor, Witchel, et al. 2006; Azziz et al. 2009b). Based on these three criteria, several phenotypes of PCOS exists (Table 1).

The International Guideline in PCOS in 2018 was endorsed by 37 societies internationally and superseded past diagnostic criteria (Teede, Misso, Costello, Dokras, Laven, Yildiz, et al. 2018).

Table 1:Various phenotypes of PCOS (adapted from (Azziz et al. 2009a)*)*

Potential Phenotypes										
Features	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**
Hyperandrogenemia	+	+	+	+	−	−	+	−	+	−
Hirsutism	+	+	−	−	+	+	+	+	−	−

Oligo-anovulation	+	+	+	+	+	+	−	−	−	+
Polycystic ovaries	+	−	+	−	+	−	+	+	+	+
NIH 1990 criteria	√	√	√	√	√	√				
Rotterdam 2003 criteria	√	√	√	√	√	√	√	√	√	√
AE-PCOS 2006 criteria	√	√	√	√	√	√	√	√	√	

In all the above criteria, it is mandatory to exclude other endocrine conditions which may cause the presenting symptoms. This includes

a. 21-hydroxylase deficiency-Certain ethnic groups such as Yupik Eskimos, Ashkenazi Jews, and Hispanic, Italian, and Yugoslav women have a high risk of having this condition. The enzyme deficiency can be complete, known as classical congenital adrenal hyperplasia (CAH) or partial, which is known as non-classical CAH. While the clinical features are usually indistinguishable from PCOS, a serum 17-hydroxy progesterone level of <200 nmol/L in the follicular phase rules out the differential (Speiser et al. 2018).

b. Thyroid dysfunction- both hypo- and hyperthyroidism can present with menstrual irregularities and hair loss. A normal serum thyroid stimulating hormone and thyroxine rules out the differential (“Polycystic Ovary Syndrome - Differentials | BMJ Best Practice” n.d.).

c. Hyperprolactinaemia- High prolactin can present with oligo-amenorrhoea. Normal prolactin levels help rule out this differential (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004).

d. Cushing's syndrome-high cortisol and androgen levels can result in obesity, menstrual irregularities, and hirsutism. Therefore, screening for Cushing syndrome when there is an index of suspicion is recommended.

e. Androgen-secreting neoplasms-a 9AM serum testosterone> 5 nmol/L or serum dehydroepiandrosterone sulphate>7000 microg/L should raise suspicion for a possible androgen secreting tumour. (Elhassan et al. 2018a; Idkowiak et al. 2019).

f. Syndromes of severe insulin resistance-associated with acanthosis nigricans and one should consider fasting insulin levels when there is a degree of clinical suspicion (Brown et al. 2017).

g. Androgenic/anabolic drugs- a detailed medication and supplements history can help rule this out.

h. Hypogonadotropic hypogonadism and premature ovarian failure- usually present with oligo-/amenorrhea without any hyperandrogenaemia. Serum luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels can help resolve this differential (“Polycystic Ovary Syndrome - Differentials | BMJ Best Practice” n.d.).

i. Apparent cortisone reductase deficiency - a rare condition with reduced function of 11beta-hydroxysteroid dehydrogenase type 1 can result in reduced activation of cortisone to cortisol. Therefore, adrenocorticotrophic hormone (ACTH) levels increase which stimulate the adrenal glands to produce more androgens as a by-product. This can mimic symptoms of PCOS. This condition can be diagnosed by a very low ratio of cortisol over cortisone metabolites (D. N and PM 2005).

1.1.2 Epidemiology

The prevalence of PCOS varies by the diagnostic criteria applied with NIH having lowest and Rotterdam criteria having the highest prevalence (Broekmans et al. 2006; Rashidi et al. 2014). In a cross-sectional study of 392 women aged between 18 and 45 years, the prevalence of PCOS under National Institutes of Health (NIH), Rotterdam and Androgen Excess and PCOS (AE-PCOS) Society criteria was 6.1, 19.9 and 15.3%, respectively (BO et al. 2012). Similar results were reported in Australian and Iranian cohorts (March et al. 2010; FR et al. 2011).

The prevalence of PCOS using NIH criteria has been mostly reported in Caucasian population in the America (Knochenhauer et al. 1998), Greece (Diamanti-Kandarakis et al. 1999) and Spain around 4.0 to 6.5% (Asunción et al. 2000). Limited work has been published studying the prevalence of PCOS in other ethnicities. A study of 400 unselected consecutive women aged 18–45 years in the USA (223 Black, 166 White) reported a higher but not statistically significant difference in the prevalence of PCOS (4.8% in whites and 8.0% in blacks) (Azziz et al. 2004). The prevalence of PCOS among the Asian populations has been reported from 5.6% in the Southern Chinese population (Li et al. 2013) and 6.3% in SriLankan women (Kumarapeli et al. 2008) and 5.7% in Thai women (Vutyavanich et al. 2007). Further limited work exists studying the impact of the ethnic differences in epidemiology and prevalence on phenotypes and disease severity. A study by Wijeyaratne et al. reported that South Asians with anovulatory PCOS seek treatment at a younger age, have more severe symptoms, and have higher fasting insulin concentrations and lower insulin sensitivity than Caucasians (Wijeyaratne et al. 2002). Recently, a task force established by the Androgen Excess and PCOS (AE-PCOS) Society drafted a research resource for

epidemiologic and phenotypic studies in PCOS which provides guidelines on study design and execution, insights into the limitations and alternatives and protocols to be used, taking into consideration a global perspective (Azziz 2019).

1.1.3 Clinical features

The clinical features of PCOS are defined the classical triad of menstrual irregularities, polycystic appearance of ovaries and clinical and/or biochemical manifestation of hyperandrogenaemia. However, recent evidence suggests that PCOS is a life-long metabolic condition likely to affect female health from childhood through to post-menopause. Recent work by Risal et al. showed that daughters of mothers with PCOS have a five-fold increased risk for PCOS (Risal et al. 2019). More importantly, they showed that prenatal androgen exposure and not obesity led to transgenerational reproductive and metabolic dysfunction in rodent models. Another study by Gunning et al., showed subtle cardiometabolic dysfunction in early childhood in otherwise healthy weight children of women with PCOS (Wilde et al. 2018; Gunning et al. 2019; Torchen et al. 2016b).

On a superficial level, clinical consequences of this condition include subfertility, irregular menses and signs and symptoms of androgen excess. However, clinicians should be aware of the significantly increased risk of metabolic complications across the female lifespan in women with PCOS, underpinned by androgen excess and insulin resistance (figure 1). Women with PCOS have been shown to have more central obesity phenotypes. Increased fat accumulation in the hepatocytes in response to androgen excess, eventually resulting in non-alcoholic fatty liver disease (NAFLD). Androgen excess is proportionally related to beta-cell dysfunction. Ectopic lipid accumulation in skeletal muscle with androgen excess influences glucose-regulating pathways resulting in insulin resistance (figure 2). The origins of androgens and their

mechanistic role inducing metabolic dysfunction in PCOS are discussed in detail in the following sections.

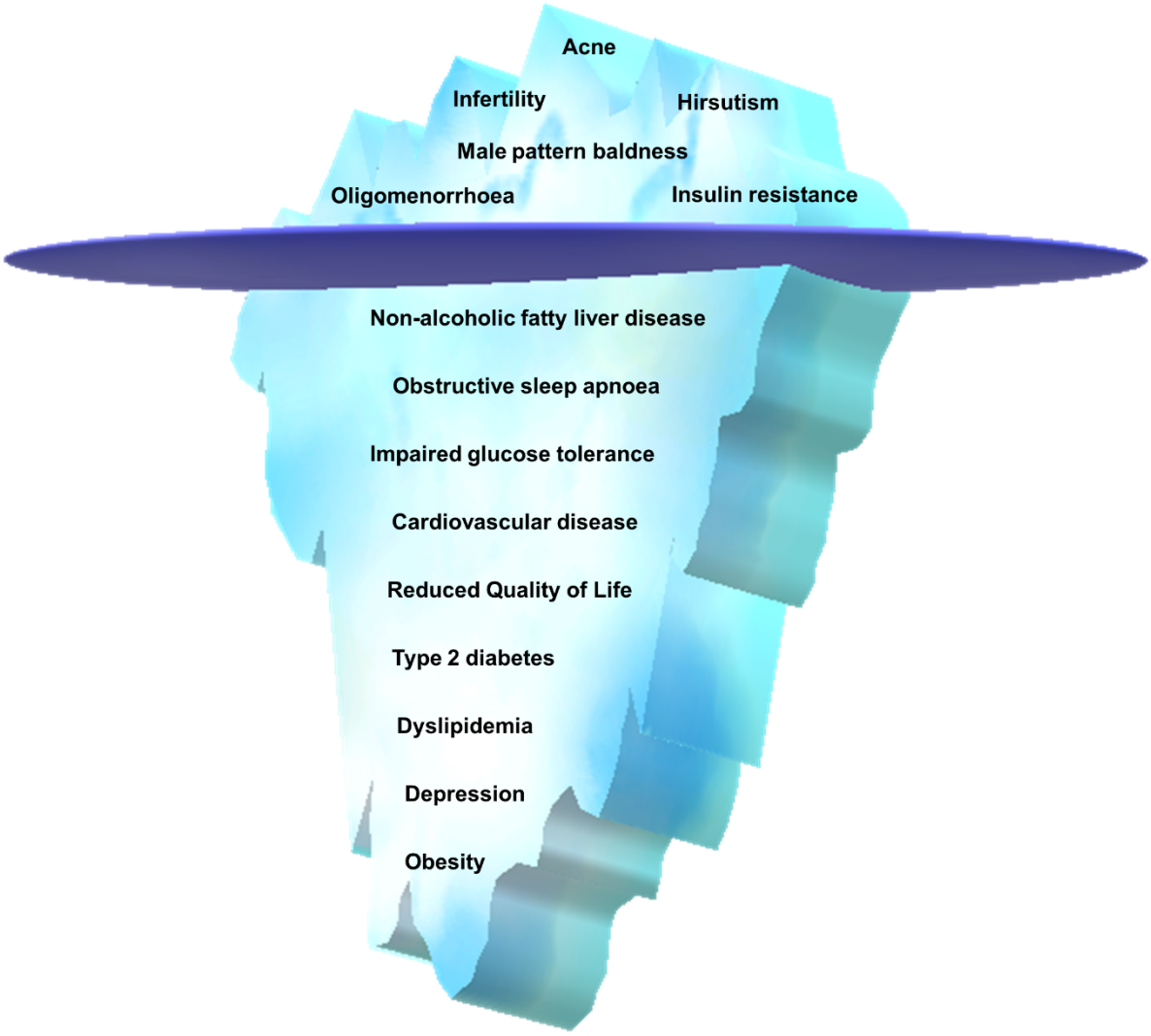


Figure 1: Iceberg phenomenon in PCOS: Several cardiometabolic features are associated with PCOS (Kempegowda et al. 2020).

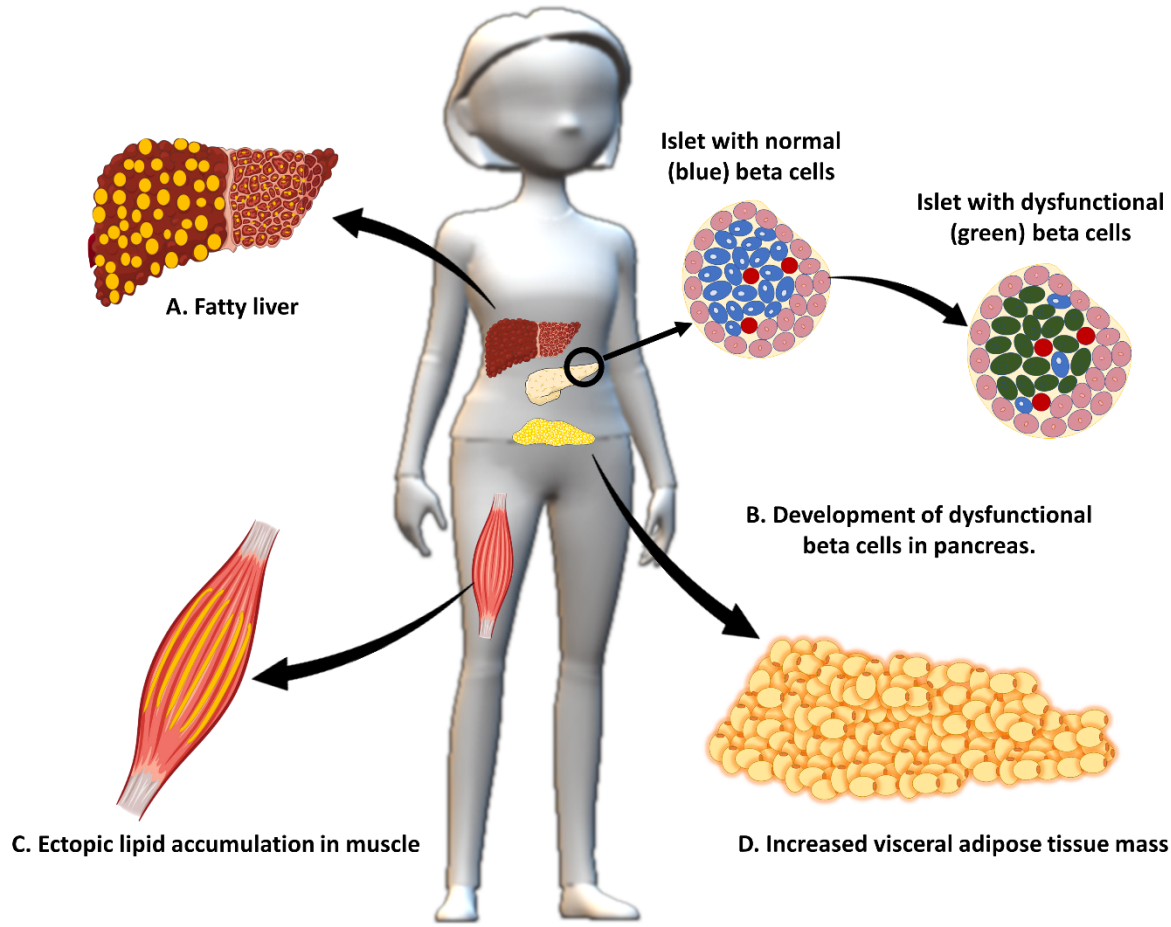


Figure 2: Impact of androgen excess on metabolic target tissues (Kempegowda et al. 2020)

(A) Increased fat accumulation in the hepatocytes in response to androgen excess, eventually resulting in NAFLD, (B) Androgen excess is proportionally related to beta-cell dysfunction, (C) Ectopic lipid accumulation in skeletal muscle with androgen excess influences glucose-regulating pathways resulting in insulin resistance, (D) under the influence of androgens, women with PCOS have been shown to have more central obesity phenotypes

1.2 Physiological androgen biosynthesis, metabolism, and action

1.2.1 Physiology of human female androgen biosynthesis

Androgens are responsible for the development of male characteristics such as male pattern body hair, muscle bulk, and deep voice; androgens also impact on sexual function and reproductive capacity in both sexes. Apart from their role in reproduction and sexual health, androgens also play an important role in human metabolic health in both men and women (Lina Schiffer, Arlt, and Storbeck 2018a). In women, androgens also play an important role in general well-being, libido, energy levels, muscle mass and strength and bone mass (Wiebke Arlt et al. 1999; Raisz et al. 1996; Shifren et al. 2000; K. K. Miller et al. 2001; Snyder 2001). The origins of androgen excess in PCOS have not been comprehensively delineated, but adrenals, ovaries and adipose tissue collectively contribute to the bulk of circulating androgen burden in the disorder (Bozdag et al. 2016) (figure 3 and 4).

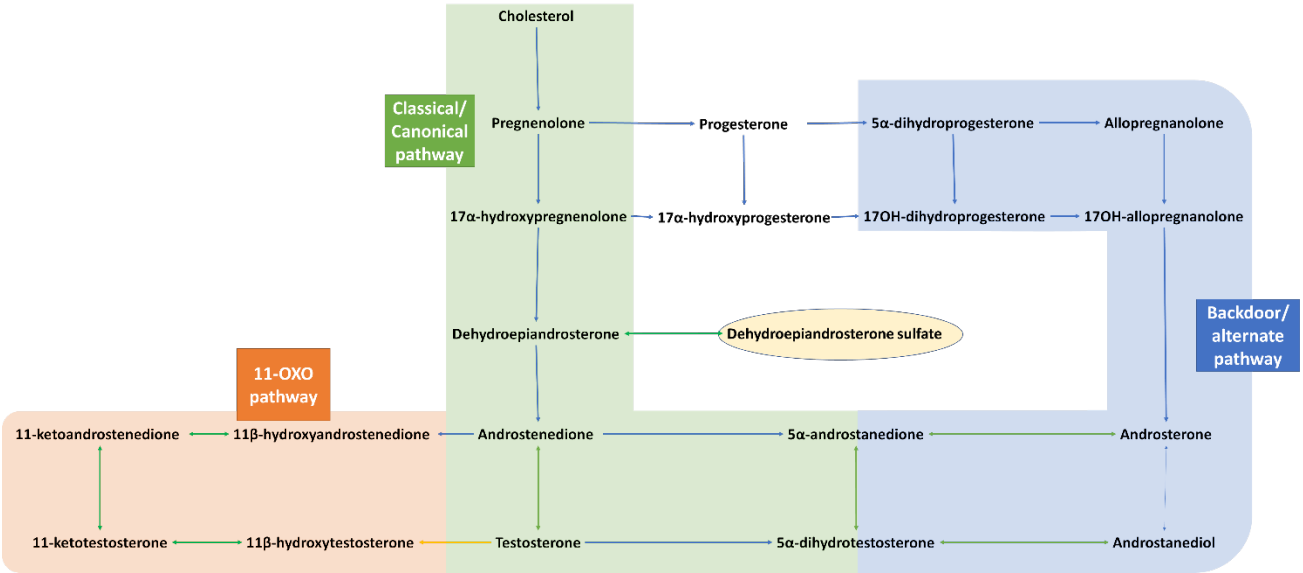


Figure 3: Various pathways of generating potent androgens.

Testosterone (T) is the most abundant potent androgen derived from the classic pathway of androgen generation. T can further be converted to 5α-dihydrotestosterone (DHT), which is 10 times more potent than T in binding and activating the androgen receptor. DHT can also be derived through an alternative androgen biosynthesis pathway, sometimes also termed backdoor pathway. Recently, a new class of androgens has been discovered, the 11-oxygenated androgens. Of these, 11-ketotestosterone is found to have equal potency as T and have equal affinity to the androgen receptor.

1.2.2 Classic androgen biosynthesis pathway

Androgens are synthesized in the ovaries and adrenal glands catalysed by a series of steroidogenic enzymes, especially the rate limiting cytochrome P450 (CYP) 17A1 enzyme, responsible for the synthesis of the classic androgen pathway precursor dehydroepiandrosterone (DHEA). In the classical pathway, Cholesterol is first converted to pregnenolone by cholesterol side-chain cleavage enzyme P450c17 which then converts the latter to 17-hydroxypregnenolone (17Preg). 17,20 lyase activity of the P450c17 enzyme converts 17Preg to dehydroepiandrosterone (DHEA). DHEA is converted to androstenedione by 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) in both the adrenal and testis and by 3β-hydroxysteroid dehydrogenase type in several peripheral tissues. Mainly in the gonads, but to a minor degree also in the adrenal and to a larger degree in peripheral tissues, androstenedione is converted to testosterone, by 17β-hydroxysteroid dehydrogenase type 3 (HSD17B3) and 17β-hydroxysteroid dehydrogenase type 5 (AKR1C3). T is converted by 5α-reductase type 1 and type 2 enzymes in the gonads (type 2) and in the skin and other peripheral organs (mostly type 1) into the more potent androgen DHT (Pretorius et al. 2016a).

1.2.3 Alternative pathway to DHT

17-hydroxyprogesterone (17OHP) can be 5α-reduced by 5α-reductase type 1 to 5α-pregnan-17α-ol-3,20-dione, which is then 3α-reduced by aldoketoreductase (AKR) 1C2 or AKR1C4 to yield 17OH-allopregnanolone. The 17,20 lyase activity of P450c17 enzyme catalyses the conversion 17OH-allopregnanolone to androsterone. Androsterone is then converted by testicular 17βHSD3 or by adrenal/peripheral tissue 17βHSD5 (AKR1C3) to yield androstanediol, which is 3α-oxidized by 17βHSD6 to yield DHT; similarly, androsterone can be converted to DHT via 5a-androstanedione (JD et al. 2003; RJ 2004; Nicole Reisch et al. 2019; W. L. Miller and Auchus 2019).

1.2.4 11-oxygenated androgens

Although it was known for many decades that 11OHA4 is generated from A4 in the adrenal, but it was considered as negligible, inactive by-product of adrenal steroidogenesis (Pretorius et al. 2016b). Almost all 11-oxygenated steroids are synthesized in the adrenal gland with cytochrome P450 11β-hydroxylase (CYP11B1) being the most important and involved enzyme. This enzyme utilizes A4 and T as substrates, yielding 11β-hydroxyandrostenedione (11OHA4) and, to a much lesser degree, 11β-hydroxytestosterone (11OHT), respectively (Adina F. Turcu and Auchus 2017). Rege et al. measured steroids in adrenal vein samples using LC-MS/MS and showed that 11OHA4 is the most abundant unconjugated C19 steroid product of the human adrenal gland and that its synthesis is further enhanced by exogenous adrenal stimulation with ACTH (J et al. 2013). In our recent work, we showed that peripheral blood mononuclear cells preferentially activate 11-oxygenated steroids to produce 11-ketotestosterone, a steroid as active and potent as testosterone from the classic pathway (Lina Schiffer et al. 2021).

1.2.5 Peripheral (pre-receptor) androgen metabolism

Several studies have reported a systemic upregulation of 5α-reductase activity as a significant feature in women with PCOS (Stewart et al. 1990; Chin et al. 2000; Fassnacht et al. 2003; Vassiliadi et al. 2009; Torchen et al. 2016a), with consequently increased activation of testosterone to 5α-dihydrotestosterone (DHT).

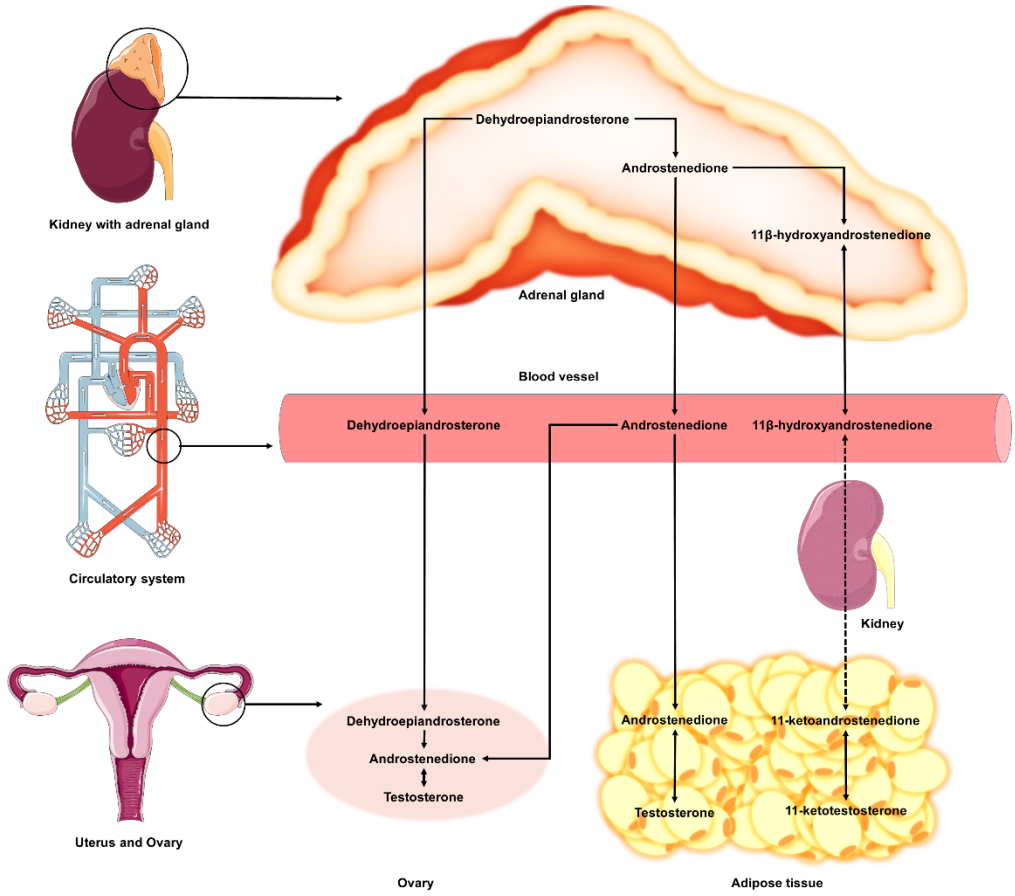


Figure 4:Adrenal, ovarian and peripheral androgen metabolism in PCOS.

Androgenic precursors are secreted predominantly by the adrenal glands, and activated to potent androgens in the ovaries and peripheral tissues. Expression of key androgen-activating enzymes in peripheral tissues such as adipose tissue highlight an important role for extra-adrenal and -ovarian androgen generation.

1.2.6 Androgen receptor and biological action

After the secretion by the ovaries and/or adrenals into the circulation, androgenic precursors are further activated in peripheral target tissues into more potent androgens that bind to the cytosolic androgen receptor (AR), which subsequently translocate to the nucleus where it functions as a transcription factor after binding to DNA, resulting in increased transcription of genes encoding for factors important for androgenic biologic activity. The concentration of androgens in peripheral target tissues of sex steroid action are determined by

(1) the total concentration of the androgenic steroids in the circulation,

(2) whether they are bound to sex hormones binding globulin (SHBG) or albumin, important regulators of bioavailability, and

(3), the availability of mechanisms for cellular influx and efflux.

Circulating androgens must cross the plasma membrane of the target cells to be metabolized by intracellular enzymes and/or to activate the AR. While unconjugated steroids can freely diffuse across the plasma membrane, conjugated steroids are hydrophilic and hence need to be actively transported inside the cell. Once in the cell, these steroids will need to be deconjugated before they can be metabolized and/or interact with the androgen receptors (Lina Schiffer, Arlt, and Storbeck 2018b; Giorgi and Stein 1981).

Combining human-based in vivo and ex vivo study approaches, our group has shown that the androgen-activating enzyme aldoketoreductase type 1 C3 (AKR1C3), which converts androstenedione to testosterone as well as 11OHA4 to 11KT, is a major driver of adipocyte-specific androgen excess and that its activity in adipose tissue is a

major source of PCOS-related androgen excess (O'Reilly, Kempegowda, Walsh, et al. 2017a). This will be discussed in detail in the adipose tissue section below.

1.3 Androgen biosynthesis and metabolism in PCOS (Origins of androgen excess in PCOS)

1.3.1 Adipose tissue, obesity, fat mass distribution and androgen excess

Adipose tissue forms the largest store of conserved energy, in the form of triglycerides, in the human body. The process of adipocyte differentiation from stem cells is complex and involves a variety of signals for gene regulation, histone modification, and protein modification by ubiquitin (Lowe, O'Rahilly, and Rochford 2011). There are two distinct types of adipose tissue - brown adipose tissue (BAT) and white adipose tissue (WAT). Several studies have established the role of adipose tissue beyond an energy storehouse to regulating several critical physiological processes e.g., through adipokine signals such as leptin and adiponectin. The various roles of adipokines are discussed in detail by Ouchi et al and Dimitriadis et al (Ouchi et al. 2011; Dimitriadis, Kyrou, and Randeva 2016).

Women with PCOS have been shown to have more central obesity phenotypes compared to weight- and BMI-matched controls (Cosar et al. 2008; Carmina et al. 2009; Strowitzki, Halser, and Demant 2002; Svendsen et al. 2008), which is associated with various metabolic conditions in PCOS (Zheng and Li 2016; Techatraisak et al. 2016; Durmus, Duran, and Ecirli 2017). However, these data have been inconsistent (Barber et al. 2008; Faloia et al. 2004). Some studies have also shown that although women with PCOS have android fat mass distribution, these

might not be accompanied by increased visceral fat (Boumosleh et al. 2017; Ribeiro et al. 2019). On the other hand, gluteo-femoral fat or gynecoid adiposity, low in PCOS, has been shown to be independently associated with protective lipid and glucose profile along with decreased cardiovascular and metabolic risk (Manolopoulos, Karpe, and Frayn 2010). Visceral Adiposity Index (VAI) has similar utility to the gold-standard CT scan in the evaluation of visceral adiposity (Brończyk-Puzoń et al. 2017). VAI is a gender-specific empirical mathematical model based on BMI, waist circumference (WC), triglycerides and high-density cholesterol (HDL) in healthy normal and overweight population (Marco C. Amato et al. 2010). Lim et al., reported similar VAI women with PCOS and controls in few studies. However, subgroup analysis comparing three groups—PCOS and obesity, obesity alone, and PCOS alone—revealed women with PCOS and obesity have higher VAI compared to other two groups (Lim et al. 2013). In a study on women with PCOS by Amato et al., VAI was only associated with compensatory hyperinsulinemia and there were no independent association between VAI with insulin sensitivity index (by HOMA-IR and ISI Matsuda), androgen profiles and PCOS (M. C. Amato et al. 2011). Visceral adiposity has also been previously, but not consistently, associated with elevated FAI (Cosar et al. 2008) and total T (Svendsen et al. 2008) . However, the number of studies available is too low for a systematic review to examine whether there is an association between PCOS, central obesity and androgens.

Adipose tissue is a key target of androgen action. Androgens are known to inhibit adipocyte differentiation in both animal and human cell lines (Dieudonne et al. 2000; Gupta et al. 2008; Chazenbalk et al. 2013; Blouin et al. 2010). The effects of androgen on adipose tissue can be noted from birth. Roland et al noted higher fasting glucose and impaired glucose tolerance in prenatally androgenised female mice which closely

mimics PCOS model (Roland et al. 2010). Prior to this, Nilsson et al showed that exposure to testosterone in the neonatal period resulted in insulin resistance, change in adipose tissue distribution and lean mass without significant changes in circulating androgen concentrations (C. Nilsson et al. 1998). Further, their groups showed this early exposure to androgen resulted in long lasting effects on insulin sensitivity, adipose tissue and lipid profile (Alexanderson et al. 2007). O'Reilly et al. have previously published a detailed review of the abnormalities in adipose tissue function, fat distribution and lipid metabolism in the context androgen excess (O'Reilly, House, and Tomlinson. 2014).

We have demonstrated that expression of the androgen-activating enzyme aldo-keto reductase type 1C3 (AKR1C3), which converts the weak androgen precursor androstenedione into potent testosterone, is increased in subcutaneous (SC) adipose tissue in women with PCOS. Locally generated androgens enhance *de novo* lipogenesis within SC female adipocytes, potentially predisposing to fatty acid overspill into the systemic circulation, with consequent lipotoxicity driving an adverse metabolic phenotype (O'Reilly, Kempegowda, Walsh, et al. 2017a). O'Reilly et al. also demonstrated that associated insulin resistance and hyperinsulinemia then drive AKR1C3 expression and activity within the adipocyte, raising the possibility of a vicious circle of intra-adipose androgen activation, lipid accumulation and hyperinsulinaemia.

AKR1C3 also converts the 11-oxygenated androgen precursor 11-ketoandrostenedione (11KA4) into 11-ketotestosterone (11KT), which binds and activates the androgen receptor with similar potency to T (K.-H. Storbeck et al. 2013). Recent data from the group of Karl Storbeck also demonstrate that 11KA4 is the preferred substrate for AKR1C3, which more efficiently converts it to active 11KT than its counterpart reaction, A4 to T, in the classic androgen pathway (Barnard et al.

2018a). The findings were corroborated by a recent study describing increased adipose tissue expression of AKR1C3 in women with PCOS (Amer et al. 2019). These findings define a novel intra-adipose mechanism that could contribute to androgen excess and metabolic dysfunction in PCOS.

These data strongly implicate adipose tissue as a major peripheral site of activation and metabolism of 11-oxygenated androgens in PCOS and suggest that locally generated 11-oxygenated androgens play a significant role in adipose tissue lipotoxicity. To date, however, this hypothesis has not been tested in adipose tissue of human participants using in vivo physiology approaches.

The association between adiposity, androgen excess and PCOS has been further complicated by hyperinsulinemia and insulin resistance, which exacerbate the metabolic, reproductive, and steroidogenic abnormalities observed in the disorder (Bozdag et al. 2016). A systematic review by Lim et al. (Lim et al. 2013) found women with obesity and PCOS have a higher total and free T and lower SHBG compared to those with normal BMI. Furthermore, women with both PCOS and obesity also appear to have pronounced clinical manifestations of hyperandrogenism (such as hirsutism, menstrual abnormalities, and anovulation) compared to women with PCOS and normal BMI. This effect tends to be more pronounced in the abdominal/visceral obesity phenotypes (Plymate et al. 1988; Pasquali, Gambineri, and Pagotto 2006; Gambineri et al. 2002; Lim et al. 2013). Weight loss in women with PCOS has been shown to improve clinical, metabolic, and reproductive outcomes (Panidis et al. 2008; Escobar-Morreale et al. 2005; Gambineri et al. 2002).

Insulin resistance and compensatory hyperinsulinemia in obesity inhibits hepatic production of SHBG, with a consequent increased bioavailability of androgens.

1.3.2 Liver, dyslipidaemia, and androgen excess

Several cross-sectional studies have shown an increased prevalence of non-alcoholic fatty liver disease (NAFLD) in women with PCOS; NAFLD is now on its way to become the most frequent cause of liver transplantation, driven by the global obesity pandemic, and is a forerunner of cardiovascular disease (Pais et al. 2016). A study by Petta et. al concluded that PCOS is an independent risk factor for hepatic steatosis and possibly progression to fibrosis and cirrhosis, with hyperandrogenism and insulin resistance as main determinants. (Petta et al. 2017). These associations have been observed in other studies (Cai et al. 2017; Kim et al. 2017; D. Macut et al. 2016). Our group has carried out a cohort study utilising a large primary care database in the UK, including 63,000 women with PCOS and 121,000 matched controls, revealing that the risk of NAFLD was significantly increased in women with PCOS, even in women with normal BMI (HR = 2.23, 95% CI 1.86-2.66, $p < 0.001$) (Kumarendran et al. 2018). Androgen excess (high T, low SHBG) was found to be a contributing risk factor for the development of NAFLD in PCOS in this population-based study, independent of BMI (Kumarendran et al. 2018). Similar observations were made in a meta-analysis showing a 2.3-fold increased rate of NAFLD in women with PCOS especially those who have hyperandrogenism (J. Wu et al. 2018).

There are numerous proposed mechanisms linking this hepatic manifestation of metabolic syndrome with PCOS (Djuro Macut et al. 2017; J. Wu et al. 2018). Androgen excess in PCOS suppressed low-density lipoprotein receptor RNA expression both in the adipocytes and the liver. They speculate the suppressed receptor expression might prolong plasma half-life of VLDL and LDL, potentially leading to lipid

accumulation both in the adipocytes and liver (Baranova et al. 2013). Hyperandrogenism has also been shown to induce an upregulation of AR transcripts and increased release of TNF-α (González et al. 2014), which is implicated in the development of NAFLD (Kakino et al. 2018). A study by Kakino et al. showed that the adipocyte-specific nuclear form of sterol regulatory element binding protein 1c (nSREBP-1c) transgenic mice developed similar hepatic changes to those in NAFLD, with an increased TNF-α (Shimomura et al. 1998). Follow-up studies by the same group using the same mouse model showed that TNF-α is responsible for the development of NAFLD (Kakino et al. 2018). In this study, TNF knockout nSREBP-1c mice showed an improved glucose tolerance and there was a significantly reduced prevalence of hepatic steatosis compared to the original nSREBP-1c model. This finding was also supported by culturing primary hepatocytes in the presence of TNF-α (Kakino et al. 2018). These observations support that increased TNF-α, possibly mediated by hyperandrogenism, is an important mechanism in the development of NAFLD in women with PCOS.

Our group has demonstrated androgen-mediated suppression of lipolysis and increased de novo lipogenesis in vivo and in vitro (O'Reilly, Kempegowda, Walsh, et al. 2017b). This would result in net positive fat accumulation beyond the adipocyte storing capacities causing fatty acid overspill, systemic lipotoxicity, insulin resistance and fat accumulation in the liver, thus leading to the development of NAFLD in women with PCOS. In the same study, non-targeted serum metabolome profiling showed increased concentration of glycerophospholipids and lysoglycerophospholipids in women with PCOS with androgen excess, but not in controls with normal androgen concentrations. Acute androgen exposure (oral challenge with 100mg DHEA) yielded a further increased in these metabolites in women with PCOS whereas a decrease

was observed in the BMI-matched healthy controls (O'Reilly, Kempegowda, Walsh, et al. 2017c). Both glycerophospholipids and lysoglycerophospholipids were previously observed to be increased in people with NAFLD and have been identified as potential markers of risk and progression of the condition (Anjani et al. 2015). These data shows that women with PCOS have a distinct metabolic response to androgens which might contribute to the development of NAFLD and other related conditions.

1.3.3 Pancreas, type 2 diabetes, and androgen excess

Studies have shown that there is a clear sex difference in the way the foetal pancreas reacts to androgen excess. Insulin secreted from the pancreatic beta cells is critical for glucose utilisation in the peripheral tissues. Defects in insulin secretion or action predispose to insulin resistance and type 2 diabetes mellitus. Beta cells expand rapidly during late gestation and any alteration to its expansion during this period results in long lasting deleterious effects. Navarro et al. demonstrated potentiating effects of DHT on male mice beta cell function via the glucagon-like peptide-1 (GLP-1) receptor (Navarro et al. 2016). Further, they showed male mice lacking AR had decreased glucose-stimulated insulin secretion, leading to glucose intolerance. Castration of male rats resulted in approximately 30% reduction in beta cell mass (Harada et al. 2018). Xu et al studied the transcriptome of AR-deficient islet beta cells of male mice and found altered expression of genes involved in inflammation and insulin secretion (Xu et al. 2017).

Studies in women with PCOS have also shown that androgen excess is proportionally related to beta-cell dysfunction. This has been discussed in detailed by Mauvaus-Jarvis in a review of sex steroid effects on pancreatic beta-cell function (Mauvais-Jarvis 2016). This hypothesis was further tested in female mice by exposing them to chronic androgen excess, which resulted hyperinsulinemia and insulin resistance.

However, this was not observed in female βARKO mice lacking AR expression in pancreatic beta cells (Navarro et al. 2018a). Testosterone prevents beta cell apoptosis and increases insulin mRNA levels both in vitro and in vivo in a series of studies conducted by Morimoto et al (Sumiko Morimoto et al. 2001; S Morimoto et al. 2005). Harada et al demonstrated an in vivo effect of androgens on beta cell mass and expansion in a sex specific manner. They found reduced beta cell mass and proliferation in male rats following administration of flutamide to pregnant dams. Although beta-cell mass was restored after feeding the mice a high fat diet, they had persisting glucose intolerance suggesting decreased insulin secretion (Harada et al. 2019).

Androgen exposure during intrauterine life results in several phenotypic characteristics of PCOS in nonhuman primates and sheep. When rats were exposed to testosterone during late gestation, their female offspring exhibited significant weight gain, increased adipose tissue and other traits of metabolic dysfunction (Demissie et al. 2008). Exposing rhesus monkey dams to testosterone pre-conception resulted in hyperinsulinaemia and a reduction in glucose clearance following accelerated weight gain during testosterone treatment. This transient hyperglycaemic and relative hyperinsulinaemic episodes were sufficient to induce differential programming of insulin action and secretion in their female offspring (Abbott et al. 2010).Intrauterine exposure to testosterone resulted in increased beta cell numbers in prenatally androgenised female foetuses with no effect on alpha cells (Ramaswamy et al. 2016). The same group reported upregulation of genes involved in beta cell development and function (Rae et al. 2013). Neither study (Azziz et al. 2019) found any such changes in male offspring, even when they were exposed to androgens before the male programming window. Roland et al reported fasting hyperglycaemia and impaired

glucose tolerance independent of age and changes in body composition or peripheral insulin sensitivity in prenatally androgenised female mice. Once again, no such changes were noted in male counterparts (Roland et al. 2010).

Liu et al. (H. Liu et al. 2017) demonstrated improved differentiation of pluripotent stem cells into insulin-producing cells when testosterone was added to routine differentiation medium, resulting in an upregulation of NGN3, NEUROD1 and INS genes. Zhang et al. investigated the association between free androgen index, a marker of androgen excess, with glucose tolerance in PCOS. They found a positive correlation suggestive of beta cell dysfunction in women with PCOS (Zhang et al. 2018).

Glucose-stimulated insulin secretion significantly decreases in islets treated with DHT in rodent-based in vivo studies. This is associated with significant reductions in expression of several key genes involved in islet cell mitochondrial biogenesis and mitochondrial ATP production (Wang et al. 2015). Chronic exposure to androgens resulted in increased oxidative stress in islet cells resulting in secondary beta cell failure in female mice fed on western diet (S. Liu, Navarro, and Mauvais-Jarvis 2010a; Navarro et al. 2018b). The study also reported direct androgen receptor-dependant impairment of beta cell function by inducing mitochondrial dysfunction in vitro (S. Liu, Navarro, and Mauvais-Jarvis 2010b). This is important in connection to skeletal muscle insulin resistance and failing insulin secretion would predispose women with PCOS to develop T2DM (Xu et al. 2020).

PCOS is strongly linked with insulin resistance and T2DM in population and other large-scale studies. A meta-analysis of 35 studies of women with PCOS by Moran et al reported increased odds for insulin resistance (OR 2.54, CI 1.44-4.47) and T2DM (OR 4.00, CI 1.97-8.10) compared to BMI-matched studies (L. J. Moran et al. 2010).

Legro et al conducted one of the earliest prospective studies to assess the prevalence of T2DM in PCOS. They found the prevalence of T2DM in women with PCOS to be 7.5%; it was 1.5% in lean women with PCOS, further supporting the synergistic harmful effect of obesity on insulin sensitivity in PCOS. Interestingly, 31.1% of their cohort had impaired glucose tolerance speculating whether standards of diagnosing T2DM may not identify all index cases in PCOS cohort (Legro et al. 1999). Boudreaux et al reported an incidence of 13.4% and 5.8% in women with PCOS and healthy controls respectively, with a relative risk of 2.3 times after prospective follow up over eight years. Further, obesity increased the risk by fivefold in their cohort (Boudreaux et al. 2006). One of the largest population-based survey of T2DM in PCOS was reported from Australia by Joham et al. They surveyed 9145 women who self-reported the diagnosis of PCOS, T2DM and gestational diabetes mellitus. The prevalence of T2DM was 5.1%. After adjusting to socio-demographic and other known risk factors, the odds for T2DM were significantly increased in PCOS (odds ratio 8.8, 95%CI 3.9 – 20.1, P .001). BMI was independently associated with T2DM in PCOS with every BMI increment increasing the risk of T2DM by 10% (Joham et al. 2014). A Danish national register study by Rubin et al. studying about 18000 women with PCOS and 54000 controls has also shown a higher event rate of T2DM in PCOS compared to well-matched controls, and diabetes was diagnosed on average four years earlier than in the background population (Rubin et al. 2017). The prevalence of glucose intolerance and T2DM in a cohort of 122 women with PCOS studied by Ehrmann and colleagues was 35% and 10% respectively (D A Ehrmann et al. 1999). They further followed up a subset of the glucose intolerant women with PCOS and found them to have higher post-prandial glucose compared to their baseline suggesting a progressively worsening insulin resistance in the absence of any intervention. The prevalence of

diabetes in Dutch population was much less (2.3%) compared to the American cohorts described above. However, the risk was 2.3 times higher compared to their general healthy cohorts. And this risk increased from 1.3 in 25-34 years to 9.4 times in 45-54 years (Elting et al. 2001). The study by Kauffman and colleagues suggests ethnicity plays an additive effect on insulin resistance in PCOS. Mexican American women had significantly higher insulin resistance compared to Caucasian American women, thus challenging a single population-wide screening tool (Kauffman et al. 2002).

First reported in 1980, the association of hyperandrogenism and hyperinsulinemia is firmly established (Burghen, Givens, and Kitabchi 1980; Chang RJ et al. 1983; Andrea Dunaif et al. 1989a; O'Reilly, Kempegowda, Walsh, et al. 2017d). Our group have also shown in a retrospective cohort study in a UK primary care database that women with increased serum testosterone levels have an increased risk of incident T2DM (O'Reilly et al. 2019). This was recently highlighted further by Ruth et al. In their study including 455,097 UK Biobank samples, which showed that the risk of T2DM in women was increased by 37% for every increased standard deviation of free testosterone from baseline. A higher fasting insulin was also reported in these women (Ruth et al. 2020).

Dunaif et al were amongst the first to prove women with PCOS have significant insulin resistance independent of obesity. However, obesity seemed to have a synergistic deleterious effect on glucose tolerance (Andrea Dunaif et al. 1989b). Further, they proved in their study that insulin resistance was not due to decreased insulin clearance but of a different pathology (A Dunaif et al. 1992). Since then, several researchers have studied the exact mechanisms of insulin resistance and its consequent deleterious effect on metabolism. Hypotheses to explain intrinsic insulin resistance in PCOS include mitochondrial dysfunction and lipid accumulation affecting the insulin-signalling pathway. Hansen et al. (Hansen et al. 2019) found that lean women with

PCOS have 25% lower insulin sensitivity and 40% lower plasma adiponectin levels compared to age and BMI matched controls. The finding of low levels of adiponectin has been shown to predict women with PCOS who are at high risk for developing T2DM (Sepilian and Nagamani 2005). They also reported an increased accumulation of triacylglycerol, diacylglycerol, and ceramide in skeletal muscles of PCOS women supporting the lipid accumulation theory. A retrospective population-based cohort study by Kumarendran et al. determined 1.87 (95% Confidence interval (CI) 1.78-1.97, $p<0.001$; adjustment for age, social deprivation, BMI, ethnicity, and smoking) dysglycemia risk (64,051 women with PCOS and 123,545 matched control subjects). They also conducted a nested pharmacoepidemiologic case-control study to investigate Contraceptive use in relation to dysglycemia risk (2,407 women with PCOS with [case subjects] and without [control subjects] a diagnosis of dysglycemia during follow-up) and found women with PCOS and contraception had a reduced dysglycemia risk adjusted odds ratio (aOR) 0.72, 95% CI 0.59-0.87) (Kumarendran et al. 2021).

1.3.4 Muscle and androgen excess

Muscle is one of the key organs responsible for disposing 70-80% of glucose load. Insulin stimulates a canonical signalling cascade composed of insulin receptor substrate (IRS) 1, phosphoinositide 3-kinase (PI3K), protein kinases PDK1, Akt and Rab. The overall cascade ends with translocation of glucose transporter (GLUT) 4 to the cell membrane which permits the intake of glucose from blood into the cell (Satoh 2014). Insulin resistance is a common finding in PCOS. Stepto et al. found 75% of lean PCOS and 95% of overweight PCOS are intrinsically insulin resistant (N. K. Stepto et al. 2013). Various scientists have attempted to explain insulin resistance by one of three mechanisms: (1) dysregulation and/or dysfunction at several steps in the

insulin signalling cascade, (2) lipid accumulation and (3) mitochondrial dysfunction (Carnagarin, Dharmarajan, and Dass 2015; Nigel K Stepto et al. 2019). Most of the theories about a dysfunctional insulin signalling pathway come from studies on diabetes. The earliest proposed mechanism of insulin resistance in PCOS was increased phosphorylation of serine residue on IRS 1 limiting the signal cascade (Andrea Dunaif et al. 1995). This was also shown in a later study by Corbould et al. (Corbould et al. 2005). However, these findings could not be replicated by other groups. Instead, defects distal to IRS1/2 involving Akt substrate 160 kDa (Hojlund et al. 2008; Martens et al. 2000) and other pathways were found. Nilsson et al found aberrant gene expression and DNA methylation in skeletal muscles of women with PCOS, mainly DYRK1A, which encodes an inhibitor of glycogen synthase kinase-3, SCP2, which is involved in lipid metabolism, SYNPO2, which encodes Synaptopodin protein involved in oxidation in the muscles, KLF10, which is a transcriptional repressor regulating circadian expression of various genes involved in lipid and glucose metabolism, and NAMPT, which encodes visfatin and promotes glucose uptake into skeletal muscle (E. Nilsson et al. 2018). However, many of these changes had contrasting results in the presence of androgens *in vitro* and hence remain inconclusive.

The other commonly proposed mechanisms explaining insulin resistance in PCOS include lipid accumulation and mitochondrial dysfunction. Lipid accumulation in skeletal muscle influencing glucose-regulating pathways is hypothesised to cause insulin resistance in diabetes (Samuel, Petersen, and Shulman 2010; Borén et al. 2013). Intramuscular lipid levels (triacylglycerol, sn-1.3 diacylglycerol and ceramide) were higher in women with PCOS compared to healthy controls in a study done by Hanssen et al. In this study, they found women with PCOS had 25% higher whole-

body insulin resistance compared to healthy controls. They also found lower adenosine monophosphate (AMP)-activated protein kinase and Thr172 phosphorylation in association with lower plasma adiponectin levels suggesting a role of the latter in insulin resistance (Hansen et al. 2019). Studies on the theory of mitochondrial dysfunction causing insulin resistance has resulted in contrasting evidence over the last decades (Yamada et al. 1975; Montgomery and Turner 2015). A non-targeted metabolomics analysis of skeletal muscle of mice which was treated with DHEA revealed 32 metabolites and five metabolic pathways that are significantly different compared to controls (Shen et al. 2019b). Among these, the reduced NAD+/NADH ratio affecting ATP generation was a key finding which may influence in the downstream activation of insulin signalling pathway, supporting the mitochondrial dysfunction theory. Skov et al showed impaired insulin-stimulated glucose disposal in women with PCOS associated with downregulation of mitochondrial oxidative phosphorylation genes using global genetic pathway analysis (Skov et al. 2007). Interestingly, Hutchinson et al could not explain the difference in insulin resistance between women with and without PCOS with either lipid accumulation or mitochondrial dysfunction (Hutchison et al. 2012). Taken together, the essence of these studies suggests there is perhaps a distinct mechanism of insulin resistance in PCOS. Future studies on the specific influence of androgens on insulin resistance in skeletal muscle may answer this question.

Vitamin D has been extensively studied in the recent past and has been shown to have pleotropic effects on various metabolic pathways. Vitamin D deficiency has also been associated with metabolic dysfunction in women with PCOS and androgen excess. Also, reduced 24,25-dihydroxy vitamin D was noted in a DHEA-induced mouse model of PCOS (Shen et al. 2019a). Scott et al found lower 25-hydroxy vitamin

D (25OHD) was associated with higher intramuscular adipose tissue in the thigh and increased insulin resistance in women with PCOS independent of obesity (Scott et al. 2016). Interestingly, they found no difference in the activation of insulin signalling cascade but a reduction in insulin-stimulated glucose oxidation and pyruvate dehydrogenase dephosphorylation suggesting defects in the downstream effects of the insulin signalling pathway in skeletal muscle (Scott et al. 2016).

1.4 Androgen excess and cardiovascular disease

Earlier studies investigating the association between PCOS, and cardiovascular disease reported no increased prevalence. Pierpoint et al. reviewed the case notes of 786 women who were diagnosed with PCOS between 1930 and 1979 and were followed up for an average 30 years; they did not find any increased deaths due to cardiovascular diseases in this cohort compared to national rates (Pierpoint et al. 1998). Interestingly, the same group reported higher prevalence of cardiovascular risk factors and non-fatal cerebrovascular disease in this cohort (S. Wild et al. 2000). While they concluded PCOS may have protective effects on cardiovascular disease, most of these patients did not have a hormonal profile, challenging the diagnosis and the conclusion of the study. Dahlgren et al reported a 7.4 times higher risk for myocardial infarction in women with PCOS compared to those without, using an early risk factor model (Dahlgren et al. 1992). However, the number of participants was relatively small (Dahlgren et al. 1992). Birdsall et al. reported a more extensive coronary artery disease in postmenopausal women with polycystic ovaries on ultrasound. Although the diagnoses of PCOS in this cohort could not be ascertained from their report, the study reported associations between the polycystic ovaries with hirsutism and high

free testosterone (Birdsall, Farquhar, and White 1997). Christian et al. found women with PCOS had higher coronary artery calcification compared to their age-matched controls independent of obesity (Christian et al. 2003). The incidence of coronary artery disease was four times higher in Czech women with a history of PCOS compared to the general population (Cibula et al. 2000). Although these women also had higher prevalence of T2DM, the remaining cardiovascular risk factors was comparable to the rest of the population, questioning whether PCOS is an independent risk factor for coronary artery disease (Cibula et al. 2000). Based on these findings, the Androgen Excess and PCOS society acknowledged that women with PCOS have a moderate to high risk for cardiovascular disease depending on the presence of other risk factors (R. A. Wild et al. 2010). Rees et al. studied the effects of PCOS on cardiovascular morbidity and mortality in 219,034 women with PCOS. The study yielded hazard ratios (HRs) of 1.26 (95% CI, 1.13-1.41), 1.38 (95% CI, 1.11-1.72), 1.60 (95% CI, 1.32-1.94), and 1.50 (95% CI, 1.08-2.07) for myocardial infarction, angina, and revascularization, respectively using adjusted Cox proportional hazard models (CPHMs). In a time dependent CPHM, weight gain (HR 1.01; 1.00-1.01), prior type 2 diabetes mellitus (T2DM) (HR 2.40; 1.76-3.30), and social deprivation (HR 1.53; 1.11-2.11) increased risk of progression to the composite end point (Berni, Morgan, and Aled Rees 2021).

A meta-analysis evaluating the effect of androgen excess in PCOS on metabolic parameters has shown that androgen excess is associated with higher levels of total cholesterol and lower HDL levels (Yang et al. 2016). A study by Luque-Ramirez et al. comparing hyperandrogenic to non-hyperandrogenic PCOS showed an increased mean carotid intima-media thickness independent of BMI, with the main determinant being the concentration of serum total T and A4 (Luque-Ramirez et al. 2007).

Furthermore, T has also been shown to inhibit bradykinin-induced intracellular calcium kinetics resulting in endothelial dysfunction (Rubio-Gayosso et al. 2002). Androgens are also known to impact the renal system through the upregulation of sodium channels in the proximal tubules increasing the rate of fluid reabsorption hence increasing extracellular volume and blood pressure (Quan et al. 2004; Quinkler et al. 2005). Orio et al. (Orio et al. 2004) clinically confirmed endothelial dysfunction in brachial arteries and increased cardiac intima-media thickness directly proportional to androgen excess and independent of obesity in PCOS compared to age and BMI matched controls. Kravariti et al and Luque-Ramirez et al independently confirmed both these findings in PCOS women of differing ethnicities (Kravariti et al. 2005; Luque-Ramirez et al. 2007). Recently, the role of androgen in attenuating endothelin-1 induced vasodilation and endothelin B receptor mediated nitric oxide production resulting in endothelial dysfunction was described by Usselman et al in women with PCOS (Usselman et al. 2019). These and other studies support that androgen excess is implicated either directly or indirectly in almost all proposed mechanisms to explain the increased risk for cardiovascular disease in PCOS.

1.5 Patient experience and patient reported outcomes

Patient experience and patient related outcomes are gaining prominence in recent years. Whilst it is important to continue ground-breaking scientific research, it is also necessary to ensure affected people's concerns are considered. Involving them into research helps improve satisfaction and outcomes of research.

1.5.1 Patient reported outcomes

In recent years, four concepts have gained increased focus to help place affected people at the centre of healthcare research: patient-reported outcomes (PROs),

patient-reported outcome measures (PROMs), patient-reported experiences measures (PREMs) and patient and public involvement (PPI) initiative. A patient-reported outcome (PRO) is “any report of the status of a patient’s health condition that comes directly from the patient without interpretation of the patient’s response by a clinician or anyone else” (“Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims | FDA” n.d.). PROMs are instruments that are used to measure the PROs, most often self-report questionnaires (JH et al. 2017; “Chapter 18: Patient-Reported Outcomes | Cochrane Training” n.d.). PREMs are tools and instruments that report patient satisfaction scores with a health service and are generic tools that are often used to capture the overall patient experience of health care (Weldring and Smith 2013). PREMs help us measure patient’s satisfaction of the healthcare services and thus help as a measure of interventions that focus on improving end-user experiences (The Health Foundation 2013). Patient and public involvement (PPI) is where research is “being carried out ‘with’ or ‘by’ members of the public” not just “‘to’, ‘about’ or ‘for’ them” (“What Is Public Involvement in Research? – INVOLVE” n.d.; Bagley et al. 2016).

Based on 2009 FDA PRO Guidance, Reaney et al. made the first attempts to develop a PCOS-specific PRO called Polycystic Ovary Syndrome Patient Reported Outcome (Pcos-Pro) Scale which has 39 items measuring menstruation symptoms, the daily symptoms of PCOS, and the daily impacts of PCOS. Most items are evaluated on 11-point numeric rating scales (NRS) anchored with “no [symptom/impact]” and “[symptom/impact] as bad as I can imagine”, or “not difficult” and “extremely difficult” (Reaney et al. 2015). Recently, a group of international multidisciplinary researchers got together to harmonise research outcomes for PCOS and developed the harmonizing research outcomes for PCOS (HARP) core outcome set (Al Wattar et al.

2020). This set contains three generic and 30 specific core outcomes in six specialist domains: metabolic (8), reproductive (7), pregnancy (10), oncological (1), psychological (1) and long-term outcomes (1). Adopting HARP core outcome set may minimize heterogeneity in reporting and promote research excellence in PCOS related research (Al Wattar et al. 2021). To the best of our knowledge, there are no patient and public involvement initiatives in PCOS.

1.5.2 Patient experience and patient reported outcomes in PCOS

Women affected by PCOS can experience vast consequences on their mental well-being and mood. This could manifest as depression and anxiety, or low self-esteem due to obesity, hirsutism and acne, fertility and menstrual irregularities. PCOS can also place a large burden on the NHS resources. It has been estimated that PCOS places an annual burden of £237 million (T et al. 2018). The strain on medical, psychological, and social well-being placed upon patients with PCOS is evident and therefore over the past few years, there has been a growing interest in the impact of this condition on both health and quality of life. However, there is limited research studying the correlation between body image, sexual function, depression, and PCOS. Fewer researchers have analysed this relation in women from ethnic minorities. This subgroup tends to experience a higher level of stigma regarding mental health compared to Caucasian women.A few researchers have analysed these qualities in women from ethnic minorities. This subgroup tends to experience a higher level of stigma regarding mental health compared to Caucasian women. (Bazarganipour et al. 2013a).

The UK National Institute of Health and Care Excellence (NICE) recommend healthcare professionals should “ask about emotional wellbeing and manage as appropriate”. However, there are no tailored advice to this complex disorder. Instead,

the guideline provides links to the NICE Clinical Knowledge Summaries pages for generalised eating disorders (National Institute for Health and Care Excellence 2018). This can lead to an underestimation of impact on mental health in PCOS, leading to a poor quality of life, poor self-perception of body image, and a limitation of sexual satisfaction (Elsenbruch et al. 2003).

1.5.2.1 Quality of life

Several researchers have established the significant impact of PCOS on quality of life (QOL). There exists an array of validated questionnaires and surveys to assess PCOS specific impact on QOL. Almost all these questionnaires are designed using the following principles:

a) Both physical and emotional health should be measured.

b) Items must reflect areas of function that are important to women with PCOS.

c) Summary scores should be amenable to statistical analysis.

d) The questionnaire should be relatively short, simple, and capable of being self-administered.

The most popular amongst these questionnaires is PCOSQ developed by Cronin and associates in the USA in 1998 as a self-administered questionnaire. This 26-item questionnaire are grouped into five domains: emotions (8 items), body hair (5 items), weight (5 items), infertility (4 items) and menstrual problems (4 items). The questionnaire has been extensively validated by several researchers (G. G et al. 2004; GL et al. 2004; C. S, G, and HD 2006; L et al. 2007; LEILA, BEHZAD, and ALI 2012; Bazarganipour et al. 2015; Oh 2014). However, some researchers have raised concerns that PCOSQ focuses on physical symptoms only (C and J 2002; W. S, D, and RC 2016; J. Barry et al. 2017). QOL as defined by the WHO has six domains:

physical health, psychological health, level of independence, social relationships, and environment and spirituality/religion/personal beliefs (Group 2015). Four of five domains in PCOSQ focuses on physical health alone. This led to the development of PCOSQOL, a more sensitive measure of QoL as defined by women with the condition in the United Kingdom. The questionnaire includes impact of PCOS on feminine identity; the negative impact of PCOS on family and friends; and the feeling of being under pressure to have children. Interestingly, it does not include spirituality/religion/personal belief domain which is defined in the WHO QOL. However, further validation of the PCOSQOL is necessary to assess the utility of the measure.

1.5.2.2 Mood

Several studies have established the higher prevalence of anxiety and depression associated with PCOS. Barry et al. reported women with PCOS experienced elevated anxiety and depression, significantly more than women without PCOS (J. A. Barry et al. 2011). The level of anxiety and depression may be related to BMI. This theory was investigated by Cooney et al in a systematic review of 30 cross-sectional studies, representing 3050 subjects with PCOS and 3858 controls, from 10 different countries and meta-analysis of 18 studies on depression and 9 studies on anxiety followed by meta-regression of 15 studies. They reported women with PCOS have nearly four times higher risk for depression and more than five times risk for anxiety, independent of obesity, and the symptoms are weakly associated with age, BMI, elevated testosterone, hirsutism, and insulin resistance (LG et al. 2017).

1.5.2.3 Body image concerns and weight stigma

There are some conflicting results for the association of body image concerns and weight stigma with PCOS. This is probably due to difficulties teasing out the entities independently as it tends to be intertwined with obesity and depression in women

without obesity (LM et al. 2011). Women with PCOS having hirsutism and acne have greater body dissatisfaction compared to non-hirsute women (MJ and SS 2006; CL, M, and DA 2004). Bazarganipour et al. conducted a cross-sectional study of 300 Iranian women with PCOS using Body Image Concern Inventory (BICI) and the Rosenberg's Self-Esteem Scale and found that body satisfaction and self-esteem was influenced by hirsutism, BMI, menstrual irregularities, and fertility status (Bazarganipour et al. 2013b). However, Annagur et al. reported no significant difference in body image or self-esteem between 83 women with and 64 women without PCOS in Turkey (Annagur et al. 2014). It should be noted that women in this study were younger and newly diagnosed for PCOS which may mask long term effect of PCOS on the impact of body image concerns.

1.5.2.4 Psychosexual dysfunction

While the systematic review and meta-analysis of sexual function in women with PCOS by Pastoor et al. concluded sexual function and feelings of sexual attractiveness are impaired (Pastoor et al. 2018), the impact of PCOS on the quality of sex life has several inconsistencies due to a complex nebula of literature (Glowinska et al. 2020). Anger et al. studied the relation between sexual function, obesity, psychologic depression, and serum testosterone levels in 33 premenopausal women with PCOS. They reported high levels of sexual dysfunction that negatively correlated with body image (Anger, Brown, and Amundsen 2007). Stovall et al. compared the differences in sexual function scores between women with PCOS and healthy volunteers using "changes in sexual functioning" questionnaire and found no significant difference (27.2% in PCOS versus 24.4% among controls). However, women with PCOS had a significantly lower orgasm/completion score and interestingly higher serum testosterone levels were associated with a reduced risk for sexual

dysfunction in women with PCOS (Stovall et al. 2011). Morotti et al. did not find any significant differences in the relation between mood, perceived body image, sexual behaviour, and clitoral vascularization amongst lean PCOS patients and healthy controls (Morotti E et al. 2013). Amiri et al. reported 45.8% sexual dysfunction using Female Sexual Function Index (FSFI) in women with PCOS in Iran. Logistic regression showed that there were significant associations between sexual function score and the literacy, alopecia, and infertility. However, there was no associations between low scores for any of the sexual domains and low serum total and free testosterone levels (Nasiri Amiri et al. 2017).

Healthcare professionals who manage PCOS need to be aware of the extent of impact on PCOS on various body systems. However, current educational strategies do not dwelve on this in detail. Therefore, there is a need to develop innovative ways to improve the knowledge on PCOS in clinicians.

1.6 Educational strategies

The internet, Web 2.0, and social media are rapidly expanding and transforming our society. Within education, these technologies have greatly enhanced learning environments and enabled the provision of high-quality education at a low cost. Medical education is no exception to this technological revolution. Technological advancements have led to the development of novel teaching methods with a growing use of media and smartphones for teaching and learning, termed technology enhanced learning (Latif et al. 2019a). The current COVID-19 pandemic has disrupted medical education internationally. This is owing to the limited infrastructure that exists to deliver medical education outside the boundaries of traditional means (Gill, Whitehead, and Wondimagegn 2020a). As a result, medical students and doctors in

training have missed out on months of learning essential to their training and progression (Gill, Whitehead, and Wondimagegn 2020b). This has in turn rapidly propelled the use of media for the remote delivery of medical education (Anwar et al. 2020).

The use of media in medical education and potential to enhance learning has been discussed by Hargis and Wilcox (Hargis and Wilcox 2008a). Different types of media possess their own unique characteristics and possible means by which they can enhance learning. These include text documents, infographics, podcasts, videos, webinars, social media, and comics. An educator's choice of media and mode of delivery should consider the context and learner's needs (Wong, Greenhalgh, and Pawson 2010).

The literature around media selection to meet various teaching and learning needs has shown that selection of media should depend on: (i) the contents to be taught; (ii) the structure of the content; and (iii) the skills to be developed (intellectual, psychomotor, or affective skills) (TRENAMAN 1967; Mayer 2009a; T. Bates 1984). Amoah also suggested cost-effectiveness and the target audience as additional factors that should be considered (Amoah 2011). Different types of media allow for different information to be conveyed about the same content. Furthermore, using a combination of media has been shown to result in deeper understanding of the content (Durbridge 2014; Mayer 2009b). This is because learning requires the mental integration of information which is made easier when the content is presented in various formats.

During my time doing PhD, I have conceptualised and developed two educational strategies- Simulation via Instant Messaging-Birmingham Advance (SIMBA) and

Concise Medical Information Cines (CoMICs) using the concepts described by Malcolm Shepherd Knowles(Lippitt and Knowles 1984).

SIMBA and CoMICs emerged from three points of frustration among medical students and junior doctors in training:

1. lecture-based learning was not helping us translate much into clinical application- While medical students and junior doctors gain substantial theoretical knowledge with their university degree, majority of these students are not able to successfully apply this in everyday tasks of practice. A wealth of evidence exists in both nursing and midwifery (Cheraghi, Salsali, and Safari 2010; Factor, Matienzo, and de Guzman 2017) and medicine (N. Van Dijk, Hooft, and Wieringa-De Waard 2010) sectors to support this statement.
2. nearly impossible systems to follow-up patients from initial presentation to follow-up after definitive management (Kendall, Hesketh, and Macpherson 2005; Gilbert et al. 2012; Timm 2013)
3. a time- and resource-limited simulation-based system (Melson et al. 2020d).

I describe each of these below in a bit more detail.

1.6.1 SIMBA

SIMBA a virtual simulation-based learning model that I started in July 2019. Learners interact with moderators (mostly medical students) simulating real-life clinical cases through WhatsApp, followed by case discussions (Melson et al. 2020d). While lecture-based learning has it place, some prefer to learn by doing or simulating. And it is

important we respect different styles of learning and promote equitable opportunities to access diverse range of learning platforms. Simulation-based learning (SBL) helps with this (Gaba 2004). However, there are limited models, most are expensive, and some are without strong pedagogic backing (Al-Elq 2010).

SIMBA is based on Kolb's 4-stage experiential learning cycle (Kolb DA 1984). The workings of SIMBA involve a continuous interaction between the session lead, which usually is a medical student and an expert in the field on which simulation-based cases are conducted. As a first step for SIMBA, I decide on the speciality we wish to simulate the cases with the help of SIMBA team. The session lead in turn works with four other team members to deliver various aspects of the session. I have regular meetings with the session lead and provide overall supervision and mentorship, helping them learn in the process. More detailed visual explanation in Figure 5.

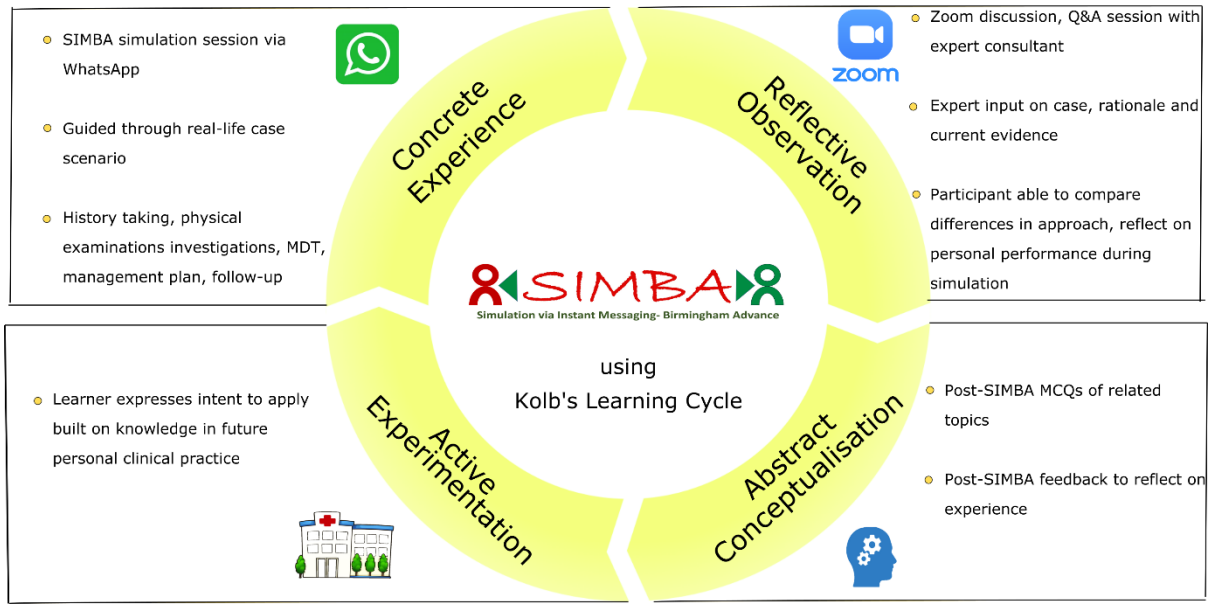


Figure 5SIMBA replicating Kolb's 4-stage experiential learning cycle.

While the participants' benefit from improving their confidence to manage simulated cases, those medical students involved in delivering the session eventually

understand the underpinning pedagogy of simulation-based learning. Session leads in our previous sessions have thanked in for this opportunity. One memorable comment was from a third-year medical student “I am thankful for your help and mentorship. It’s an entirely different experience to lead a session. This helped me understand the vast amount of preparation that goes into delivering each session.”

Over time, the members of SIMBA team have developed independence in their role to a point where they start becoming mentors to their apprentice. They start to understand the finer details when they start to teach how to do things creating a group of skilled medical students who can become future leaders in medical education. Similar work has been shown elsewhere (Bovill, Bulley, and Morss 2011).

1.6.2 CoMICs

CoMICs are bite-sized videos consisting of illustrations and infographics created on a whiteboard animation to simulate traditional classroom teaching and to keep viewers engaged. CoMICs is built on the concepts of maximising impact on learner’s intrinsic and extrinsic load on working memory. (Van MerriÃ«nboer and Sweller 2010; Mayer 2010)

Although there are currently innumerable resources available to learn about medicine at the touch of finger, only a handful of them have received end user feedback or were created by end user with sound expert advice. Several studies have shown the lack of engagement or connection if there is no end user involvement (Blili, Raymond, and Rivard 1998; Langton et al. 2003).

I choose a topic on which our team create a script is prepared based on latest scientific evidence which is then converted into video. These videos are then critically reviewed by experts to ensure accuracy. I work with the medical students and experts to ensure

that the contents of the video are not only easily digestible but accurate and based on the most up-to-date information.

CoMICs not only helps medical students learn the topic but also inculcates good learning concepts in these medical students so they can apply them when they rise up to the level of becoming educators in the future. A medical student who is part of the team recently feedback saying “this is an excellent opportunity for me to express my creativity to understand the medical condition better and also work in collaboration with other likeminded individual helping me build my network”

So what? Like SIMBA, members of CoMICs team have developed independence in their role and currently mentoring other medical students. This is helping to spread the concepts of good practices in medical education through peer-to-peer learning.

Each CoMICs start off with selecting the topics. I have coupled this process with SIMBA so there is a harmony of the simulated topics and CoMICs videos. I assign a member of CoMICs team to each CoMIC who then interacts with the members of the SIMBA team to gain the draft storyboard. I oversee this process and ensure smooth interaction between the two teams. The team member in charge of this CoMIC develops the first draft of the CoMICs using the concepts of bite-sized learning and whiteboard animation (Mayer et al. 2005; Morgan 2010; Young et al. 2014; Türkay 2016).

I then review the first draft to ensure style uniformity compared to previous CoMICs following they are sent for expert reviews. Experts feed their comments and suggestions directly to the medical student who made the CoMIC. The pre-final version is sent to me for a final review of style and content. The final version is then circulated to all involved and we release a new CoMIC every week as part of our

#CoMICWednesday initiative on social media. Regular intervals are shown to increase audience and build anticipation for acquiring knowledge. Overall, CoMICs has foundations built of classic pedagogy while catering to the modern day needs for education in a fast-paced world.

1.6.3 Documents/Text

Text, combining written language and still graphics, appear in a variety of formats including but not limited to textbooks, PDF documents, journal articles, blogs, and notes (A. W. (Tony) Bates 2015a). Text is useful when abstraction and generalisation is needed to aid analysis, critical thinking, and evaluation of the content (A. W. (Tony) Bates 2015b). Documents summarising national and international guidelines are used for Simulatio via Instant Messaging-Birmingham Advance (SIMBA) during the post-simulation debrief sessions. PDFs of guidelines have proved useful to present large amounts of information about medical conditions in a systematic way including important questions for history taking, appropriate physical examinations and investigations leading to a diagnosis, and appropriate management. This has helped to increase the participants' knowledge and confidence in managing cases with reference to the guidelines. In the future, these documents could be distributed to participants prior to the simulation session, following a flipped or inverted classroom model, with the aim of promoting self-directed learning and a more personalised learner experience (Hew and Lo 2018; Lage, Platt, and Treglia 2000; "Swanwick, T (2014). Chapter 12: E-Learning. Understanding Medical Education: Evidence, Theory and Practice. Chichester, John Wiley & Sons. Pp 166 - Google Search," n.d.).

1.6.4 Infographics

The use of infographics in medical education stems from a pedagogical need to employ visual learning ("Teaching with Infographics: Practicing New Digital Competencies and Visual Literacies - Journal of Pedagogic Development | University of Bedfordshire," n.d.). Flowcharts present complicated diagnostic and management pathways in a clear and straightforward manner (Martin et al. 2019; "Public Relations Writing : Form & Style / Doug Newsom, Jim Haynes - Trove," n.d.; Balkac and Ergun 2018). Infographics also allow information from written text and documents to be presented visually to aid abstraction.

In SIMBA, infographics are used to present complex information regarding the approach to specific pathologies. Images of the investigation results for the cases are sent to the participants upon request, clearly showing the investigated parameters, results and normal reference ranges in tables (Duquia et al. 2014). The use of PowerPoint animation mimics real-life imaging systems, enabling participants to view radiological images and improving their confidence in recognising pathologies and making diagnoses. Furthermore, the use of PowerPoint presentations by the chairs during the debrief session increases learner engagement and promotes the retention of information (Susskind 2005). PowerPoint presentations are also delivered by the chairs to the medical students who are moderators, to familiarise them with the cases and underlying pathologies. This makes learning two-way and enhances the moderators' understanding of the cases, thus improving their performance.

Alongside SIMBA, we have developed an infographic-based medical educational initiative called Concise Medical Information Cines (CoMICs). We use illustrations and infographics compiled into bite-sized videos to provide an overview of various medical topics, aimed at medical students and junior doctors. These are uploaded to

YouTube® and available on public domain. Examples include adrenal incidentaloma (youtu.be/K2te9ZExKV0), Cushing syndrome (youtu.be/cliG3u_6wW8), mild autosomal cortisol excess (youtu.be/PnFUseE3ng0), with more information on our website bit.ly/simbasimulation.

1.6.5 Podcast/audio

Podcasts are audio broadcasts or files uploaded on the internet (Latif et al. 2019b). Owing to the low cost, ease of production, and general appeal, podcasting has become increasingly popular, with many medical organisations and societies producing podcasts to deliver medical education (Latif et al. 2019b). Podcasts may also improve soft skills such as active listening, empathy, and compassion ("How Podcasts Make Me an Empathetic Physician | Medical Humanities," n.d.). Acceptance rates and satisfaction with podcasts is well-reported, with learners devoting more time to listening to podcasts and perceiving them as more beneficial compared to traditional textbooks and journals (Latif et al. 2019b). Other examples of using audio in medical education include recordings of expert discussions and patient interviews (Cho, Cosimini, and Espinoza 2017; Wilson, Petticrew, and Booth 2009).

Although we have not used podcast or audio files in SIMBA to date, we recognise the potential uses of the aforementioned medium in the future, for example audio files of heart or breathing sounds. This may help to make SIMBA simulation sessions more realistic and applicable to real-life clinical practice. The limitations of podcasts include the difficulties for people with hearing impairments and variations with spoken language compared to text (A. W. (Tony) Bates 2015c).

1.6.6 Video

The medium of video possesses unique characteristics that cannot be replaced by other media (A. W. (Tony) Bates 2015d). It is a much richer medium compared to text, infographics and audio due to the additional characteristic of offering dynamic pictures (A. W. (Tony) Bates 2015e). It has been demonstrated that medical education videos uploaded to video-sharing platforms such as YouTube® can rapidly reach an international audience, thus vastly expanding their impact (Topps, Helmer, and Ellaway 2013).

As SIMBA is a novel training programme in medical education and to learners, we commence each simulation session by showing an animated video demonstrating an example of participant-moderator interaction. This is an effective and efficient means to familiarise participants with the SIMBA model. We have also uploaded videos to YouTube® to disseminate the SIMBA model widely among the medical education community and wider medical profession. The debrief and expert discussion sessions are also recorded for remote access by the participants at a later stage to further consolidate learning.

1.6.7 Social Media

Social media has emerged as a powerful and economical tool for global connection, collaboration, and education. Platforms such as Facebook®, LinkedIn®, and Twitter® can be used to disseminate information in an easily retrievable format within medical education (Hargis and Wilcox 2008b). Social media facilitates knowledge sharing, with the potential to rapidly reach an international audience, and can be viewed as an open access resource in medical education (Latif et al. 2019b). It offers an informal learning environment which fosters engagement, interaction, and a real-time dialogue that

traditional means of communication do not (Forgie, Duff, and Ross 2013). Social media platforms can be used to share new scientific developments and free, open access materials to enhance learning (Mayes 2015).

The use of WhatsApp® as an educational platform for SIMBA greatly increases the interaction and engagement levels of the sessions which is essential for effective simulation. Since the onset of the COVID-19 pandemic, we have rapidly expanded SIMBA on an international scale as our response and solution to the disruption of medical training worldwide. The ubiquity of WhatsApp® has made SIMBA cost-effective and accessible, with international interest and participation (Melson et al. 2020b). We use Twitter® to expand our reach and share details of upcoming sessions to an international audience.

1.6.8 Video Conferencing & Webinars

Webinars are online seminars broadcasted live through the internet (Knipfer et al. 2019). They are an example of a synchronous tool, regarded as the most advanced form of computer-mediated communication which facilitates interaction, active participation, and immediate feedback. This requires more resources but has the potential to greatly enhance audience participation and learning (Gandsas et al. 2002; Sandhu et al. 2017).

The COVID-19 pandemic and subsequent lockdown led to a surge in popularity of platforms such as Microsoft Teams® and Zoom® to facilitate remote work and collaboration. Since then, we have held multiple international simulation sessions, largely over Zoom®, across the specialties of endocrinology, gastroenterology, and acute internal medicine. In the future, SIMBA could supplement the need for in-person training days and promote ease of access.

1.6.9 Cartoons/Comics

Cartoon or comic materials are increasingly being used as learning aids in medical education, particularly in graphic medicine (Junhasavasdikul et al. 2017). They attract the reader's interest and provide a pleasurable reading experience. Because of this, comics could become increasingly popular within medical education. A study demonstrated that cartoon-based learning tools led to an improvement of 96% in post-learning test scores of healthcare professionals (Sim et al. 2014).

1.7 Hypothesis and Aims

During my PhD, I developed three hypotheses with the help of my supervisors and colleagues in the research group. Firstly, determining the reference range of various steroids in otherwise healthy population will help us understand the distinct steroid signatures in PCOS and its various subgroups. Secondly, I hypothesised that people with PCOS have a high emotional illbeing burden which is not usually evaluated. Lastly, we can improve the understanding between healthcare professionals and people with PCOS if we bring them together. To test these hypotheses, I devised three aims:

- Establish the distinct androgen signature in a healthy population
- Investigate whether people with PCOS have a high prevalence of anxiety, depression, and body dysmorphia
- Take steps to include people with PCOS in designing and delivering education regarding the condition can help us reduce the gaps in knowledge, attitude, and practice of PCOS.

2 Chapter 2: General Methods

The procedures described in this chapter are commonly used throughout this doctoral thesis. Any methods specific to individual chapters are described separately in the appropriate section

2.1 Steroid analysis by mass spectrometry

2.1.1 Principles of steroid analysis by mass spectrometry

Mass spectrometry (MS) was perhaps one of the biggest leaps in analytical scientific advancement of 20th century. In the analysis of steroid concentrations in biological fluid and matrices, it is among one of the most successful approaches to improve specificity problems inherent in immunoassays (Shackleton 2010; Keevil 2016; Krone et al. 2010). In MS, mass-to-charge ratio of ions are measured, and the results are presented as a plot of intensity as a function of the mass-to-charge ratio. The four-step operating principles of mass spectrometry involve Ionisation, Fragmentation, Separation, and Detection. The process involves bombarding the sample, which may be solid, liquid or gas, with a beam of electrons. This may either break the sample into positively charged fragments or might just make the sample positively charged without breaking it. These charged particles are then separated by accelerating them towards an electric or magnetic field and ions of the same mass-to-charge ratio cluster together. These ions are then identified using an electron multiplier, a vacuum-tube like structure which multiplies the incident charge. Results are displayed as a spectrum and the molecules are identified by either correlating known masses (e.g. an entire molecule) to the identified masses or through a characteristic fragmentation pattern (Downard 2004).

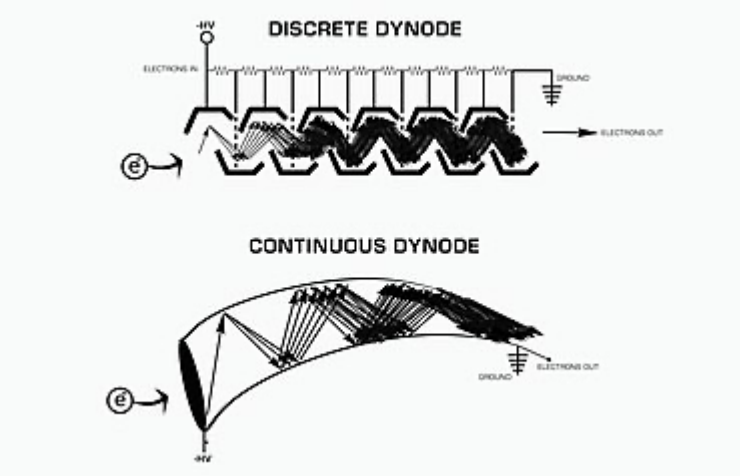


Figure 6: Principles of electron multiplier (image from Wikipedia, originally uploaded by Nikob7 on 9 April 2019. This file is used in this thesis under the Creative Commons Attribution-Share Alike 4.0 International license.).

Another analytical concept of note is chromatography. It is a technique of separating a mixture into two phases, one stationary and the other moving in a definite direction (McMurry 2011). Different constituents of the mixture have different affinities for the stationary phase and thus stay longer or shorter on the stationary phase. This can be visualised on a graph where different peaks and patterns correspond to different components of the mixture. Paper chromatography, Gas chromatography (GC) and liquid chromatography (LC) are the three most common types of chromatography used in analytical chemistry.

Sweeley and Horning were the first use mass spectrometry for endocrine studies using GC in 1960 (SWEELEY and HORNING 1960). Three years late, Eneroth, Hellström and Ryhage combined GC with MS and identified human sterols in faeces (Eneroth, Hellstrom, and Ryhage 1964). As steroids are polar compounds, they readily move from an aqueous to an organic environment which allows for simple liquid-liquid extractions. LC and GC are the two major chromatography techniques linked to mass

spectrometers to separate a steroid mixture into specific steroid fractions. After chromatographic separation the steroids sequentially enter the ionisation source of the MS. Positive identification of a compound was achieved through the four parameters: Matching retention time, Identical molecular weight, Identical unique fragmentation patterns by MS/MS, and Library searches

2.1.2 Serum multi-steroid profiling by tandem mass spectrometry

Liquid chromatography-tandem mass spectrometry (LC–MS/MS) has started to become the method of choice for steroid hormone assay. It needs very minute volume of sample, high sensitivity and specificity and quick results compared to traditional immunoassays (Keevil 2016). Various LC-MS/MS methods for adrenal hormone analyses in the serum have been reported (Taylor et al. 2017; Soldin and Soldin 2009; Sánchez-Guijo et al. 2015; Moal et al. 2007; Koal et al. 2012; Stolze et al. 2016; Marcos and Pozo 2016). Recently, Keefe et al. published LC-MS/MS method to extract and measure 13 steroids in PCOS (Keefe et al. 2014). One of the main drawbacks of LC-MS/MS is the limited number of analytes that can be quantified in each run (K. H. Storbeck et al. 2018). Also, some classes of steroids such as Δ5 and 5α/β-reduced steroids, ionise poorly resulting in inadequate limits of quantification (Wudy et al. 2018).

The recent advent of commercial ultra-high performance supercritical fluid chromatography (UHPSFC) systems may, however, offer an alternative as UHPSFC combines many of the strengths of both GC and LC. It uses supercritical carbon dioxide which can behave as both liquid and gas further enhancing chromatographic efficiency and resolution, making it ideal for extracting steroids (K. H. Storbeck et al. 2018).

We applied the principles of LC-MS/MS to extract steroids from our serum samples which is described in detail in relevant chapter.

2.2 Education strategies

Here, I describe the general model of SIMBA. The adaptation of SIMBA to educate healthcare professionals and people with PCOS is described in detail in later chapters.

Each SIMBA session starts off by appointing a volunteering medical student as the session lead. I meet them for a one-to-one discussion to discuss how much they understand their role and what is expected. I recommend them to use a Gantt chart with activity, start date, end date, person responsible for the activity, and progress bar so they can easily visualise and quantify various pedagogies, thus helping the session lead to breakdown the entire activity into bite-size ensuring a steady progress over time. The session lead is usually part of the team which usually manages the session's various aspects and thus the lead is familiar with their team and how they function. I then introduce the session lead to the expert who will lead the discussion during the session. This is usually a consultant with a special interest in the field. With this process, I establish a direct communication channel between the session lead and expert while I retain the role of a mentor and supervisor to ensure the progress and help address any problems they may encounter.

During the preparation phase, I supervise the final version of the transcript to be used in the session to ensure there is a right balance in the information provided and complexity to engage the participants. I also arrange regular meetings with the session lead to review the Gantt chart and ensure they are well supported by the expert and their team members.

On the day of the session, I introduce the session lead in the welcome who then do a short presentation to explain what SIMBA is and how it works to get an overview of the day.

Following simulation, I host a zoom session where the expert discusses the simulated cases and the rationale behind decisions and participants reflect on the concrete experience gained through simulation. Interactive discussions are essential to ensure cognitive engagement during the online discussion and are critical for constructing new understanding and knowledge (Alvermann, Hynd, and Qian 1995; Zhu 2006).

Over time, these session leads become supervisors to future session leads, thus taking over my role as described above. In turn, I move up a purely mentoring role for the team thus facilitating learning by doing amongst medical students.

Results

The results are structured in a journal article style, each including its own introduction followed by the methods, results, and discussion.

3 Establishing distinct androgen signatures in healthy population

3.1 Introduction

Circulating androgens and their precursors are produced by the gonads and the adrenal glands in both men and women. However, androgen biosynthesis in the gonads and adrenal glands is differentially regulated and generates different types of androgen precursors.

Gonadal androgen biosynthesis produces the classic androgen precursor androstenedione (A4) and the active classic androgens, testosterone (T) and 5α-dihydrotestosterone (DHT). Gonadal steroidogenesis begins with puberty and declines gradually with age in men and more rapidly in women during the peri-menopause, and is primarily regulated by pituitary gonadotrophins, i.e. via the hypothalamic-pituitary-gonadal axis(Andersen and Ezcurra 2014).

Adrenal biosynthesis produces the classic androgen precursor dehydroepiandrosterone (DHEA), which serves as substrate for the generation of active androgens in peripheral tissues(L Schiffer, Barnard, et al. 2019). DHEA can be inactivated to its sulfate ester DHEAS or activated in the classic androgen pathway in the adrenals contributing to circulating concentrations of A4 and, to a lesser degree, T. Adrenal DHEA biosynthesis declines with age in adults (W Arlt 2004) and is stimulated by ACTH and hence follows the diurnal pattern of hypothalamic-pituitary adrenal axis activation(Nieschlag et al. 1973; Rosenfeld et al. 1971).

The adrenal gland also produces significant amounts of the 11-oxygenated androgen precursor 11β-hydroxyandrostenedione (11OHA4) (Rege et al. 2013), which is generated through hydroxylation of A4 by steroid 11β-hydroxylase CYP11B1, the same enzyme that catalyses the final step of cortisol biosynthesis (Swart et al. 2013). While the ability of the adrenal to produce 11OHA4 is known for decades, 11OHA4 was previously considered an inert metabolite. However, in recent years it has been demonstrated that in peripheral tissues

11OHA4 can be activated to 11-ketoandrostenedione (11KA4) and 11-ketotestosterone (11KT) (Swart et al. 2013; Pretorius et al. 2016b). Importantly, 11KT binds and activates the androgen receptor with similar potency and efficacy as T and the 11KT metabolite 11β-hydroxytestosterone (11OHT) is a partial androgen receptor agonist (Rege et al. 2013; Pretorius et al. 2016b). In peripheral tissues such as adipose, 11KT is generated from 11KA4 by aldo-keto reductase 1C3, AKR1C3, which can also convert A4 to T, but has a significantly higher catalytic activity for the activation of 11-oxygenated androgens (Quinkler et al. 2004; Barnard et al. 2018b). The expression of AKR1C3 in adipose tissue is upregulated by insulin (O'Reilly, Kempegowda, Walsh, et al. 2017b) and reduced by weight loss in women (Quinkler et al. 2004).

11KT is the major circulating active androgen in women (O'Reilly, Kempegowda, Jenkinson, et al. 2017; Davio et al. 2020) and has been highlighted as a potential disease activity biomarker in women with polycystic ovary syndrome (O'Reilly, Kempegowda, Jenkinson, et al. 2017) and congenital adrenal hyperplasia (A F Turcu et al. 2016; Jones et al. 2017; Bacila et al. 2019).

3.2 Objective

To inform the understanding of the physiological variations of 11-oxygenated androgens in healthy women and men, we comprehensively studied the physiological variation of 11-oxygenated and classic androgens in serum and saliva, including diurnal and menstrual variation, and examining the influence of age and body mass index (BMI) in a large healthy volunteer cohort with a broad age range.

3.3 Participants and methods

3.3.1 Sample collection

The collection of serum and saliva samples from healthy volunteers identified through advertisement by word of mouth and social media to recruit from the community received ethical approval by the Science, Technology, Engineering and Mathematics Ethical Review Committees of the University of Birmingham, UK (ERN_17-0494, ERN_17-0494B) and the Mayo Clinic, Rochester, MN, USA (IRB ID 18-009787). Inclusion criteria were age 18 years or above and provision of written informed consent prior to study participation. Exclusion criteria were any acute or chronic disease affecting steroid biosynthesis or metabolism, the intake of any medication known to interfere with steroid biosynthesis or metabolism except for use of hormonal contraceptives (combined oral contraceptives, contraceptive depot injection or implant).

A standardised questionnaire was used to record demographic data including age and BMI; for women the use of hormonal contraceptives and menopausal status were recorded. If no information on menopausal status was provided, women aged 50 years or older were considered post-menopausal. Premenopausal women not using hormonal contraception were asked on which day of their menstrual cycle the sample was collected, defining the day of the start of their last menstrual bleed as day 1.

Blood samples were collected in the morning before 11:00h and serum samples were stored at -80 °C. Saliva samples were collected by passive drool; morning samples were collected between waking up and 10:00h. To avoid contamination by trace blood or other substances, participants were asked to avoid brushing teeth for two hours, to avoid eating for one hour and to rinse their mouth with water 10-15 min prior to the

saliva sample collection. Saliva samples were frozen at -20 °C, then defrosted, and centrifuged at 2500*g* for 5-10 min; the clear supernatant was aliquoted and stored at -80 °C until analysis.

3.3.1.1 Serum steroid analysis by LC-MS/MS

Unconjugated steroids were quantified using a previously published and validated multi-steroid profiling liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay (Lina Schiffer et al. 2022). In brief, 200 µL of serum were mixed with isotopically labelled internal standards and following protein precipitation with 50 µL acetonitrile samples were extracted by liquid-liquid extraction with 1 mL methyl *tert*-butyl ether. The dried organic phase was reconstituted in the mobile phase and steroids were chromatographically separated using a Phenomenex Luna Omega C18 column (1.6µm, 100Å, 2.1 x 50mm) and a water-methanol gradient. Ammonium fluoride was introduced by post-column infusion and steroid quantification was performed on a Waters Xevo TQ-XS mass spectrometer using electrospray ionisation in positive ion mode.

In brief, DHEAS was extracted and quantified using a separate validated assay (Foster et al. 2020; Chadwick, Owen, and Keevil 2005). Internal standard (DHEAS-d2) was added to 20 µl of serum followed by 20 µl of ZnSO4 then100 µl of acetonitrile. The samples were then centrifuged and 100 µL of the solution was transferred to a new vial, dried and reconstituted in 200 µl of methanol/water prior to liquid chromatography tandem mass spectrometry analysis(Chadwick, Owen, and Keevil 2005). DHEAS was quantified against a calibration series ranging from 250 to 8000 ng/ml.

3.3.1.2 Salivary steroid analysis by LC-MS/MS

As previously described (Chadwick, Owen, and Keevil 2005; L Schiffer, Adaway, Arlt, et al. 2019), 300 µL of saliva were mixed with isotopically labelled internal standards

and extracted by supported liquid extraction using 1 mL dichloromethane. Progesterone, 17α-hydroxyprogesterone (17OHP), A4, T, 11OHA4 and 11KT were quantified using previously published assays (L Schiffer, Adaway, Baranowski, et al. 2019; L Schiffer, Adaway, Arlt, et al. 2019) on a Waters Xevo TQ-S mass spectrometer. For a subset of morning saliva samples, 17OHP, A4, T, 11OHA4 and 11KT were measured by a modified version of the published assay using a Waters Xevo TQ-XS mass spectrometer. For this assay, chromatography was performed using a Waters Acquity HSS T3 (1.8 µm, 100 Å, 2.1 x 50 mm) column using a gradient of 2 mmol/L ammonium acetate and 0.1% (v/v) formic acid in water and acetonitrile. The lower limit of quantitation was 5 pmol/L for T, 10 pmol/L for A4, 12.5 pmol/L for 17OHP, 6 pmol/L for 11KT and 45 pmol/L for 11OHA4. The assay was linear up to 50,000 pmol/L for T, 100,000 pmol/L for A4, 150,000 pmol/L for 17OHP, 100,000 pmol/L for 11KT and 200,000 pmol/L for 11OHA4. Recovery was shown to be 92.5-109.8% for all analytes, inter-assay precision was <8.6% (<13.7% at lower limit of quantitation, LLOQ) and inter-assay bias from nominal concentrations was <8.8% (<15.6% at LLOQ).

The analytical performance of the two assays measuring salivary 17OHP, A4, T, 11OHA4 and 11KT was compared using saliva samples from multiple donors (n=46-59). The mean relative difference between the assays was within -5 % and 5.8 % and the concentrations determined with the two assays strongly correlated ($r>0.93$, $p<0.0001$). The data generated by the two assays was hence combined for analysis.

3.4 Statistical analysis

Statistical analysis was performed using Stata v.16 and SPSS version 27 (IBM Corp.) with graphs generated using Prism 9 for macOS Version 9.2.0 (GraphPad Software, LLC). Due to non-normality of steroid outcome, data were summarised using medians and interquartile ranges (IQR) and comparisons were made using non-parametric tests, utilising Mann-Whitney U-test and Wilcoxon signed-rank test as appropriate. Steroid concentrations below the LLOQ were replaced by 0.5*LLOQ for the statistical comparisons.

Each steroid outcome was log-transformed prior to regression analysis. For each steroid a linear model was fitted to estimate the association with age and BMI, with adjustment for centre recruited from. Models were fitted for male and female participants separately. Results were expressed as approximate percentage changes per unit change in the characteristic, with corresponding 95% confidence intervals.

3.5 Results

3.5.1 Characteristics of the participants

We collected morning serum samples from 292 healthy volunteers (167 women, 57%; 125 men, 43%), with a similar age range for men (22-95 years) and women (21-91 years). We included 76 (46%) premenopausal and 89 (54%) postmenopausal women. Fifteen of the premenopausal women (20%) either received hormonal oral contraceptives (n=7) or contraceptive depot injections or implants (n=8); none of the postmenopausal women was on HRT. Menstrual-cycle dependent serum steroid

concentrations were studied in 32 women, who reported the day of their menstrual cycle at the time of blood collection.

Morning saliva was collected by 83 healthy volunteers (51 women, 37 pre- and 14 postmenopausal; 32 men). Twenty-five volunteers (12 premenopausal women, age 24-39 years; 13 men, age 20-35 years) additionally collected a 7-timepoint saliva profile (07:00h, 09:00h, 11:00h, 13:00h. 15:00h, 19:00h, 23:00h). Twelve women collected diurnal saliva profiles during both the follicular and luteal phase of the menstrual cycle. In addition, eight premenopausal women not on hormonal contraceptives collected morning saliva samples during seven consecutive days both in the follicular and the luteal phase (days 1-7 and days 18-24, respectively); individual median values were used for statistical comparisons between follicular and luteal phase.

We observed significant positive correlations between age and BMI in both men ($r=0.3482$, $p<0.0001$) and women ($r=0.4928$, $p<0.0001$; Figure 7**)**. Hence, we used multiple linear regressions to delineate the distinct effects of age and BMI, respectively, on serum steroid concentrations in the sex-specific analysis presented below. Postmenopausal women had a significantly higher BMI than premenopausal women ($p<0.001$, Table 2). Therefore, the comparison of steroid concentrations of pre- and postmenopausal women were not adjusted for BMI.

3.5.2 Serum and saliva steroid profiles in men and women

Serum concentrations of the classic androgen precursors DHEA and A4 were similar in men and women while, expectedly, the circulating concentrations of T and DHT were higher in men (Figure 8**A+B**). The 11-oxygenated androgens had similar serum concentrations in men and women (Figure 8**C+D**). Concentrations of 11OHA4 were

the highest of all 11-oxygenated androgens and were higher than the concentrations of A4 and similar to the concentrations of DHEA. Sex- and age-specific reference ranges for classic and 11-oxygenated androgens in serum are summarised in Table 3; results for other steroids are provided in Table 4.

Salivary A4 and T concentrations were higher in men than in women. Interestingly, salivary 11KT concentrations were higher in men than in women despite similar concentrations of its adrenal precursor 11OHA4; 11KT was higher than T in both men and women (Figure 8**E+F**). Salivary and serum concentrations of A4, T, 11OHA4 and 11KT from the same individuals correlated closely ($p<0.0001$; Figure 9).

3.5.3 Serum steroid concentrations across the adult age range

The classic androgen precursors DHEAS, DHEA and A4 and the active androgens T and DHT appeared to decline with age in both men and women (Figure 10**)** and the regression model demonstrated a clear impact of increasing age for all those steroids except for DHT in men (Table 5). In keeping with this, postmenopausal women had lower serum DHEAS, DHEA and A4 compared to premenopausal women (Table 2).

11-oxygenated androgen concentrations did not change significantly with increasing age except for 11OHT, which appeared to increase in both older men and women (Figure 11), but the linear regression model did not confirm an influence of age on 11OHT (Table 5**).**

3.5.4 Effect of BMI on serum steroids concentrations

Circulating concentrations of DHEA, DHEAS and A4 showed no BMI-dependent variation (Table 5). By contrast, the active androgens T and DHT decreased with increasing BMI, more pronounced in men (Figure 12, Table 5).

The 11-oxygenated androgen precursors 11OHA4 and 11KA4 did not vary with BMI (Table 5). By contrast, the active 11-oxygenated androgens, 11OHT and 11KT appeared to increase with increasing BMI (Figure 12). A dominant effect of BMI rather than age on the decrease of T and DHT and the increase in 11KT and 11OHT was supported by the linear regression model, with a slightly larger effect seen for men (Table 5).

3.5.5 Menstrual cycle variations in salivary and serum steroids

Serum concentrations of progesterone and its metabolites 5α-dihydroprogesterone (5αDHP) and allopregnanolone (alloP) were significantly increased during the luteal phase (Figure 13**).** Morning salivary progesterone and 17OHP concentrations were significantly higher during the luteal phase, reflective of ovulation and luteal body formation (Figure 14**A+B**, **Figure 10**).

Salivary A4, T, 11OHA4 and 11KT (Figure 14**C-F**, **Figure 10**) and serum concentrations of classic and 11-oxygenated androgens (Figure 15, Figure 17) of did not differ significantly between follicular and luteal phase of the menstrual cycle except for serum DHEA, which was higher in the luteal phase.

3.5.6 Diurnal variation of salivary steroids in pre-menopausal women and men

Salivary progesterone concentrations were below the limit of quantification at all time points over the day during the follicular phase in all but one of the female participants and increased during the luteal phase without demonstrating a diurnal pattern (Figure 18**A**).

Salivary concentrations of 17OHP, classic androgens A4 and T as well as 11-oxygenated androgens 11OHA4 and 11KT showed a clear diurnal pattern during the follicular phase in women (Figure 18) and in men (Figure 19), with the highest concentrations observed in the morning followed by a gradual decline with a nadir in the late evening. 11OHA4 and 11KT, which are exclusively derived from adrenal steroidogenesis, showed stronger diurnal variation than A4 and T (Figure 18**G+H**, Figure 19**E**). A clear diurnal pattern was maintained for circulating concentrations of the 11-oxygenated androgens throughout the menstrual cycle while the diurnal pattern for A4 and T concentrations was less distinct in the luteal than in the follicular phase (Figure 18).

3.5.7 Impact of hormonal contraceptives on serum and salivary steroids in pre-menopausal women

For the women who provided serum samples, there were no differences in age and BMI between premenopausal women with and without hormonal contraceptives (Table 6). Expectedly, women on hormonal contraceptives had significantly lower serum concentrations of Prog and its metabolites 5αDHP, alloP and 17OHP (Table 6). Serum A4 concentrations were significantly lower in women taking hormonal contraceptives, indicative of a decreased ovarian contribution. However, serum T was not affected by hormonal contraceptives. Serum concentrations of adrenal-derived androgens and precursors (DHEA, 11OHA4, 11KA4, 11KT) were not affected by hormonal contraceptives.

Similar to the observations in serum, salivary 17OHP and A4 concentrations were significantly decreased in women taking hormonal contraceptives (Table 6). Interestingly, while we did not observe differences in serum T and 11KT, salivary T

and 11KT concentrations were significantly lower in women on hormonal contraceptives (Table 6).

3.6 Discussion

The active 11-oxygenated androgen 11KT and its 11-oxygenated precursors have been established as useful biochemical markers of adrenal androgen excess over recent years (O'Reilly, Kempegowda, Jenkinson, et al. 2017; A F Turcu et al. 2016; Bacila et al. 2019; Kamrath et al. 2018), in addition to the classic androgens, testosterone and 5α-dihydrotestosterone. Aiming to improve the utility of 11-oxygenated androgen measurements in the clinical laboratory, we set out to characterise the physiological variation of 11-oxygenated androgen concentrations in healthy individuals by multi-steroid profiling in serum and saliva. The effect of age (Davio et al. 2020; M A Skiba et al. 2019), BMI (M A Skiba et al. 2019; Davio et al. 2020) and menopause (Nanba et al. 2019), and variations due to menstrual cycle (M A Skiba et al. 2019) and diurnal rhythm (A F Turcu et al. 2021; Nowotny et al. 2021) have previously been studied for 11-oxygenated androgen concentrations in serum in several cohorts, however, most of those were of limited size (Table *3*). In this study, we comprehensively analysed the impact of all these variables on classic and 11-oxygenated androgens and their precursors in the second largest cohort to date, analysing serum steroids in 290 healthy volunteers and salivary steroids in a sub-group of 83 volunteers recruited from a community setting in the UK.

A key finding of our study is the differential impact of BMI on circulating androgen concentrations, with a decrease in classic androgens and an increase in 11-oxygenated androgens with increasing BMI. This points to adipose tissue as an

important determinant and source of 11-oxygenated androgen production, in line with previous findings on increased 11-oxygenated androgens in women with polycystic ovary syndrome with androgen excess, insulin resistance and obesity (O'Reilly, Kempegowda, Jenkinson, et al. 2017). While classic androgens decreased with BMI in our healthy volunteer cohort, serum DHEAS showed an increase, which is noteworthy considering that DHEAS is the primary biochemical androgen marker for PCOS in premenopausal women(Elhassan et al. 2018b). In contrast to our study, where we found a significant positive correlation of age and BMI, in the cohort studied by Davio *et al*. (Davio et al. 2020) no association between age and BMI was observed. A likely explanation for this might be that in the US American cohort the younger individuals already had high rates of obesity, though this cannot be verified, as no age-specific breakdown of BMI ranges was provided by Davio et al. (Davio et al. 2020). However, they reported a positive association of 11KT with BMI in men and additionally a positive association of 11OHT and a negative association of 11KA4 with BMI in women (Davio et al. 2020). Collectively, their observations and our current findings indicate that, while BMI does not affect the adrenal biosynthesis of 11-oxygenated androgens, it plays a role for the regulation of their peripheral activation and, thus, biological action. The most important enzyme for the activation of 11KA4 to 11KT is AKR1C3. We have previously shown that AKR1C3 expression in subcutaneous, but not omental, adipose tissue from women correlates significantly with BMI, is reduced after weight loss (Quinkler et al. 2004) and upregulated by insulin (O'Reilly, Kempegowda, Walsh, et al. 2017b). It should be noted that the catalytic activity of AKR1C3 is significantly higher for the conversion of 11KA4 to 11KT compared to the conversion of A4 to T (Quinkler et al. 2004; Barnard et al. 2018b). This means that increased fat mass and increased insulin resistance will upregulate

AKR1C3 activity, which and consequently increases the generation of 11-oxygenated androgens.

While studies on AKR1C3 in male adipose tissue are missing, it is plausible that increased AKR1C3 activity in adipose tissue can explain BMI-related increases in circulating 11KT concentrations in both sexes. However, in men, the metabolic impact of the decrease in T and DHT with increasing BMI will be much more significant than any increase in 11-oxygenated androgens. While we found 11-oxygenated androgen concentrations to be similar between men and women, gonadal T production by far exceeded the circulating 11-oxygenated androgen pool in men, irrespective of changes due to increasing age and BMI.

In line with previous observations (Davio et al. 2020; Nanba et al. 2019; M A Skiba et al. 2019; Haring et al. 2012; Eisenhofer et al. 2017) we found that serum concentrations of the classic androgen precursors DHEA and A4 and the active androgens T and DHT decline with age. The serum concentrations of 11-oxygenated androgens, however, did not change with age, despite the age-related decrease in DHEA and A4, which are the immediate precursors of 11-oxygenated androgen biosynthesis in the adrenal gland. The generation of C19 steroids, i.e. androgens, from their C21 precursors takes place predominantly in the zona reticularis of the adrenal gland, which co-expresses the enzymes CYP17A1 and CYB5A (Dharia et al. 2004), which are crucial for biosynthesis of DHEA, the immediate precursor of A4. The zona reticularis also expresses AKR1C3, which converts A4 to T (Nakamura et al. 2009). Due to the age-related reduction of the zona reticularis (Nakamura et al. 2015; Tezuka et al. 2021) the adrenal production of A4 and T is expected to decrease with age. However, the enzyme CYP11B1, which is required for the formation of 11OHA4 from A4, is expressed in the zona fasciculata, which does not change with age (Tezuka et

al. 2021). The decreased levels of adrenal A4 in older individuals appear to still serve as a sufficient substrate pool to feed the generation of 11-oxygenated androgens by CYP11B1. Consistent with this hypothesis, a recent preliminary report indicated that the CYP11B1 K_m value for A4 is significantly lower than that for its other substrates 11-deoxycortisol and 11-deoxycorticosterone (Sophia Zheng et al. 2021).

Davio *et al.* (Davio et al. 2020)recently studied a large cohort comprising healthy men (n=319) and women (n=271). They reported that the 11-hydroxy androgens (11OHA4, 11OHT) increased with age in women, while the 11-keto androgens (11KA4, 11KT) decreased with age in men. In our study of 125 men and 165 women, we observed an apparent increase in 11OHT with age that vanished after adjustment for BMI while 11KA4 decreased with age after adjusting for BMI.

Using saliva day profiles, we have shown in this study that 11-oxygenated androgen concentrations follow a clear diurnal pattern in both sexes, with peak concentrations in the morning and lowest concentrations in the late evening, reflecting their adrenal origin and regulation of their biosynthesis through the hypothalamic-pituitary-adrenal axis. This pattern was more pronounced for the direct adrenal precursor 11OHA4 compared to 11KT, which is predominantly generated from 11OHA4. As participants did not collect saliva samples during the night, we cannot draw any conclusions on the exact timing of the early morning peak in androgen concentrations. Previous work had already established the diurnal pattern of 11-oxygenated androgens for men in serum (A F Turcu et al. 2021) and for men and women in saliva (Nowotny et al. 2021). We now show that in women this pattern is maintained across the menstrual cycle, while it is reduced in the luteal phase for the classic androgens A4 and T. Additionally, we establish that the morning concentrations of 11-oxygenated androgens in serum and saliva do not vary between follicular and luteal phase. While it is usually recommended

to collect samples for the analysis of androgen excess in the follicular phase, this does not appear to be relevant for the measurement of 11-oxygenated androgens.

Interestingly, we observed that the increases in progesterone concentrations during the luteal phase of the menstrual cycle results in simultaneous increases in its metabolites 5αDHP and alloP, which are also intermediates of the alternative DHT biosynthesis pathway (Auchus 2004). The alternative DHT biosynthesis pathway has been established as a source of active androgens in congenital adrenal hyperplasia and during fetal development (N Reisch et al. 2019; W Arlt et al. 2004). This raises the question as to whether the alternative pathway of DHT biosynthesis might contribute to the generation of active androgens in conditions of elevated circulating progesterone such as the luteal phase of the menstrual cycle or pregnancy.

Previous studies on the effect of hormonal contraceptives on total circulating T concentrations in women have led to contradictory results with some reporting reduced T concentrations (Søeborg et al. 2014), while others did not find any differences compared to women not taking hormonal contraceptives (Eisenhofer et al. 2017; Bae et al. 2019; Bermon et al. 2014). In this study we observed significantly reduced concentrations of T and 11KT in saliva of women on hormonal contraceptives compared to women not taking hormonal contraceptives, but not in serum. This suggests that alterations in the peripheral generation of T and 11KT from their circulating precursors, at least in part, drive differences in androgen concentrations in hormonal contraceptive users.

The strengths of our study are (i) the inclusion of large numbers of participants whose health status was verified, (ii) steroid measurements by validated tandem mass spectrometry assays, (iii) concurrent measurement of androgens from the classic, 11-

oxygenated and alternative DHT pathways, and (iv) steroid measurements in both serum and saliva including assessment of diurnal and menstrual cycle variations. Our study has several limitations. Firstly, our study was cross-sectional by design, thus, future longitudinal studies with clinically well-characterised cohorts are needed to assess the physiological role of sustained 11-oxygenated androgen concentrations with ageing. We used a longitudinal design to study alterations in salivary androgens across the menstrual cycle, but the relatively low number of participants represents a limitation. Secondly, though we measured salivary steroids that are reflective of free, unbound serum steroid concentrations, we measured the total concentrations of the analytes in serum and, therefore, cannot conclude on the variation of their free or bioavailable serum concentrations. This is of particular importance in the context of the menstrual cycle and hormonal contraceptives, as oestrogens increase hepatic sex hormone-binding globulin production. Of note, the affinity of the 11-oxygenated androgens for sex hormone binding globulin has not been determined to date.

In conclusion, 11-oxygenated androgens form a stable circulating pool of androgens during adulthood, while classic androgens decline with age and are subject to menstrual cycle-dependent variation. BMI is a key factor in the regulation of 11-oxygenated androgen activation in peripheral tissues, namely adipose tissue, warranting further investigation.

3.7 Conclusion

In conclusion, 11-oxygenated androgens form a stable circulating pool of androgens during adulthood, while classic androgens decline with age and are subject to menstrual cycle-dependent variation. BMI is a key factor in the regulation of 11-

oxygenated androgen activation in peripheral tissues, namely adipose tissue, warranting further investigation.

Table 2: Effect of menopause on serum steroid concentrations. All serum steroid concentrations are given in nmol/L, except for DHEAS (µmol/L). Statistical comparison between premenopausal women (not on hormonal contraceptives) and postmenopausal women was performed by Mann-Whitney U Test.

	Premenopausal women Median (IQR)	**Postmenopausal women** Median (IQR)	**Fold difference of median** (post -vs pre-menopausal)	***p***
n	61	89		
Age (years)	30.0 (26.0, 37.0)	63.0 (55.0, 75.0)	N/A	<0.001
BMI (kg/m^2)	22.1 (20.8, 24.6)	25.7 (24.2, 31.5)	N/A	<0.001
Preg	3.0 (1.3, 5.3)	0.9 (0.3, 1.9)	0.0	<0.001
Prog	2.8 (<0.3, 34.5)	<0.3 (<0.3, <0.3)	0.0	0.230
5αDHP	<0.6 (<0.6, 1.7)	<0.6 (<0.6, 0.5)	0.0	0.230

alloP	<0.6 (<0.6, 2.3)	<0.6 (<0.6, <0.6)	0.0	0.230
17Preg	4.7 (<3.0, 6.0)	<3.0 (<3.0, 3.1)	0.0	0.088
17OHP	2.9 (0.9, 5.4)	<0.6 (<0.6, 0.8)	0.0	<0.001
F	252 (205, 380)	288 (240, 386)	0.1	0.062
E	47.1 (41.0, 54.4)	44.0 (37.2, 48.0)	-0.1	0.022
DHEA	9.6 (6.0, 14.6)	5.2 (3.2, 8.3)	-0.5	<0.001
DHEAS	4.6 (3.2, 5.6)	1.8 (1.0, 3.1)	-0.6	<0.001
A4	2.7 (1.8, 3.9)	1.1 (0.7, 1.8)	-0.8	<0.001
T	0.6 (0.5, 0.9)	0.4 (<0.4, 0.6)	0.0	0.347
DHT	<0.3 (<0.3, 0.5)	<0.3 (<0.3, <0.3)	0.0	0.230
11OHA4	7.2 (5.3, 10.0)	8.8 (5.9, 12.1)	0.2	0.063
11KA4	3.2 (2.3, 3.8)	1.8 (1.2, 3.2)	-0.4	<0.001
11OHT	0.4 (<0.3, 0.5)	0.6 (0.4, 0.9)	0.0	<0.001
11KT	0.7 (0.4, 1.0)	0.9 (0.6, 1.3)	0.0	0.208

Table 3: Sex- and age-specific reference ranges (median and 5th to 95th centile range) for serum classic and 11-oxygenated androgens. Values below the lower limit of quantification (LLOQ) are indicated as < LLOQ for the measurement of the respective steroid.

	Men <50 years (n=42-48)	**Men ≥50 years** (n=65-76)	**Women <50 years** (n=71-84)	**Women ≥50 years** (n=71-81)
DHEAS (μmol/L)	6.0 (2.7-12.0)	2.3 (0.82-6.6)	4.6 (1.6-8.2)	1.5 (0.41-4.1)
DHEA	8.1 (2.5-27.0)	5.0 (1.5-12.0)	9.6 (4.2-20.0)	5.0 (1.3-16.0)
A4	1.5 (0.54-5.0)	1.7 (<0.70-3.2)	2.3 (0.71-5.3)	1.1 (<0.70-2.9)
T	13.0 (8.3-19.0)	12.0 (6.5-22.0)	0.61 (<0.35-1.2)	0.45 (<0.35-1.2)
DHT	1.4 (0.60-2.3)	1.1 (<0.34-2.2)	0.17 (<0.34-0.80)	<0.34 (<0.34-0.36)
11OHA4	7.6 (2.9-14.0)	8.5 (4.6-16.0)	7.5 (3.4-14.0)	8.4 (3.9-16.0)
11KA4	3.5 (1.42-6.2)	2.1 (0.60-5.2)	3.2 (1.6-5.4)	1.8 (0.64-4.2)
11OHT	0.47 (<0.33-1.1)	0.72 (<0.33-1.5)	0.39 (<0.33, 0.78)	0.63 (<0.33-1.2)
11KT (nmol/L)	0.86 (<0.33-2.2)	0.81 (0.36-1.8)	0.70 (<0.33-1.6)	0.94 (0.37-1.7)

Table 4: Sex- and age-specific reference ranges for serum steroid concentrations. Concentrations are given as median (5^{th} centile, 95^{th} centile). Values below the lower limit of quantification are indicated as < lower limit of quantification.

	Men <50 years (n=42-48)	**Men ≥50 years (n=65-76)**	**Women <50 years (n=71-84)**	**Women ≥50 years (n=71-81)**
Prog	<0.32 (<0.32, 0.37)	<0.32 (<0.32, 0.37)	<0.32 (<0.32, 59)	<0.32 (<0.32, 0.39)
5α-DHP	<0.63 (<0.63, <0.63	<0.63 (<0.63, 0.71)	<0.63 (<0.63, 3.9)	<0.63 (<0.63, 0.83)
alloP	<0.63 (<0.63, 0.77)	<0.63 (<0.63, <0.63)	<0.63 (<0.63, 4.1)	<0.63 (<0.63, <0.63)
17OHP	4.1 (1.4, 8.9)	2.0 (0.68, 6.0)	1.7 (<0.61, 8.8)	<0.61 (<0.61, 1.4)
F	250 (118, 494)	322 (204, 446)	257 (157, 622)	290 (175, 588)
E	47 (27, 65)	44 (33, 61)	47 (31, 65)	44 (28, 61)

Table 5: Relationship between serum androgens and age and BMI, respectively, in men and women. n=132-150 women, n=105-118 men. Steroid concentrations below the lower limit of quantification (LLOQ) were replaced by 0.5 x LLOQ for the purpose of statistical comparison. The data was modelled using multiple linear regressions. β is indicated with its 95% confidence interval in brackets.

	Women		**Men**	
	Age	**BMI**	**Age**	**BMI**

Steroid	***β*** (% change / year) (95% CI)	***p***	***β*** (% change / kg/m^2) (95% CI)	***p***	***β*** (% change / year) (95% CI)	***p***	***β*** (change / kg/m^2) (95% CI)	***p***
Classic androgens and precursors								
DHEAS	-3.76 (-4.51, -3.01)	<0.0001	1.74 (-0.15, 3.63)	0.070	-2.51 (-3.35, -1.67)	<0.0001	-1.72 (-4.40, 0.95)	0.204
DHEA	-3.87 (-4.67, -3.08)	<0.0001	0.62 (-1.42, 2.66)	0.549	-3.01 (-3.95, -2.06)	<0.0001	-2.36 (-5.34, 0.62)	0.119
A4	-3.41 (-4.39, -2.43)	<0.0001	-1.25 (-3.76, 1.26)	0.327	-1.41 (-2.29, -0.53)	0.001	-1.80 (-4.5, 0.96)	0.199
T	-1.20 (-2.14, -0.25)	0.013	-0.83 (-3.26, 1.59)	0.497	-0.83 (-1.59, -0.06)	0.034	-2.32 (-4.73, 0.09)	0.059

DHT	-0.98 (-1.58, -0.38)	0.002	-1.62 (-3.16, -0.08)	0.039	-0.40 (-1.21, 0.42)	0.337	-5.54 (-8.10, -2.98)	<0.0001
11-oxygenated androgens and precursors								
11OHA4	0.14 (-0.55, 0.83)	0.692	-0.45 (-2.16, 1.26)	0.604	-0.01 (-0.72, 0.70)	0.975	2.22 (-0.10, 4.55)	0.061
11KA4	-0.56 (-1.34, 0.23)	0.166	-0.13 (-2.08, 1.82)	0.897	-0.89 (-1.82, 0.03)	0.058	1.80 (-1.24, 4.84)	0.242
11OHT	0.04 (-0.78, 0.85)	0.925	1.97 (-0.11, 4.06)	0.064	0.24 (-0.69, 1.18)	0.605	2.78 (-0.16, 5.72)	0.064
11KT	-0.11 (-0.94, 0.71)	0.787	1.68 (-0.44, 3.79)	0.119	0.08 (-0.86, 1.03)	0.860	3.05 (0.08, 6.03)	0.044

Table 6: Effect of hormonal contraceptives on serum and salivary steroid concentrations. All concentrations are given in nmol/L for all serum steroids, except for DHEAS, which is in µmol/L; salivary steroid concentrations are in pmol/L. Statistical comparison of steroid concentrations in premenopausal women not taking (Not on HCs) and those on hormonal contraceptives (On HCs) was performed by Mann-Whitney U Test.

	Not on HCs Median (IQR)	**On HCs** Median (IQR)	**Fold difference of median** (on HC vs not on HC)	***p***
Serum steroids				
n	61	15		
Age (years)	30.0 (26.0-37.0)	26.0 (23.0-32.0)	N/A	0.060
BMI (kg/m^2)	22.1 (20.8-24.6)	21.6 (20.1-26.6)	N/A	0.993
Preg	0.3 (0.3, 2.1)	0.3 (0.3, 0.3)	0.0	0.014

Prog	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.0	0.620
5αDHP	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	0.0	0.620
alloP	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	0.0	0.620
17OHPreg	1.5 (1.5, 1.5)	1.5 (1.5, 1.5)	0.0	0.480
17OHP	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	0.0	0.062
F	252 (205, 380)	314 (253, 492)	0.2	0.050
E	47.1 (41.0, 54.4)	52.8 (46.5, 59.5)	0.1	0.030
DHEA	9.6 (6.0, 14.6)	10.8 (8.5, 14.4)	0.1	0.422
DHEAS	4.6 (3.2, 5.6)	5.0 (4.0, 6.4)	0.1	0.327
A4	2.1 (0.4, 3.7)	0.4 (0.4, 0.4)	-0.8	<0.001
T	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.0	0.620
DHT	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.0	0.620
11OHA4	7.2 (5.3, 10.0)	8.5 (5.4, 11.2)	0.2	0.357
11KA4	3.2 (2.3, 3.8)	3.4 (2.5, 5.0)	0.1	0.414
11OHT	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.0	1.000
11KT	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.0	0.620

Salivary steroids				
n	32	9		
Age (years)	29.0 (28.0-35.0)	25.0 (24.0-27.0)	N/A	<0.001
BMI (kg/m^2)	22.0 (20.3-24.9)	21.0 (21.0-24.1)	N/A	0.967
17OHP	56.4 (24.2, 111)	6.3 (6.3 18.2)	-0.9	<0.001
A4	222 (152, 301)	103 (82.5, 140)	-0.5	<0.001
T	15.3 (9.4, 24.1)	8.0 (2.5, 13.2)	-0.5	<0.001
11OHA4	496 (315, 741)	417 (226, 615)	-0.2	0.120
11KT	232 (180, 316)	139 (96, 202)	-0.4	<0.001

Table 7: Previously reported serum steroid concentrations (nmol/L) of classic and 11-oxygenated androgens as measured in healthy subjects by tandem mass spectrometry. n.m., not measured.

	Subject	**DHEA**	**A4**	**T**	**DHT**	**11OHA4**	**11KA4**	**11KT**	**11OHT**
Previously reported data in healthy women									

Caron et al. 2021 (Caron, Turcotte, and Guillemette 2021)	Follicular phase age range 20–40 years n=10; mean ± SEM	11.2±0.8	2.8±0.1	0.6±0.0	0.2±0.0	5.3±0.4	0.8±0.1	0.8±0.1	0.3±0.0
	Luteal phase age range 20–40 years n=10; mean ± SEM	9.4±0.5	3.8±0.1	0.6±0.0	0.2±0.0	4.6±0.4	0.8±0.1	0.9±0.1	0.3±0.0
	postmenopausal women age range 51–70 years	14.5±0.5	3.0±0.2	1.1±0.1	0.2±0.0	11.6±0.6	1.2±0.0	1.8±0.1	0.8±0.0

	n=10; mean ± SEM								
Davio et al. 2020 (Davio et al. 2020)	women age 55.0±20.2 years n=271; mean ± SD	n.m.	1.9±1.2	1.0±0.5	n.m.	4.4±2.5	0.5±0.2	0.9±0.4	0.5±0.4
Nanba et al. 2019 (Nanba et al. 2019)	premenopausal women age range 27-39 years n=100; median (IQR)	8.1 (5.4, 14.0)	2.1 (1.6, 3.0)	1.0 (0.8, 1.4)	n.m.	0.1 (0.0, 0.1)	1.2 (0.9, 1.8)	0.9 (0.6, 1.3)	0.5 (0.3, 0.8)
	postmenopausal women	2.7 (1.8, 4.7)	1.0 (0.8, 1.4)	0.7 (0.5, 1.1)	n.m.	6.5 (4.7, 9.6)	1.1 (0.8, 1.5)	0.9 (0.7, 1.2)	0.7 (0.4, 0.9)

	age range 62-78 years n=100; median (IQR)								
Skiba et al. 2019 (Skiba et al. 2019)	Follicular phase age range 18-19 years n=163; median (range)	5.3 (1.0, 21.3)	1.8 (0.6, 5.4)	0.3 (0.0, 0.9)	n.m.	n.m.	8.8 (0.1, 28.8)	1.3 (0.3, 7.6)	n.m.
	mid-cycle phase age range 18-19 years n=184; median (range)	4.9 (0.4, 23.5)	2.1 (0.6, 7.9)	0.4 (0.1, 1.0)	n.m.	n.m.	7.7 (1.1, 31.7)	1.3 (0.0, 5.8)	n.m.
	Luteal phase	4.9 (0.1, 23.5)	2.0 (0.5, 7.9)	0.3 (0.0, 1.0)	n.m.	n.m.	8.0 (0.1, 31.7)	1.3 (0.0, 7.6)	n.m.

	age range 18-19 years n=241; median (range)								
O'Reilly et al. 2017 (O'Reilly et al. 2017)	women; median age 28 (IQR 23-32) years n=49; median (IQR)	7.1 (4.2, 11.8)	n.m.	0.3 (0.2, 0.5)	n.m.	6.8 (4.9, 12.5)	2.7 (2.0, 3.9)	1.5 (1.2, 1.8)	0.2 (0.1, 0.3)
Turcu et al. 2016 (Turcu et al. 2016)	19 men and 19 women, reported together, no details on age n=38; median (IQR)	6.1 (4.1, 11.0)	n.m.	0.9 (0.4, 10.7)	n.m.	3.9 (2.3, 5.1)	1.0 (0.7, 1.4)	1.7 (1.0, 2.6)	0.5 (0.3, 0.7)
Previously reported data in healthy men									

Caron et al. 2021 (Caron, Turcotte, and Guillemette 2021)	men age range 21–62 years n=9; mean ± SEM	8.2±0.3	2.4±0.1	18.7±0.6	1.3±0.0	4.4±0.2	0.5±0.0	1.1±0.3	0.6±0.0
	men age range 60–72 years n=10; mean ± SEM	4.9±0.2	2.4±0.1	19.6±0.8	1.3±0.1	6.8±0.3	0.8±0.0	1.5±0.1	0.5±0.0
Schröder et al. 2021 (Schröder et al. 2021)	men; mean age 36 (range 23-68) years n=12; median (IQR)	n.m.	n.m.	14.2 (10.3, 18.1)	n.m.	3.7 (3.0, 5.3)	0.5 (0.4, 0.6)	0.7 (0.6, 0.9)	0.4 (0.3, 0.6)

Davio et al. 2020 (Davio et al. 2020)	men age 57.1±18.7 years n=319; mean ± SD	n.m.	1.6±0.7	16.0±6.8	n.m.	5.1±2.5	0.6±0.3	0.9±0.5	0.6±0.3
Turcu et al. 2021 (Turcu et al. 2021)	Men; median age 24 (range 19-29) years n=10; median (IQR) circadian peak & nadir	n.m.	2.7 (2.7, 2.8)	13.5 (13.0, 14.0)	n.m.	8.6 (8.2, 9.0)	2.1 (2.0, 2.1)	1.4 (1.3, 1.4)	0.6 (0.6, 0.6)
		n.m.	1.1 (1.0, 1.2)	9.4 (8.7, 10.1)	n.m.	0.7 (0.4, 1.1)	0.4 (0.3, 0.5)	0.3 (0.3, 0.3)	0.0 (0.0, 0.1)

	Men; median age 63 (range 61–75) years n=10; median (IQR) circadian peak & nadir	n.m.	2.1 (2.0, 2.1)	12.7 (12.2, 13.3)	n.m.	7.3 (6.9, 7.7)	1.5 (1.4, 1.6)	1.0 (1.0, 1.0)	0.5 (0.5, 0.5)
		n.m.	1.0 (0.9, 1.0)	9.6 (8.9, 10.2)	n.m.	1.7 (1.4, 2.1)	0.6 (0.5, 0.7)	0.4 (0.4, 0.4)	0.2 (0.2, 0.2)

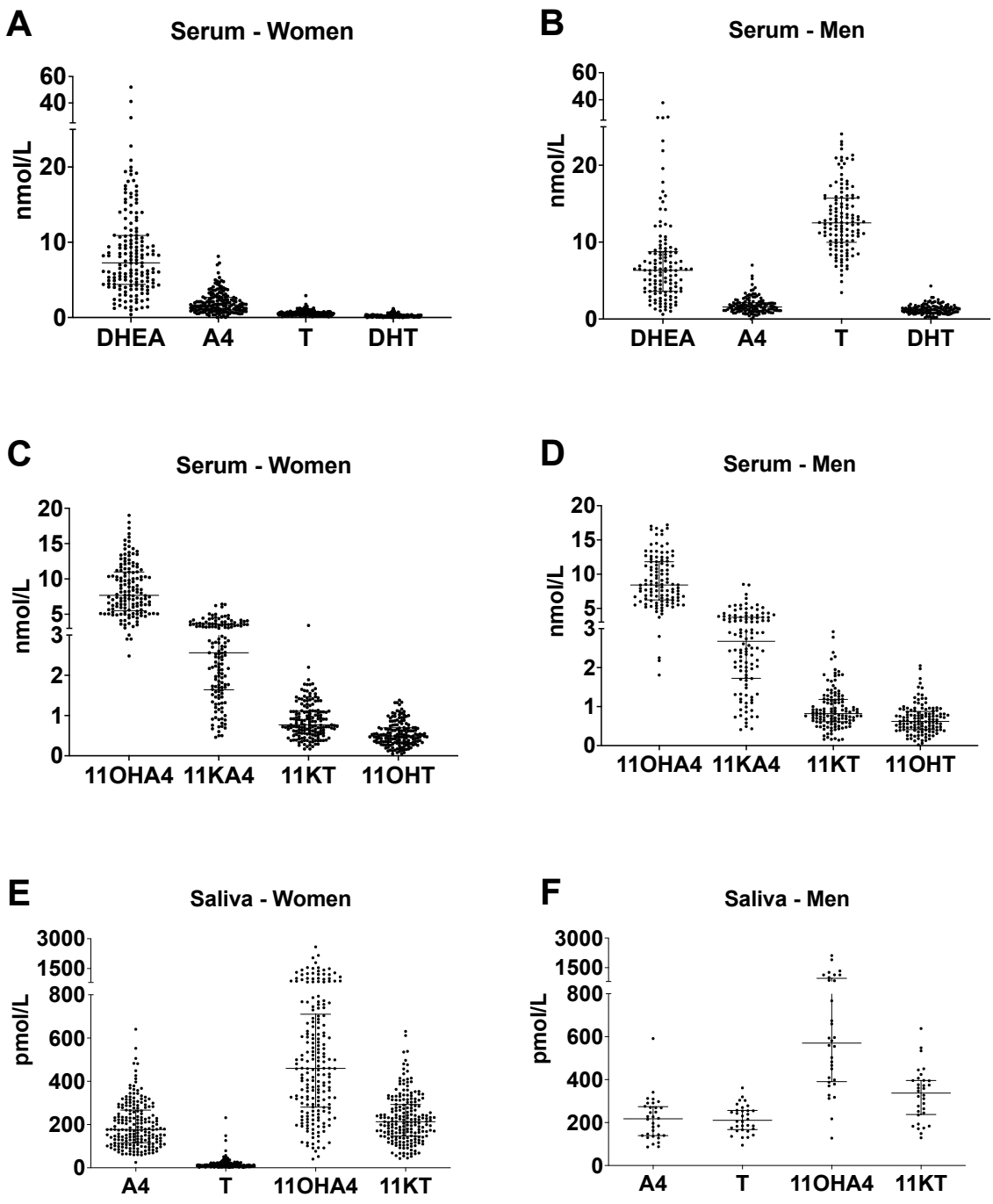


Figure 7: Classic (A, B) and 11-oxygenated androgens concentrations (C, D) in serum and saliva (E+F)

125 men and 167 women gave one serum sample; 32 men gave one saliva sample; 51 women gave a total of 199 saliva samples. Individual data points, median and interquartile range are indicated.

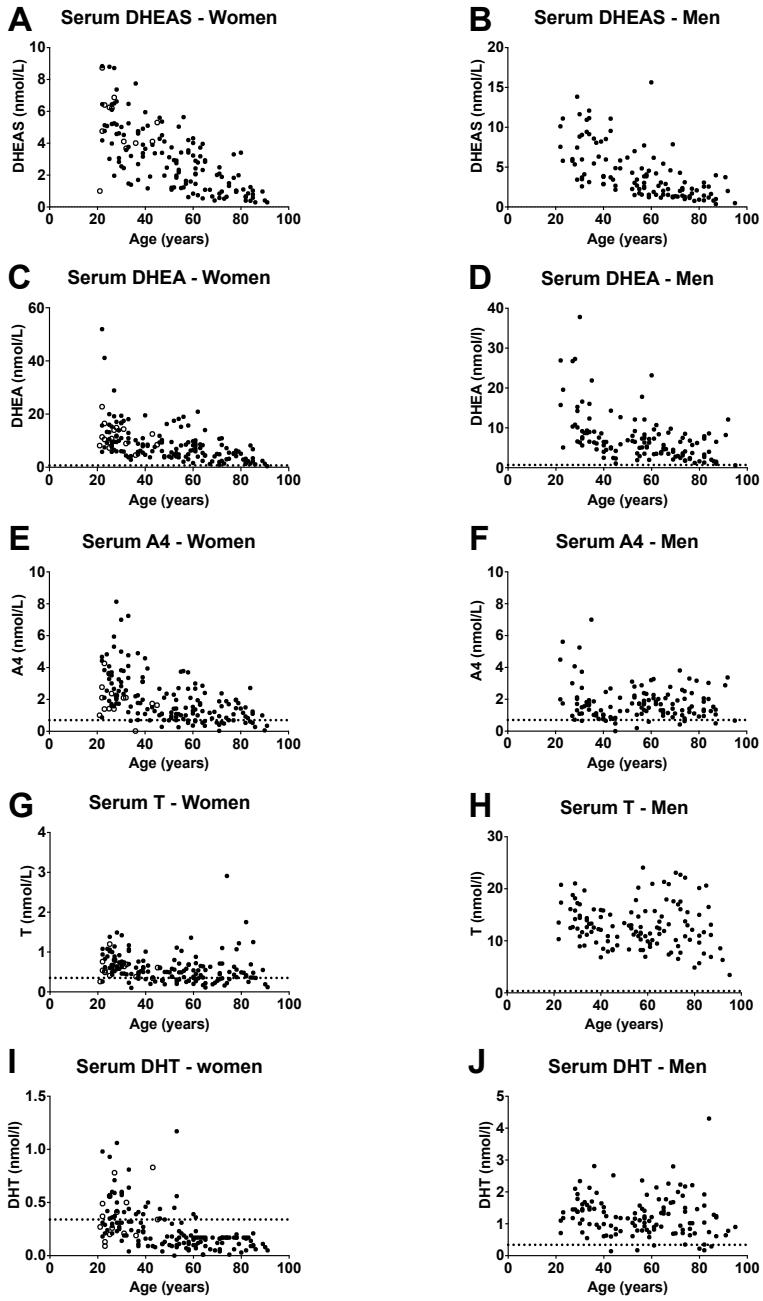


Figure 8: Serum concentrations of classic androgens across the adult age range in women (n=167) and men (n=125).

Women on hormonal contraceptives are shown as open circles. The dotted line indicates the lower limit of quantification. (A, B) DHEAS, dehydroepiandrosterone sulfate; (C, D) DHEA, dehydroepiandrosterone; (E, F) A4, androstenedione; (G, H) T, testosterone; (I, J) DHT, 5α-dihydrotestosterone.

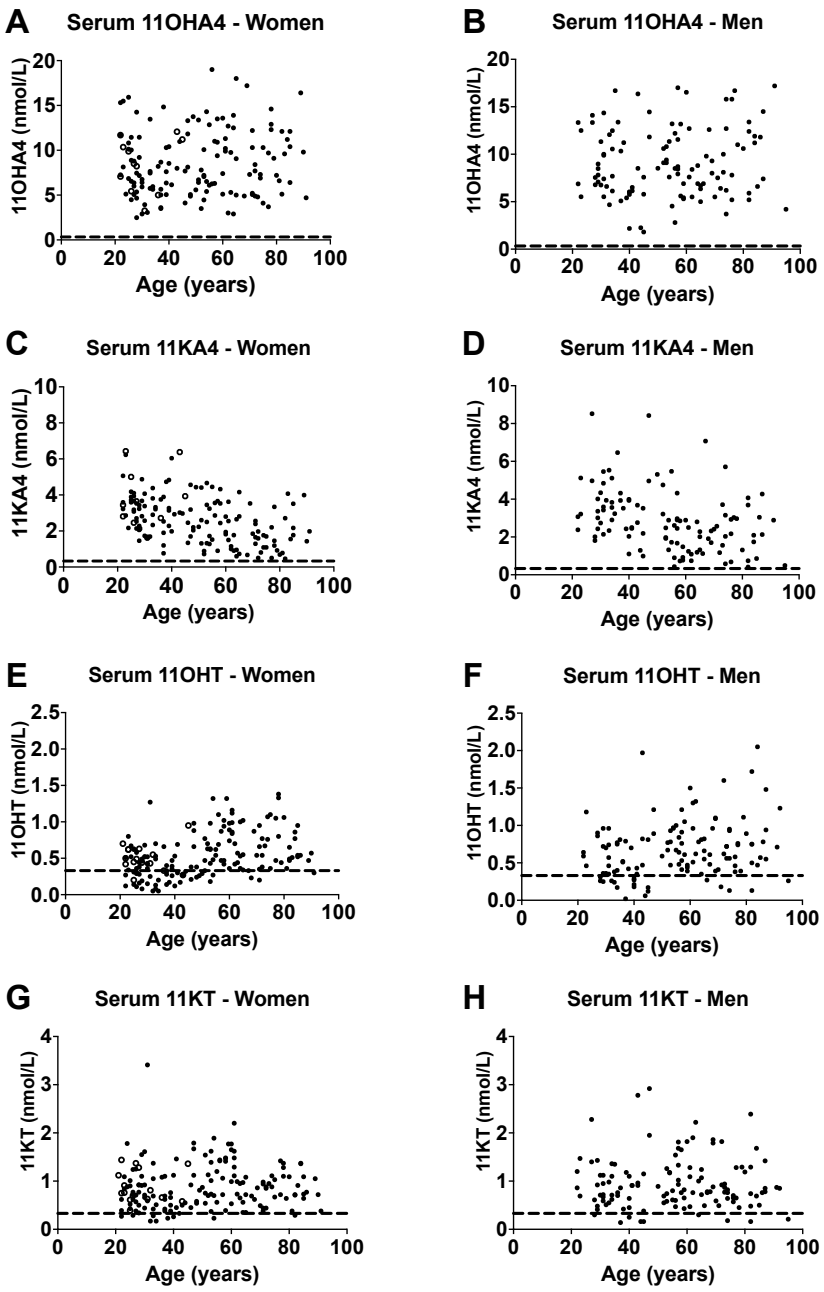


Figure 9: Serum concentrations of 11-oxygenated androgens across the adult age range in women (n=167) and men (n=125).

Women on hormonal contraceptives are shown as open circles. The dashed line indicates the lower limit of quantification. (A, B) 11OHA4, 11β-hydroxyandrostenedione; (C, D) 11KA4, 11-ketoandrostenedione; (E, F) 11OHT, 11β-hydroxytestosterone; (G, H) 11KT, 11-ketotestosterone.

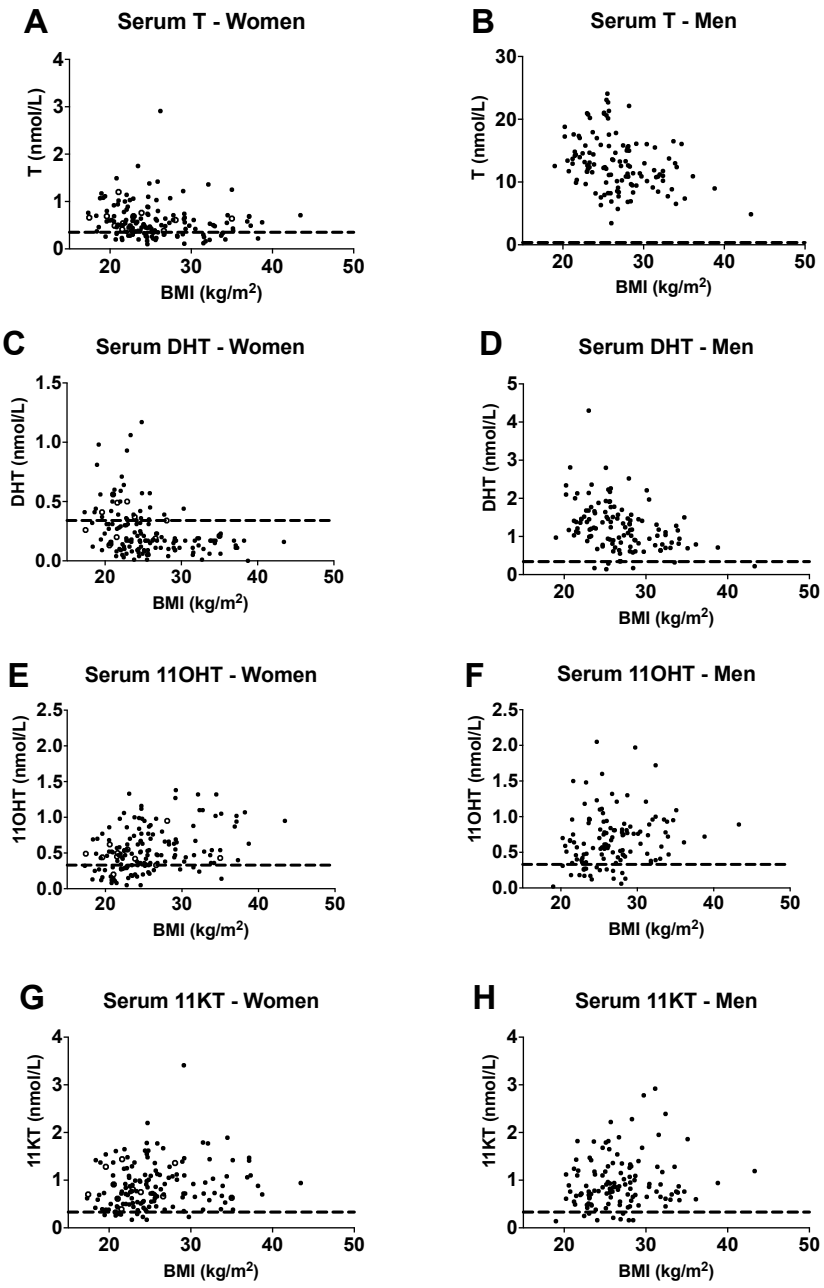


Figure 10: Serum concentrations of active classic and 11-oxygenated androgens across the spectrum of body mass index (BMI) in women (n=167) and men (n=125).

Women on combined contraceptives are shown as open circles. The dashed line indicates the lower limit of quantification. T, testosterone; DHT, 5α-dihydrotestosterone; 11OHT, 11β-hydroxytestosterone; 11KT, 11-ketotestosterone.

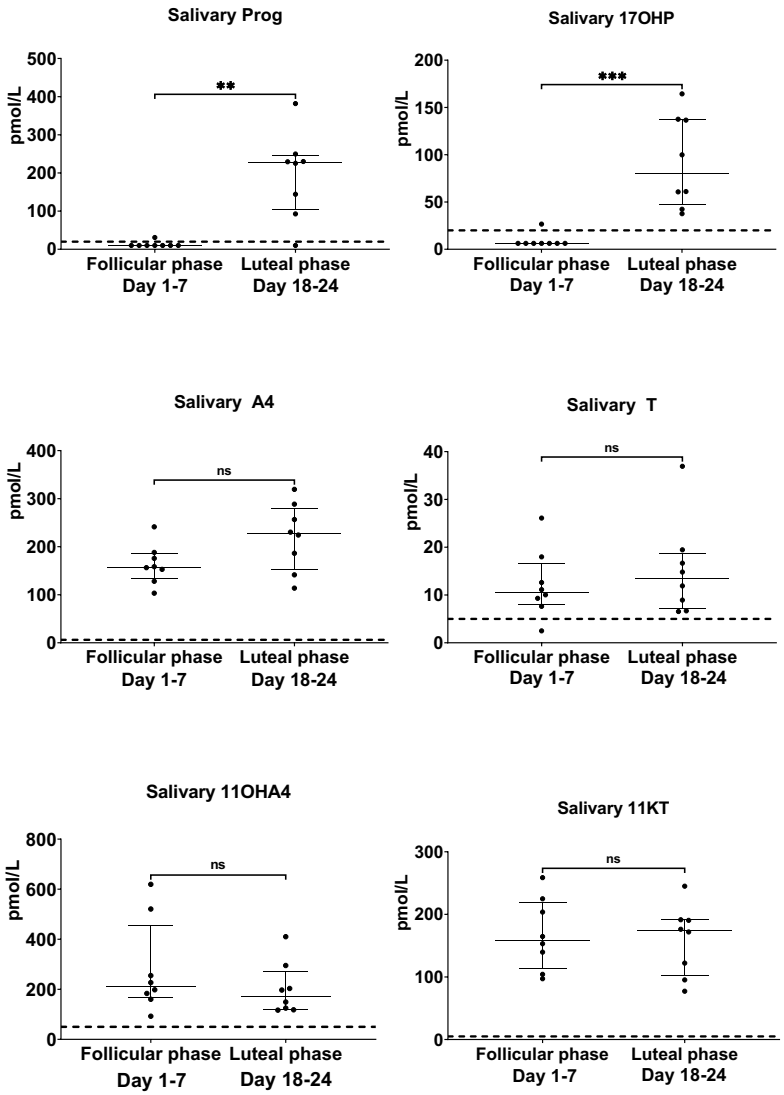


Figure 11: Salivary steroids during follicular (days 1-7, n=8 women) and luteal phase (days 18-24, n=8 women) of the menstrual cycle in.

The dashed line indicates the lower limit of quantification. Median and interquartile range are indicated. Steroid concentrations were compared between the two phases by Mann-Whitney U test. ns, not significant; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. Values below the LLOQ were replaced by 0.5*LLOQ for the statistical comparisons. (A) Prog, progesterone; (B) 17OHP, 17α-hydroxyprogesterone; (C) A4, androstenedione; (D) T, testosterone; (E) 11OHA4, 11β-hydroxyandrostenedione; (F) 11KT, 11-ketotestosterone.

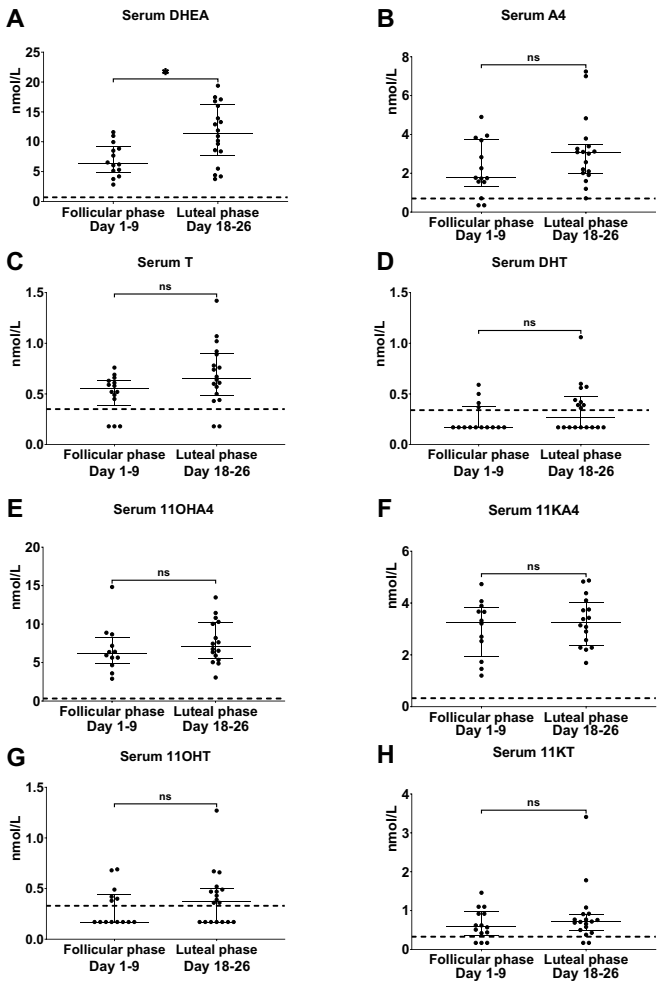


Figure 12: Serum androgens during follicular (days 1-9; n=12-14) and luteal phase (days 18-26, n=16-18) of the menstrual cycle.

The dashed line indicates the lower limit of quantification. Median and interquartile range are indicated. Steroid concentrations were compared between the two phases by Mann-Whitney U test. ns, not significant; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. (A) DHEA, dehydroepiandrosterone; (B) A4, androstenedione; (C) T, testosterone; (D) DHT, 5α-dihydrotestosterone; (E) 11OHA4, 11β-hydroxyandrostenedione; (F) 11KA4, 11-ketoandrostenedione; (G) 11OHT, 11β-hydroxytestosterone; (H) 11KT, 11-ketotestosterone.

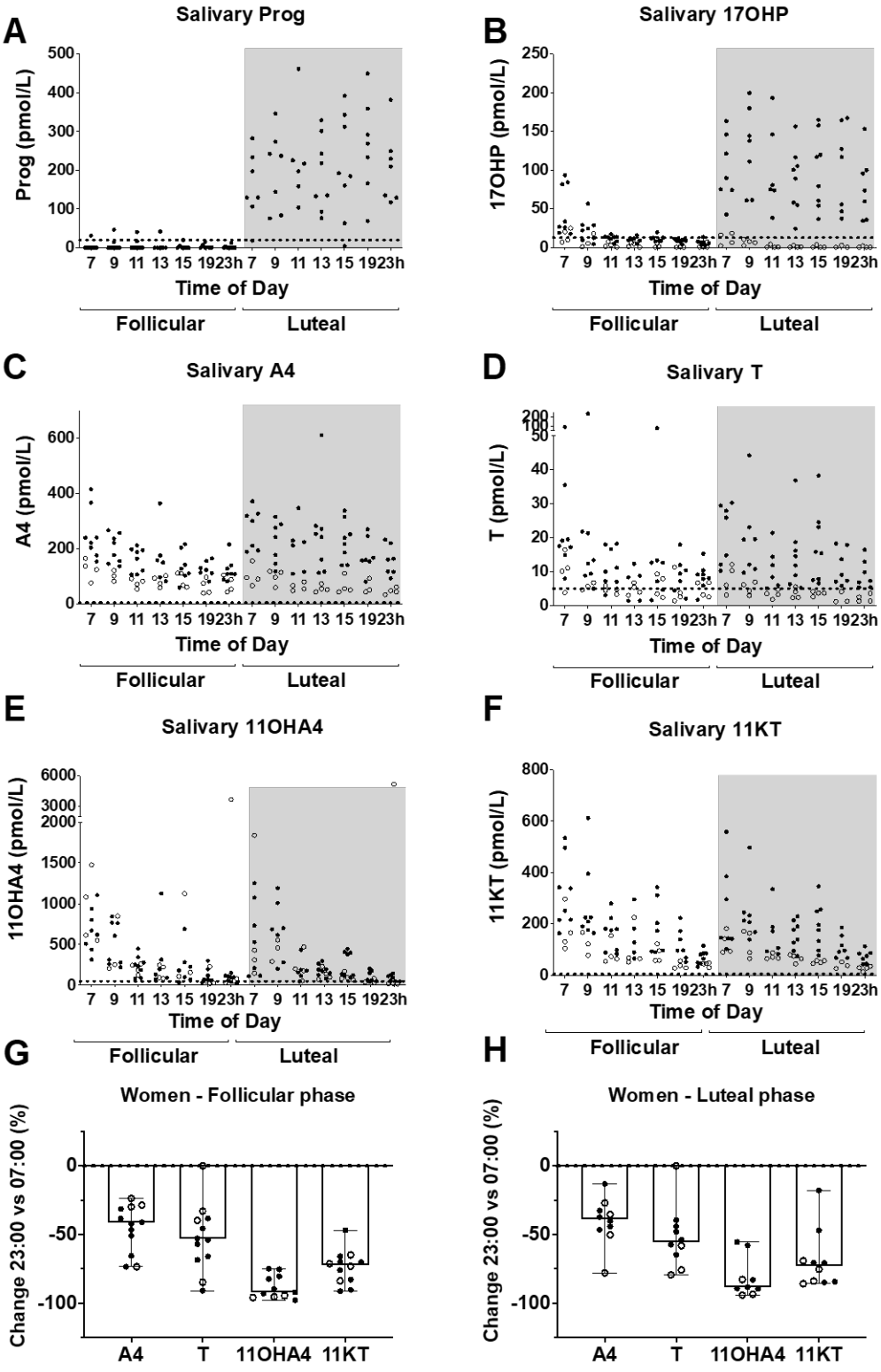


Figure 13: Diurnal variation of salivary steroids in premenopausal women during follicular and luteal phase of the menstrual cycle.

8 women not taking any hormonal contraceptives (solid circles) and 4 women on contraceptives (open circles) collected seven saliva samples at defined times over 24 hours on a day during follicular phase (days 1-8) and on a day during luteal phase (days 18-24, grey background). The dashed line indicates the lower limit of quantification. (A) Prog, progesterone; (B) 17OHP, 17α-hydroxyprogesterone; (C) A4, androstenedione; (D) T, testosterone; (E) 11OHA4, 11β-hydroxyandrostenedione; (F) 11KT, 11-ketotestosterone. Percentage change of saliva steroids over the day were calculated for follicular (G) and luteal phase (H). Therefore, saliva steroid concentrations at 23:00 were compared to concentrations at 07:00. Bars represent the median, whiskers the range.

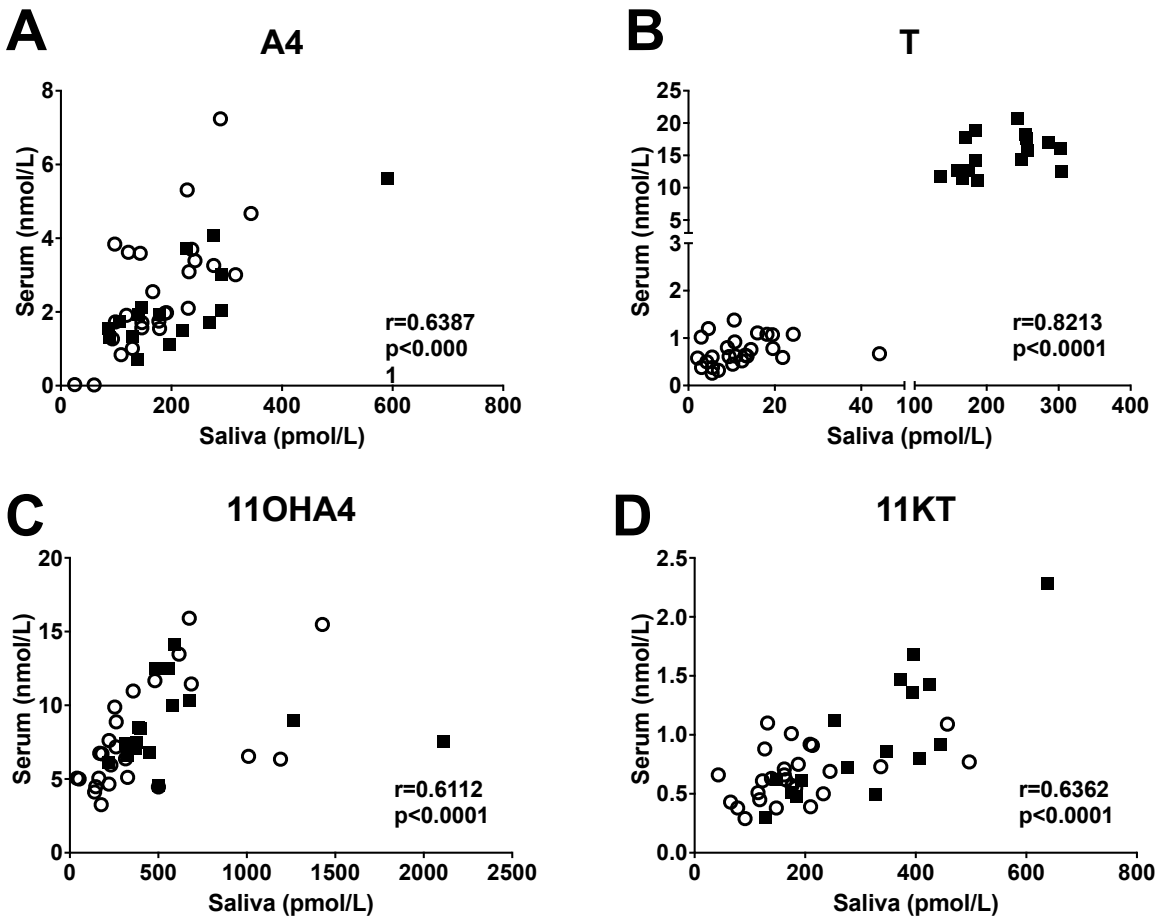


Figure 14: Correlation between saliva and serum steroid concentrations. Women (n=26) are shown as open circles, men (n=16) as solid squares.

A4, androstenedione; T, testosterone; 11OHA4, 11β-hydroxyandrostenedione; 11KT, 11-ketotestosterone.

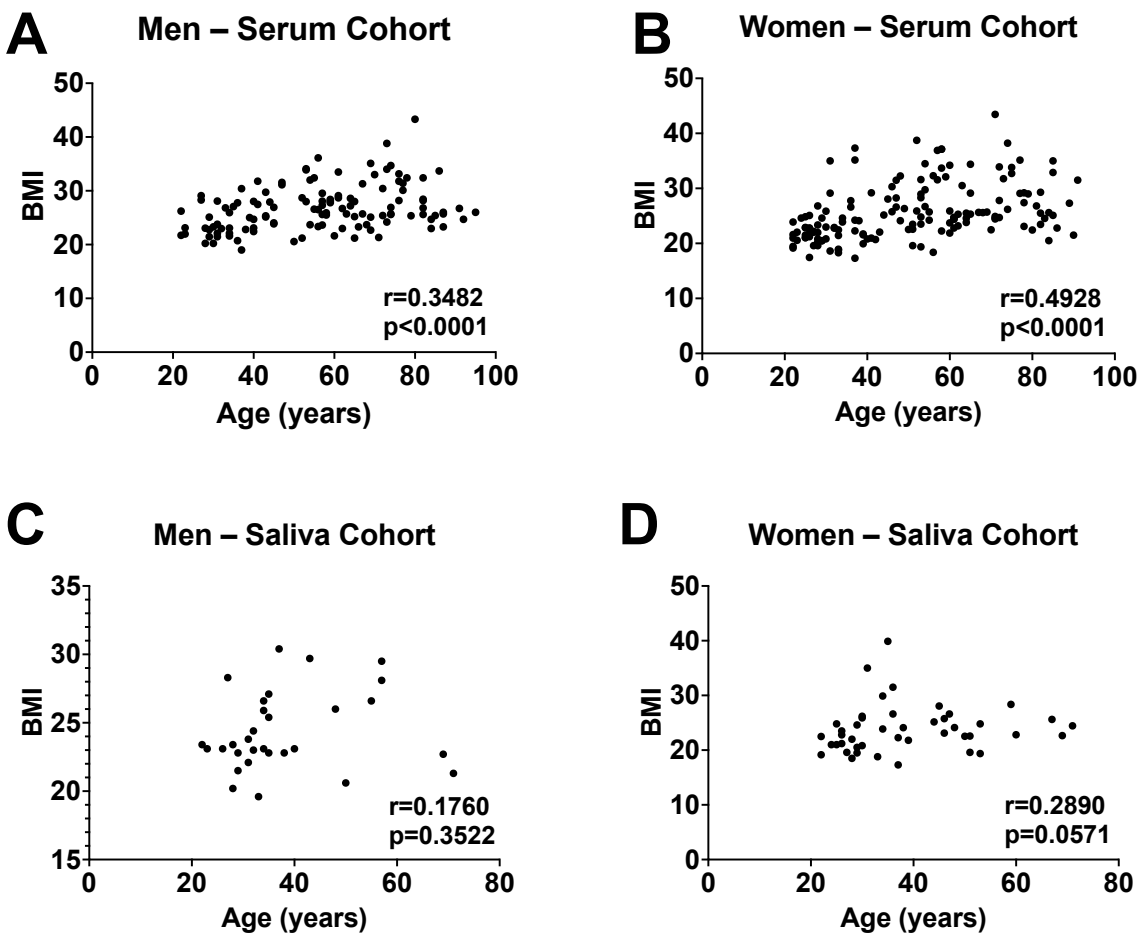


Figure 15: Correlation of age and BMI in the cohort of healthy volunteers who provided serum samples. (A) Men, n= 125; (B) Women, n=167.

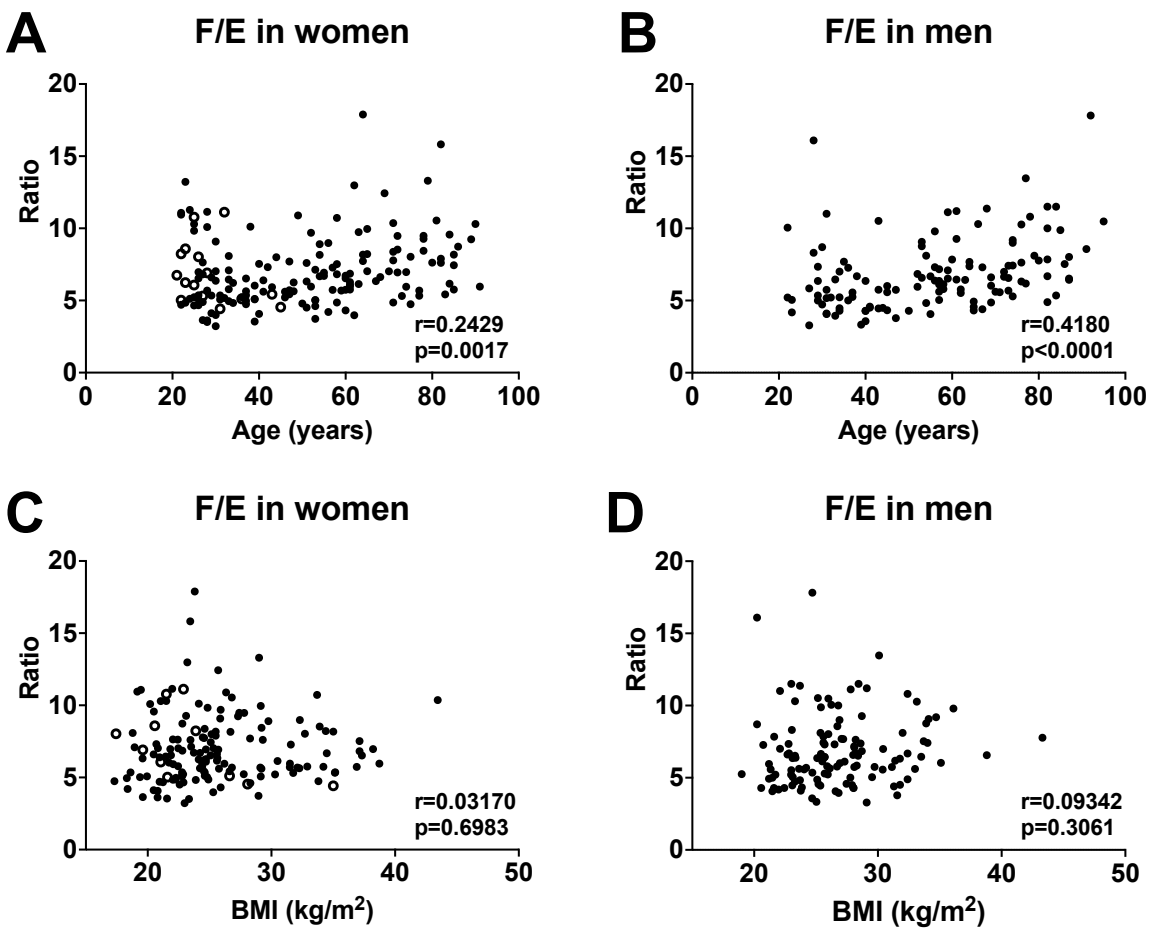


Figure 16: Ratio of serum cortisol (F) over cortisone (E) across the adult age and BMI range in women (A and C, n=167) and men (B and D, n=125). Serum F/E represents systemic 11β-hydroxysteroid dehydrogenase activity.

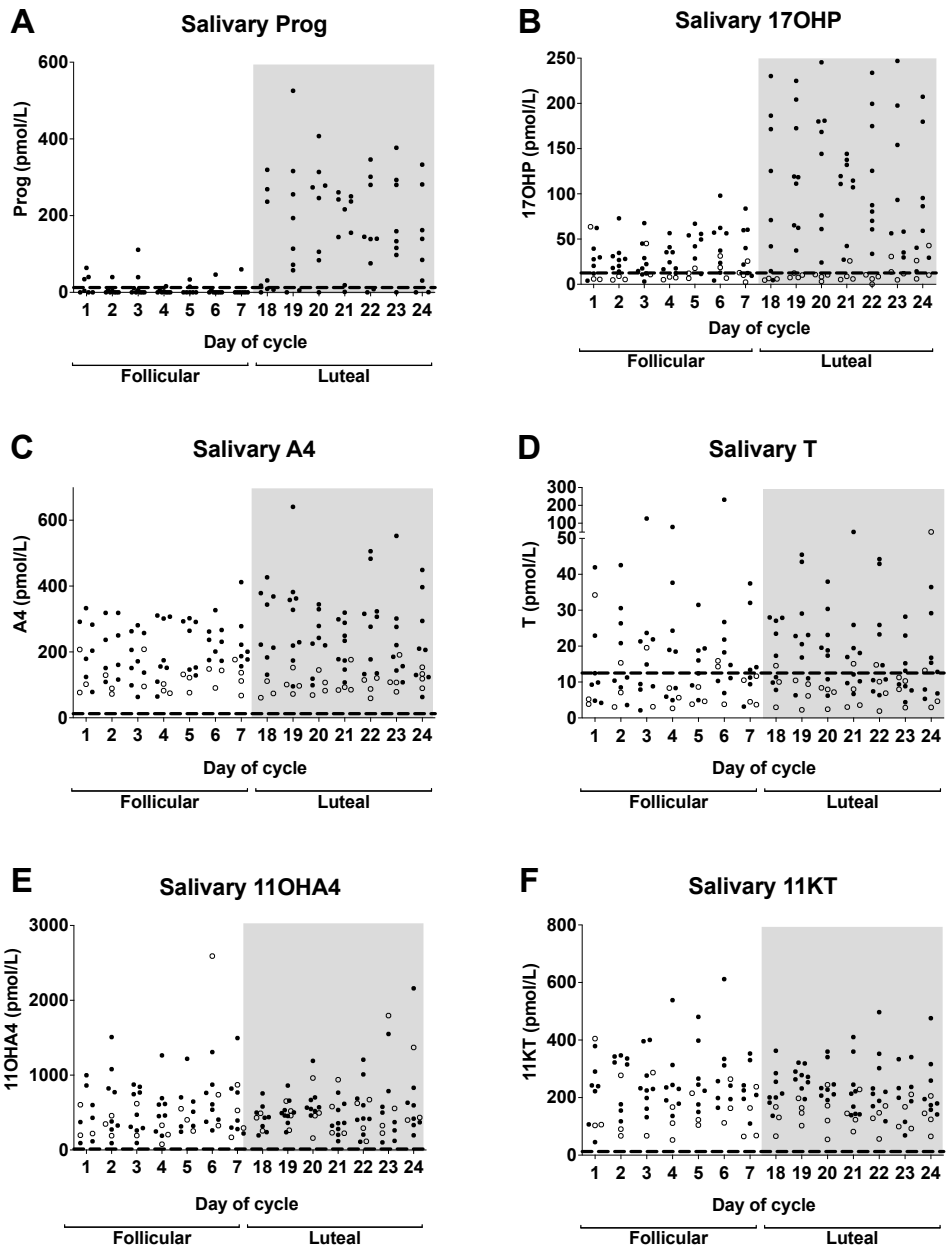


Figure 17: Daily variation of salivary steroids during follicular (days 1-7) and luteal phase (days 18-24) of the menstrual cycle in 13 women.

Day 1 is the start date of the menstrual bleed. Women on combined contraceptives (4/13) are shown as open circles. The dashed line indicates the lower limit of quantification. (A) Prog, progesterone; (B) 17OHP, 17α-hydroxyprogesterone; (C) A4, androstenedione; (D) T, testosterone; (E) 11OHA4, 11β-hydroxyandrostenedione; (F) 11KT, 11-ketotestosterone.

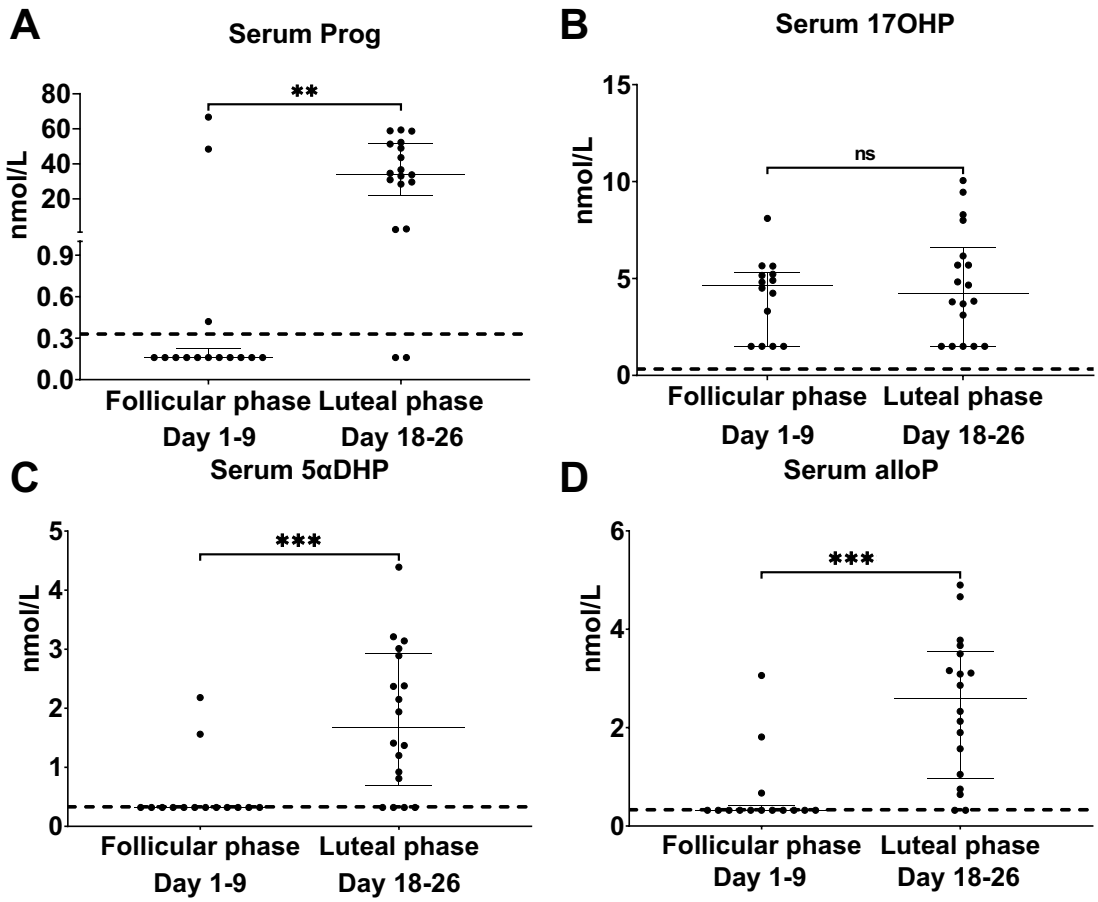


Figure 18: Serum progesterone and its metabolites in follicular (days 1-9, n=14) and luteal phase (days 18-26, n=18) of the menstrual cycle.

The dashed line indicates the lower limit of quantification. Median and interquartile range are indicated. Steroid concentrations were compared between the two phases by Mann-Whitney U test. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. (A) Prog, progesterone; (B) 17OHP, 17α-hydroxyprogesterone; (C) 5αDHP, 5α-dihydroprogesterone; (D) alloP, allopregnanolone (5α-pregnane-3α-ol-20-one).

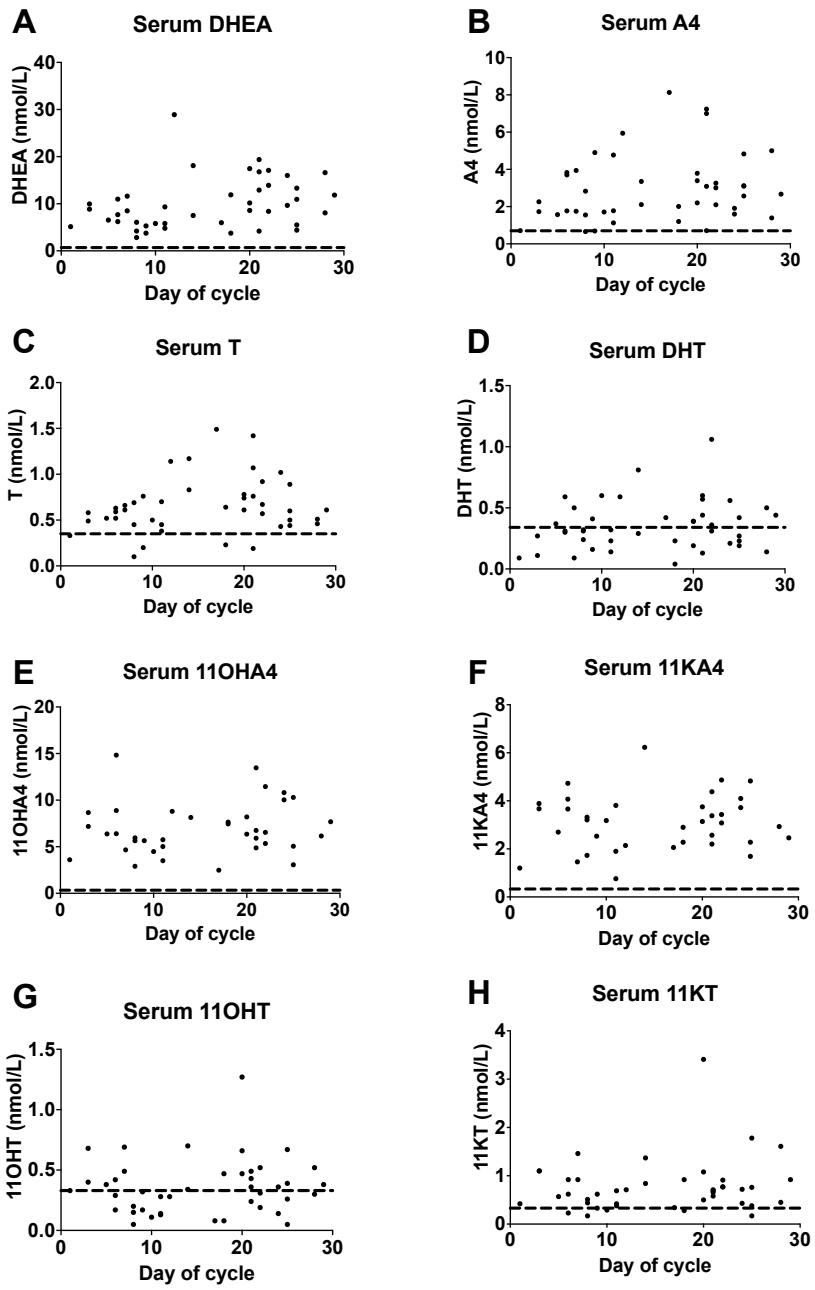


Figure 19: Serum androgens across the menstrual cycle (n=43).

Day 1 is the start date of the menstrual bleed. The dashed line indicates the lower limit of quantification. (A) DHEA, dehydroepiandrosterone; (B) A4, androstenedione; (C) T, testosterone; (D) DHT, 5α-dihydrotestosterone; (E) 11OHA4, 11β-hydroxyandrostenedione; (F) 11KA4, 11-ketoandrostenedione; (G) 11OHT, 11β-hydroxytestosterone; (H) 11KT, 11-ketotestosterone.

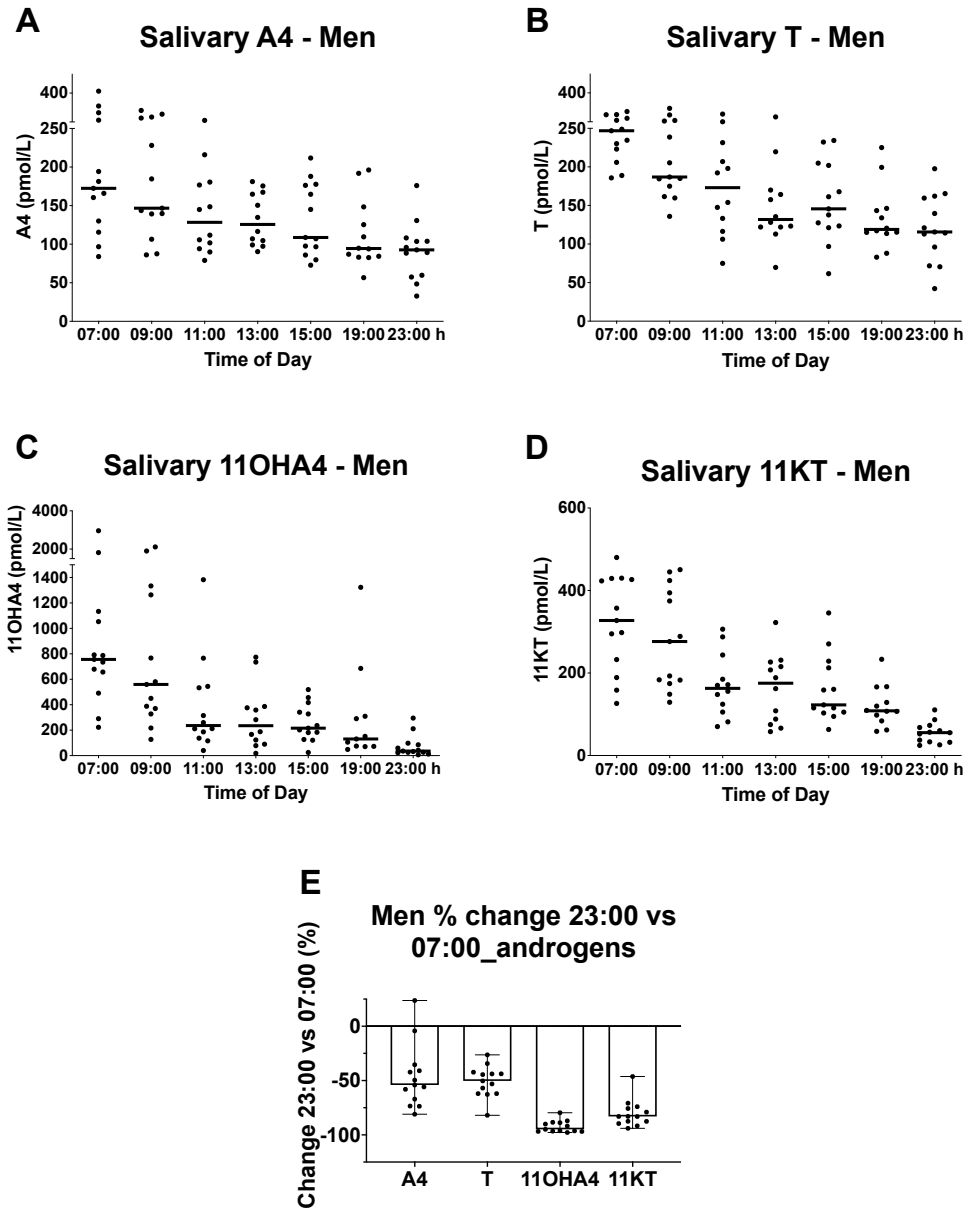


Figure 20: Diurnal variation of saliva steroids in men. 13 men (age range 20-35) collected seven saliva samples at defined times over 24 hours.

The line represents the median. 17OHP, 17α-hydroxyprogesterone; (A) A4, androstenedione; (B) T, testosterone; (C) 11OHA4, 11β-hydroxyandrostenedione; (D) 11KT, 11-ketotestosterone. Percentage change of saliva steroids over the day were calculated (E) by comparing the saliva steroid concentrations at 23:00 to the concentrations at 07:00. Bars represent the median, whiskers the range.

4 Experiences of people with PCOS: An international survey on emotional and psychosexual wellbeing in people with polycystic ovary syndrome- Blue Morpho study

4.1 Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting an estimated 10-15% of women of reproductive age with multi-system manifestations (David A. Ehrmann 2005). The prevalence varies worldwide, with PCOS diagnosed in up to 26% of women of reproductive age in India (C. G. Solomon 1999). It is characterised by hyperandrogenism, menstrual disturbance, and subfertility and patients with PCOS present with a range of reproductive, psychological, or metabolic symptoms, where women of South Asian origin disproportionately suffer more symptoms than any other ethnic group (Sirmans and Pate 2013; Mehta, Kamdar, and Dumesic 2013). Studies have reported the burden of PCOS on patients' quality of life, highlighting the impact on emotional wellbeing with a documented increased presence of depression and anxiety symptoms among patients with PCOS (Hahn et al. 2005; Laggari et al. 2009; Månsson et al. 2008).

Body image is the mental perception of one's body and attitude towards one's physical self, appearance, health, sexuality, and normal functioning (Bazarganipour et al. 2013a). Persistent dissatisfaction with one's appearance, leading to chronic distress and worry impacting day-to-day activities, is referred to as Body Dysmorphic Disorder

(BDD) (Veale 2004). BDD has been shown to adversely affect psychological functioning, increasing the risk of depression, anxiety and self-harm among sufferers (Otto et al. 2001). However, few studies have evaluated perceived body image in people with PCOS and, by extension, the prevalence of BDD in people with PCOS (Bazarganipour et al. 2013a).

Female Sexual Dysfunction (FSD) is a persistent disorder causing difficulty in experiencing personally satisfying sexual activities (World Health Organization 2018). Sexual dysfunction is estimated at 21–28% among premenopausal women (Geiss et al. 2003). FSD is associated with obesity, metabolic syndrome, and androgen excess, commonly seen in people with PCOS. Whilst some studies reveal a higher prevalence of FSD in people with PCOS; concerns persist around the methodological quality of the literature available (Loh et al. 2020).

The United Kingdom (UK) National Institute of Health and Care Excellence (NICE) guidelines recommend that healthcare professionals ask patients with PCOS about emotional wellbeing and body image concerns during consultations. However, it lacks tailored advice and instead signposts to generalised eating disorders, which may contribute to underestimation of the impact of PCOS on emotional wellbeing (National Institute for Health and Care Excellence 2018).

Some studies have highlighted the varied prevalence of mental health conditions. However, alongside body dysmorphia and sexual dysfunction, there is limited evidence for people with PCOS in the community focusing on emotional and psychosexual wellbeing. Few papers have analysed the impact of these factors in an ethnic minority group globally and beyond people in western culture (Bazarganipour et al. 2013a). This cross-sectional study took the novel approach exploring the

influence of ethnicity and nationality on emotional and psychosexual wellbeing in women diagnosed with PCOS in the community.

4.2 Objectives

1. To estimate the prevalence of anxiety, depression, and body dysmorphic disorder in women with PCOS stratified by ethnicity and nationality.
2. To estimate the association between non-white ethnicity and UK nationality and validated scores that measure sexual dysfunction, emotional and psychological illbeing compared to white ethnicity and Indian nationality in women with PCOS.

4.3 Materials and methods

This cross-sectional study (Blue Morpho) was conducted using an online survey which included three parts. The first part included details and rationale for the survey, general data protection regulation and consent. Those who consented were directed to the next section, which requested information on their socio-demographic details of the participant and details about their diagnosis of PCOS. This followed the third section, which included validated questionnaires on four domains: Emotional wellbeing (anxiety and depression), body image, weight-related stigma, and sexual function.

4.3.1 Standardised questionnaires

The four standardised questionnaires we used are summarised in table 2 and described in detail below.

Several questionnaires exist to measure anxiety and depression. Of these, the most used is the Hospital Anxiety and Depression Score (HADS), A 14-item scale that determines a person's level of anxiety and depression (Zigmond and Snaith 1983a). A score of 8-10 is a borderline case, and >10 is a case of anxiety or depression. A

recent systematic analysis and meta-analysis has further confirmed the high sensitivity and specificity of the questionnaire to screen for anxiety and depression (Y. Wu et al. 2021).

Of the various questionnaires and surveys available to measure body image concerns and weight stigma, we focus our discussion on two self-reported surveys: Body Image Concern Inventory (BICI) and Beliefs About Obese Persons Scale (BAOP). BICI is a self-reported measure of dysmorphic appearance concerns (Littleton, Axsom, and Pury 2005). It evaluates dissatisfaction with appearance, checking and camouflaging of perceived appearance defects, reassurance seeking about appearance, and social concerns and avoidance related to appearance defects. The survey was validated using college students who are otherwise well and further with a cohort of population having elevated dysmorphic concern. The measure is scored by summing all the items. Scores can range from 19 to 95 (higher scores represent higher levels of dysmorphic concern). A score >71 is characteristic of individuals with Body Dysmorphic Disorder ("Heather Leigh Littleton's Body Image Concern Inventory" n.d.).

BAOP measures the extent that an individual believes obesity is under the control of a person with obesity. It contains 8-items rated on a six-point Likert rating scale which assesses beliefs about the causes of obesity (− 3 = strongly disagree to 3 = strongly agree). With a total score of 24, a higher score indicates stronger beliefs that people with obesity cannot control their weight status (Allison, Basile, and Yuker 1991a).

Female Sexual Function Index (FSFI)- A questionnaire assessing domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain) and provides a score regarding sexual function.

Table 8: Four validated questionnaires included in the Blue Morpho study. The research team tried to contact questionnaire authors regarding copyright, and no concerns were raised, and implied permission was established.

Hospital Anxiety and Depression Score (HADS) (Zigmond and Snaith 1983b).	A 14-item scale that determines a person's level of anxiety and depression. A score of 8-10 is a borderline case, and >10 is a case of anxiety or depression.
Body Image Concern Inventory (BICI) (Littleton, Axsom, and Pury 2005; Ghadakzadeh et al. 2011).	A self-reported measure of dysmorphic appearance concerns. A score >71 is characteristic of individuals with Body Dysmorphic Disorder.
Female Sexual Function Index (FSFI) bias (Allison, Basile, and Yuker 1991b).	A questionnaire assessing domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain) and provides a score regarding sexual function.
Beliefs About Obese Persons Scale (BAOP)	An 8-item Likert rating scale which assesses beliefs about the causes of obesity.

4.3.2 Design and data collection

We collected data during two time periods, September-October 2020, for people based in the UK and June-July 2021, for people based in India. We started our sample

population by launching a targeted social media campaign centred on PCOS Awareness Month in September in collaboration with two national patient support groups, Verity and PCOS Vitality (Verity 2021; PCOS Vitality 2021). During June and July 2021, we collaborated with two patient support groups in India, PCOS Loqus and PCOS Club India (PCOS LOQUS 2021; PCOS Club India 2021). All participants were recruited via social media posts supported by patient groups and were provided with a direct link to the first introductory part of the online survey, as detailed above.

People who self-reported a PCOS diagnosis confirmed by a healthcare professional were included. All responses without a self-reported PCOS diagnosis were excluded from the analysis.

4.3.3 Statistical analysis

Statistical analysis was performed using STATA 14.2. All exposure measures were calculated as per the guidance of the validated questionnaires in the literature: HADS anxiety score, HADS depression score, BICI score, BAOP score and FSFI score. Median and interquartile ranges (IQR) for the scores and frequency and percentages the diagnoses were reported for all patients and for patients stratified by their nationality and ethnicity status. For analysis, primary exposure variables such as ethnicity and country of birth were recoded as dichotomous variables (White British or White Irish vs the remaining ethnic groups; United Kingdom vs India, respectively) due to low samples in each individual category.

Logistic regression models were used to obtain adjusted odds ratios and 95% confidence intervals (CI) for each diagnostic outcome variable (derived from the scores' cut-off) such as anxiety, depression, and BDD. Linear regression models were used to obtain adjusted regression coefficients and 95% CI for each continuous

outcome variable (HADS: anxiety and depression scores; BICI scores; BAOP scores; FSFI domain scores. Adjustments were made for the following independent variables in the logistic and linear regression models: age category, level of education, marital status, and parity.

4.4 Results

1060 women consented to complete the survey, of which 1008 had a self-reported diagnosis of PCOS made by a healthcare professional and were included in the study. Most of the participants were in the 26-35 age category (44.8%), had an undergraduate degree (44.9%), were in full-time employment (47.6%), were single (53.9%), and did not have children (84.1%). The full characteristics are presented in

Table 9.

The scores of emotional and psychosexual wellbeing, and the prevalence of anxiety, depression and BDD for the entire cohort is given in

Table 10. Of 1003 people completing the HADS survey, 611 (60.6%) and 245 (24.3%) had anxiety (HADS score ≥11), and depression (HADS score ≥11), respectively. 83 (8.3%) suffered from both anxiety and depression, and 138 (13.8%) had neither anxiety nor depression. The prevalence of borderline diagnosis (HADS score 8-10) of anxiety and depression were 18.9% (n=191) and 26.7% (n=269), respectively. Based on BICI scores of greater than 72, 38.5% (n=388) individuals were classified as having BDD.

4.4.1 Impact of ethnicity on emotional and psychosexual wellbeing

Emotional, psychological, and sexual wellbeing were compared between those of white ethnicity (n=392) and non-white ethnicity (n=611). Results of the linear regression and logistic regression are shown in

Table 11.

Women with PCOS of non-white ethnicity had higher scores of depression (beta=1.33; 95% CI 0.68-1.99; p<0.001) and reported higher incidence of depression (OR 1.96; 95% CI 1.41-2.73; p<0.001) when compared to white ethnic women. A similar pattern was seen for anxiety, albeit not at a statistically significant level.

There were significant associated differences between ethnicity and psychosexual wellbeing. Lower BICI scores (beta=-7.48; 95% CI -10.21 - -4.75; p<0.001) and BAOP scores (beta=-2.70; 95% CI 3.94 - -1.45; p<0.001) were reported for women of non-white ethnicity, mirroring the prevalence of BDD diagnosis that was lower in non-white ethnic women compared to white ethnic women (OR 0.57; 95% 0.41-0.79; p=0.001). Women of white ethnicity had higher FSFI scores (beta=-3.05; 95% CI -4.59- -1.52; p<0.001), denoting higher sexual wellbeing when compared to women of non-white ethnicity. This significant difference translates to the majority of FSFI domains: arousal

(beta= -0.40; 95% CI -0.73- -0.07; p=0.017), lubrication (beta=-0.53; 95% CI -0.90- -0.16; p=0.005), orgasm (beta=-0.48, 95% CI -0.84- -0.12; p=0.009), satisfaction (beta=-0.89; 95% CI -1.13- -0.66; p<0.001) and pain (beta=-0.89; 95% CI -1.27- -0.52; p<0.001).

4.4.2 Impact of the country of birth on emotional and psychosexual wellbeing.

Differences between emotional and psychosexual wellbeing were investigated between participants born in the United Kingdom (n=433) and India (n=453), and these results are shown in

Table 12.

Women with PCOS in the India had lower emotional wellbeing when compared to those born in the UK. The participants born in the India reported a higher anxiety score (beta=1.09; 95% CI 0.34-1.84; p=0.004), and higher prevalence of anxiety (OR 1.57; 95% CI 1.00-2.46; p=0.049) after adjusting for age, educational status, marital status, and parity. Similarly, women born in India reported higher depression scores (beta=1.64; 95% CI 0.92-2.36; p<0.001) and higher prevalence of depression (OR 2.20; 95% 1.52-3.18; p<0.001).

Women in the UK reported higher degrees of psychological illbeing: higher BICI scores (beta=-11.96; 95% CI -14.96- -8.96; p<0.001), higher prevalence of BDD diagnosis (OR 0.42; 95% CI 0.29-0.61; p<0.001) and weight stigma BAOP scores (beta=-3.38; 95% CI -4.77- -2.00; p<0.001). Investigation into sexual wellbeing, revealed participants born in the UK has higher FSFI scores overall (beta=-3.50; 95% CI -5.20- -1.81; p<0.001), denoting improved sexual wellbeing when compared to participants born in India. This significance was reflected within the majority of FSFI domains: arousal (beta=-0.43; 95% -0.79- -0.07; p=0.019), lubrication (beta=-0.60; 95% CI -1.01- -0.19; p=0.004), orgasm (beta=-0.60; 95% CI -0.99- -0.20; p=0.003), satisfaction (beta=-1.05; 95% CI -1.31- -0.79; p<0.001) and pain (beta=-0.98; 95% CI -1.38- -0.57; p<0.001).

4.5 Discussion

Exploring the impact of PCOS on emotional and psychosexual wellbeing is important to provide an individualised, holistic approach alongside clinical care. Our study found the significant impact of ethnicity and nationality on emotional and psychosexual wellbeing in women with PCOS.

Investigation into the impact of anxiety and depression in people with PCOS is extensive. Barry *et al.* conducted a systematic review and meta-analysis demonstrating people with PCOS tend to experience mildly elevated anxiety and depression, which supports the findings of high prevalence of anxiety and depression in the study's cohort (J. A. Barry, Kuczmierczyk, and Hardiman 2011). It may suggest an underestimation of the prevalence of emotional distress in the community as most studies focus on people attending secondary care services.

Features of PCOS such as acne, hair loss, weight gain and hirsutism have been linked to lower levels of self-esteem and greater fear of negative appearance evaluation (de Niet et al. 2010; Bazarganipour et al. 2013a). Our results support the high incidence of body image concerns amongst people with PCOS. Interestingly, women of white ethnicity and women born in the UK showed significantly higher body image concern and weight stigma scores and prevalence of BDD compared to those born in India and of non-white ethnicity. To the best of our knowledge, there is no current literature investigating the impact of psychological wellbeing, body image concerns, and weight stigma in PCOS, highlighting the importance of these results support the knowledge that country of birth and ethnicity may impact the phenotypic presentation of PCOS (Sendur and Yildiz 2021). Future investigations on the impact of ethnicity are needed to inform guidelines to better tailor care for these people who have a higher risk of suffering from psychological illbeing. Further to this, consideration of the impact of the environment is important to highlight, particularly where people born in the United Kingdom reported higher psychosexual illbeing, which may be associated with societal stigma.

Sexual dysfunction in people with PCOS is important to explore due to characteristic complications of obesity, hyperandrogenism and anovulation. Eftekhar *et al.*

investigated sexual dysfunction with a similar methodology, utilising the FSFI questionnaire, and concluded that people with PCOS suffered considerably from sexual dysfunction (Eftekhar et al. 2014). A particular focus is required for people of non-white ethnicity with potential sexual satisfaction dysfunction, which is also reflected in the population born in India. The consideration of the cultural differences of openness when discussing domains of sexual function is important when interpreting FSFI results from different nationalities. This is supported by literature where it is noted Indian women were less likely to discuss and seek assistance with sexual health with a healthcare professional, with socioeconomic factors and family tradition influencing disclosure (Puthuchira Ravi and Athimulam Kulasekaran 2014). This study aids the need for appropriate screening of people with PCOS for sexual wellbeing and proposing targeted interventions to bridge the health communication gaps in sexual health.

4.5.1 Limitations

The cross-sectional study design reduces the ability to minimise confounding factors, such as data collection during the Coronavirus disease 2019 pandemic, which may influence wellbeing. There are also limitations in reaching women via support and advocacy groups which may attract a specific cohort. However, this study aimed mainly to highlight the problem and further in-depth analysis in the form of case-control methodology will consolidate these results and confirm findings. In addition, results were adjusted for participant demographics, minimising the influence of these factors, and strengthening the conclusions. In this study, the absence of baseline, non-PCOS controls prevents us from confirming notable trends that can be attributed to PCOS alone and confounding factors such as social and educational factors should be considered. Alongside this, all participants self-reported a PCOS diagnosis by a

healthcare professional, which could not be verified and therefore may bias results. Also, the cohort completing the survey may bias against those unable to access social media or online surveys. However, unlike other studies focusing on clinic attendance, this study aims to capture people in the community, which are often neglected and may be more representative of the PCOS population.

4.6 Conclusion

Our study investigating emotional and psychosexual wellbeing in women with PCOS reveals high rates of anxiety, depression and body dysmorphic disorder, poor body image, weight stigma and sexual dysfunction. In particular, this emotional and psychosexual illbeing can be influenced by ethnicity and birthplace. This warrants the need for regular in-depth universal screening and emphasises the role of a psychologist in the PCOS multidisciplinary team to provide comprehensive care and efforts to improve awareness amongst primary healthcare professionals when managing women with PCOS in the community.

Table 9: Socioeconomic and clinical characteristics in PCOS patients

Variable	Frequency, n (%)
Age group (years)	
17 or younger	10 (1.0)
18 – 25	390 (38.7)
26 – 35	452 (44.8)
36 – 45	128 (12.7)
46 – 55	26 (2.6)
56 or older	2 (0.2)
Ethnicity	
Asian or Asian British Bangladeshi	5 (0.5)
Asian or Asian British Indian	487 (48.3)
Asian or Asian British Pakistani	10 (1)
Black or Black British African	8 (0.8)
Black or Black British Caribbean	11 (1.1)
Mixed Background	23 (2.3)
White British	384 (38.1)
White Irish	11 (1.1)
Other	69 (6.8)
Education	
Postgraduate degree	283 (28.1)
Undergraduate degree	453 (44.9)
A-levels or equivalent	184 (18.3)

GCSE or equivalent	56 (5.6)
No formal qualifications	6 (0.6)
Other	26 (2.6)
Occupation	
Full-time employment	480 (47.6)
Part-time employment	158 (15.7)
Retired	2 (0.2)
No paid work	368 (36.5)
Marital status	
Married/Civil Partnership	342 (33.9)
Cohabitating	107 (10.6)
Separated/Divorced	16 (1.6)
Single	543 (53.9)
Number of children	
0	848 (84.1)
1	84 (8.3)
2	60 (6.0)
3	15 (1.5)
4+	1 (0.1)

Table 10: Scores of validated questionnaires for the full cohort.

	N	Median (IQR)	Frequency, n (%)
Emotional wellbeing			
HADS Anxiety score	1003	12 (9-15)	
HADS Anxiety diagnosis	1003		611 (60.6)
HADS Depression score	1003	8 (4-10)	
HADS Depression diagnosis	1003		245 (24.3)
Psychological wellbeing			
BICI	1005	66 (52-78)	
Body Dysmorphic Disorder diagnosis	1005		388 (38.5)
BAOP	997	30 (25-35)	
Sexual wellbeing			
FSFI Desire	979	3.0 (2.4-4.2)	
FSFI Arousal	979	3.0 (0.0-4.5)	
FSFI Lubrication	979	3.9 (0.0-5.4)	
FSFI Orgasm	979	3.2 (0.0-4.8)	
FSFI Satisfaction	979	4.0 (2.8-4.8)	
FSFI Pain	979	2.0 (0.0-4.8)	
FSFI Overall	979	20.2 (7.4-26.1)	

Table 11: Scores of validated questionnaires based on white and non-white ethnicities.

	White Ethnicity (n=392) (Reference)	**Non-white Ethnicity** (n=611)	**Adjusted coefficient** (95% CI)	**Adjusted Odds Ratio** (95% CI)	***p*-value**
Emotional wellbeing					
HADS Anxiety score	11 (8-14)†	12 (9-15)†	0.523 (-0.158 - 1.204)	-	0.132
HADS Anxiety diagnosis	221 (55.9%)§	390 (63.6%)§	–	1.323 (0.884 - 1.981)	0.174
HADS Depression score	7 (4-10)†	8 (5-11)†	1.331 (0.677 - 1.985)	–	**<0.001**
HADS Depression diagnosis	84 (21.3%)§	161 (26.3%)§	–	1.963 (1.410 – 2.733)	**<0.001**
Psychological wellbeing					
BICI	72 (60-81)†	61 (47-76)†	-7.480 (-10.211- -4.749)	–	**<0.001**
Body Dysmorphic Disorder diagnosis	187 (47.3%)§	201 (32.8%)§	–	0.568 (0.408 – 0.791)	**0.001**
BAOP	32 (28-35)†	29 (23-34)†	-2.698 (-3.944 - -1.451)	–	**<0.001**
Sexual wellbeing					
FSFI Overall	23.3 (11.0-28.1)†	18.15 (6.8-24.7)†	-3.052 (-4.587 - -1.517)	–	**<0.001**

FSFI Desire	2.4 (1.8-3.6)†	3.6 (2.4-4.2)†	0.140 (-0.083 – 0.362)	–	0.219
FSFI Arousal	3.3 (1.2-4.8)†	2.7 (0.0-4.2)†	-0.399 (-0.725 - -0.072)	–	**0.017**
FSFI Lubrication	4.5 (0.3-5.7)†	3.6 (2.0-4.8)†	-0.528 (-0.900 - -0.156)	–	**0.005**
FSFI Orgasm	4.0 (0.0-5.2)†	2.8 (0.0-4.8)†	-0.479 (-0.836 - -0.121)	–	**0.009**
FSFI Satisfaction	4.4 (3.2-5.2)†	3.2 (2.0-4.8)†	-0.893 (-1.128 - -0.659)	–	**<0.001**
FSFI Pain	4.0 (0.0-5.6)†	0.0 (0.0-4.4)†	-0.893 (-1.265 - -0.522)	–	**<0.001**

† Median (IQR); § Frequency, n (%)

Table 12: Scores of validated questionnaires based on country of birth.

	United Kingdom (n=433) (Reference)	**India** (n=453)	**Adjusted coefficient** (95% CI)	**Adjusted Odds Ratio** (95% CI)	***p*-value**
Emotional wellbeing					
HADS Anxiety score	11 (8-14)†	13 (9-15.5)†	1.090 (0.341 – 1.840)	-	**0.004**
HADS Anxiety diagnosis	248 (56.8%)§	297 (65.6%)§	-	1.573 (1.002 – 2.458)	**0.049**
HADS Depression score	7 (4-10)†	8 (5-11)†	1.637 (0.916 – 2.359)	-	**<0.001**
HADS Depression diagnosis	96 (22.0%)§	123 (27.2%)§	-	2.199 (1.521 – 3.177)	**<0.001**
Psychological wellbeing					
BICI	72 (60-81)†	58 (44-73.5)†	-11.960 (-14.959 - -8.960)	-	**<0.001**
Body Dysmorphic Disorder diagnosis	210 (48.1%)§	129 (28.5%)§	-	0.420 (0.290 – 0.610)	**<0.001**
BAOP	32 (27-35)†	29 (23-34)†	-3.384 (-4.768 - -2.000)	-	**<0.001**
Sexual wellbeing					

FSFI Overall	22.45 (9.65-27.98)†	17.1 (6.4 - 24.5)†	-3.502 (-5.197 - -1.807)	-	**<0.001**
FSFI Desire	3.0 (1.8-3.6)†	3.6 (2.4-4.2)†	0.150 (-0.096 – 0.397)	-	0.231
FSFI Arousal	3.3 (1.2-4.8)†	2.7 (0.0-4.2)†	-0.431 (-0.791 - -0.070)	-	**0.019**
FSFI Lubrication	4.35 (0.3-5.7)†	3.3 (0.0-4.8)†	-0.598 (-1.010 - -0.187)	-	**0.004**
FSFI Orgasm	4.0 (0.0-5.2)†	2.8 (0.0-4.8)†	-0.595 (-0.988 - -0.202)	-	**0.003**
FSFI Satisfaction	4.4 (3.2-4.8)†	2.8 (1.6-4.4)†	-1.053 (-1.313 - -0.794)	-	**<0.001**
FSFI Pain	3.6 (0.0-5.6)†	0.0 (0.0-4.0)†	-0.975 (-1.381 - -0.568)	-	**<0.001**

† Median (IQR); § Frequency, n (%)

5 PCOS Pearls - Gathering Perceptions and Opinions from Lived Experiences of People with Polycystic Ovary Syndrome

5.1 Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine conditions affecting people of reproductive age with a global prevalence around 10% (Kovanci and Buster 2015; Deswal et al. 2020). It is associated with oligomenorrhoea or amenorrhoea, infertility, hirsutism, acne, and obesity (P. S 2018). The disease is multifactorial, and its complex pathophysiology involves multiple pathways (Khan, Ullah, and Basit 2019). A diagnosis of PCOS is made if other causes of patients' symptoms are ruled out and patients fulfil two of three diagnostic criteria (oligomenorrhoea or anovulatory cycles, biochemical or clinical signs of hyperandrogenism, polycystic ovaries seen on ultrasound scan) (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group and Group 2004).

PCOS often presents during puberty and the characteristic signs and symptoms coincide with the development of normal physiological findings during this period of life (Roe and Dokras 2011; Agapova et al. 2014). This can complicate the diagnostic process. Gibson-Helm et al. reported in their study that a third of women with PCOS report a delay in their diagnosis (M et al. 2017). Further, despite its prevalence, people with PCOS often struggle to find reputable sources of information about their condition. Although physicians are integral in the education of patients, patients often find

resources accessed at home much more helpful. It is reported that 98.2% of patients search the internet for PCOS related information (LR et al. 2020; JC and AJ 2007a). Existing educational and awareness resources for polycystic ovary syndrome (PCOS) have, to date, had limited inclusion of patient perspectives. Therefore, we conducted this mixed-methods study to understand the lived experiences, perception and opinion on the current standard of care of people with PCOS which can then help us create better-represented educational resources for the condition.

5.2 Methods

Women aged 18-60 years were invited to complete an online survey in April and May 2021. This survey was primarily promoted through patient support groups-PCOS Verity, DAISy-PCOS leadership group and PCOS Vitality. The survey started with information about the study and privacy statement. Interested participants had to complete an in-built consent as part of the study before proceeding to complete the survey. Nine closed questions in this survey focused on participant demographics such as age, gender, ethnicity, and country of residence and history of PCOS diagnosis. Participants with a formal diagnosis of PCOS were asked about the year of PCOS diagnosis, and a further four open-ended questions regarding their lived experiences at the onset of the symptoms of PCOS, their journey during diagnosis, an explanation of PCOS to their younger self, and any advice for their younger self (Appendix A). Participants had the option to share their views for the open-ended questions either as a written text or as voice notes on WhatsApp. The data from the latter was transcribed verbatim. Phone numbers of participants obtained for collection of voice note data were removed after data collection was complete. All data was anonymised at the point of analysis. Data were then coded using NVivo 12 software

and analysed using a combination of content analysis and thematic inductive qualitative methods (Barbara Downe-Wamboldt RN 2009; Bengtsson 2016) initially by two study members independently. These codes were then reviewed by two senior study members to identify common themes.

5.3 Results

A total 45 women completed the survey. 43 of 45 participants had a formal diagnosis of PCOS, the remaining two had suspected PCOS which was under active investigation and hence excluded from further analysis. Four participants opted to share their views as voice note recordings; one of them could not be contacted as they had incorrectly inputted their phone number. Therefore, data from 42 participants for the open question portion of the survey were analysed, generating 1326 references towards their experiences and perception about PCOS in total. (Appendix B)

Overall, five common themes emerged: symptoms (504 references by 42 participants), patient journey 421 references by 42 participants), knowledge (197 references by 40 participants), peer to peer advice (162 references by 41 participants), and impact of PCOS on social aspects of life (42 references by 19 participants). Participants were also arranged into groups based on age (20-29, 30-39, 40-49, 50-59) and ethnicity (White and Other). The median and interquartile range of age of participants in the White group is 37 (25.75- 41.75) and in the other group 27 (24-34). The various themes are discussed in greater detail below:

5.3.1 PCOS Symptoms

The most common symptom participants reported was poor mental health (83.3%). 90% of participants in the non-white ethnicities reported mental health issues compared to 81.3% of White group. Within this theme, low mood or depression

(54.8%) and a lack of self-worth (40.5%) were most notable. Self-worth and self-esteem issues were frequently discussed in connection with symptoms affecting participants' outward appearance, particularly weight gain, hair growth and acne. Distress due to poor mental health was most expressed by participants in their 20s (26.7%) and White individuals (18.8%).

The second most reported symptom was dermatological issues (81.0%), particularly hair related problems such as hirsutism and alopecia (73.8%). Participants in the 50-59 (100.0%) followed by 20-29 (92.3%) age group reported dermatological symptoms the most. The third most discussed symptom was menstrual issues (76.2%). This was often the initial symptom prompting seeking professional advice. Women in their 30s (83.3%) were found to most commonly report menstrual issues compared to other age groups. There were fewer reports of distress associated with this symptom compared to skin and hair concerns, unless in the context of fertility. Many participants reported being on a form of contraceptive pill helped alleviate their menstrual irregularity symptoms. The fourth most reported symptom is weight issues. Interestingly, 100.0% of non-white ethnic women reported experiencing weight problems, usually relating to considerable weight gain but also an inability to lose weight. The fifth most reported symptom is subfertility. Women in their 40s (100.0%) and of White ethnicity (43.8%) most reported this symptom.

5.3.2 Patient Journey

The most discussed aspect within patient journey was around the attitudes towards healthcare staff. 88.1% felt dissatisfied with PCOS-related healthcare support. Most women found clinicians dismissive and lacked empathy. Several participants were confused by their diagnosis and found explanations from clinicians unhelpful. The second most common theme was diagnostic experience (71.4%). Within this, a

lengthy diagnostic journey was most frequently reported (35.7%), with many finding it emotionally demanding as diagnosis often takes years. A lengthy diagnosis was reported proportionally more by people in their 20s (61.5%) and of non-white ethnic group (60.0%), compared to 28.1% in the White group. Some reported that although clinicians had suspicions of PCOS, their diagnosis got delayed due to lack of timely investigations, leaving many feeling isolated with little professional support.

The third most discussed theme is PCOS management (61.9%). Within this theme, contraception (40.5%), lifestyle changes (21.4%), and management of dermatological symptoms (21.4%) were most common. A similar finding can be seen across all age groups except 20-29, where lifestyle changes (38.5%) are reported by more participants than contraception use (30.8%). 43.8% of participants in the White group reported contraception use, with only 28.1% for lifestyle changes. Many participants describe contraception use in their adolescence for menstrual cycle regulation. The most common contraception used is the oral pill. Lifestyle changes are usually focused on diet rather than exercise, with the aim of weight loss. Several participants find lifestyle changes stressful. Methods such as shaving, laser treatment and skincare products were reported for management of excess hair growth and acne.

5.3.3 Knowledge of PCOS

The most discussed topic in knowledge of PCOS was about signs and symptoms including menstrual symptoms (27.5%), weight and eating (22.5%), dermatological issues (17.5%), mental health issues (15.0%) and fertility issues (15.0%). Weight and eating issues are the most reported description of PCOS in the 20-29 age group (38.5%) and non-white ethnic group (30.0%), compared to the White group (20.0%). Higher proportion of participants in the non-white group (40.0%) discussed mental health issues in their description of PCOS, compared to participants of white ethnicity

(6.7%). Fertility issues were most reported description by participants in their 30s (23.5%). Interestingly, none of the participants in non-white group mentioned fertility issues in their description of the condition.

Some participants used medical terminology commonly when discussing about PCOS (37.5%). Notably, the term 'hirsutism' was the most frequently used. Expectedly, participants who employ medical terminologies in their answers, often used it on multiple occasions. Further, 32.5% participants acknowledged the condition's heterogenous presentation and clearly understood what a syndrome is and described this accurately. These participants reporting this are usually in the 20-29 age group (46.2%), and belonged to non-white ethnicity (50.0%).

5.3.4 Peer-to-peer advice

A concept first established in mental health services, peer-to-peer advice can be defined as a social emotional support, frequently coupled with instrumental support, that is mutually offered or provided by persons having a health condition to others sharing a similar health condition to bring about a desired social or personal change (P. Solomon 2004).

The most common themes in peer-to-peer advice involve being proactive in own care (48.8%), becoming educated about PCOS (46.3%), mentality (46.3%) and management of condition (46.3%). Many participants recommend being proactive early in one's PCOS journey. Recommendations of proactivity are common in participants in their 50s, (80.0%), and White (51.6%). However, advice on education of PCOS was more common in participants in their 20s (58.3%) and non-white ethnicity (70.0%). Many considered education important to improve health in the long term and to advocate for themselves in the future when meeting healthcare

professionals. Advice on mentality was most discussed by participants in their 20s (58.3%) and of non-white ethnicity (70.0%). Most advice about mentality was to remain positive. Advice on management focused on lifestyle changes, particularly diet and exercise. Management advice was most common in the 40-49 age group (66.7%), and non-white group (70.0%). Many acknowledged that lifestyle changes are not a cure but are associated with better control of the condition and therefore outcomes.

5.3.5 Impact of PCOS on social aspects of life

Within this, the most common topic discussed is the societal expectations of women (52.6%). This was most discussed by participants in their 40s (66.7%) and the non-white ethnicities (75.0%). While all participants identified themselves as women, many believed PCOS rendered themselves less feminine due to the masculine symptoms associated and do not align with current beauty ideals. Some women felt the pressure to bear children.

Another aspect discussed was the condition's impact on everyday life, including school, career and interactions with their partners (47.4%). Participants sharing the social consequences of PCOS on their life are usually in their 40s (66.7%) and 50s (66.7%) and of non-ethnic races. Subfertility issues associated with PCOS are reported to cause strain on romantic relationships, with participants feeling inadequate as a partner.

The third most common theme is solidarity with other women with PCOS (42.1%). A considerable proportion of these expressions were by participants in their 20s (83.3%). Some participants acknowledge the importance of bonding with others with PCOS not only to better their emotional wellbeing but also share information and gain knowledge.

5.4 Discussion

It is vital to seek patients' perspectives to improve healthcare experiences and services. While themes of symptoms, journey and knowledge have been reported elsewhere, we report a number of new findings not previously reported. Participants emphasised the importance of peer-to-peer advice. Percy et al. found support networks led by specialist nurses were found to be a significant factor to mitigate psychological impact of PCOS, especially newly diagnosed people (CA et al. 2009). In the era of the internet, online support groups have proved to be a versatile and easily accessible source for peer-to-peer support (JC and AJ 2007a). With an ability to remain anonymous and able to tap to resources from all over the world, online support groups are turning out to be a gamechanger in managing chronic conditions like PCOS. Despite this, only 18.8% of patients joined an online PCOS support group or forum (LR et al. 2020). It may be beneficial for clinicians to signpost these groups to patients in the future. However, some disempowering processes should be considered with the use of online support groups, including anxiety because of hearing others' negative experiences and feelings of being an outsider (Holbrey and Coulson 2013).

Our participants also emphasised the impact of PCOS on their social life. Sharma et al and Carron et al underline the difficulties of women with PCOS in communities where those who struggle to conceive children suffer devaluation of their social status (Sharma and Mishra 2018; R et al. 2020). Some describe menstrual symptoms to be debilitating, affecting their school life or career. Similarly, women with PCOS reported being unable to attend tribal ceremonies for fear of unpredictable menses (R et al. 2020).

People with PCOS, particularly of non-white ethnicity reported greater delays in diagnosis, discussed more than rest of the group about mental health and societal pressures. To the best of our knowledge, this is the first study of its kind to explore the perception of people with PCOS across age and ethnicity in such detail.

Participants in our study considered some healthcare professionals to be dismissive, lacking in clarity in their explanations and empathy. Dissatisfaction with care for women with PCOS may stem from lengthy diagnostic and management process involved (M et al. 2017; Copp et al. 2019) and similar findings are reported elsewhere (Tomlinson et al. 2017; LR et al. 2020). Longer treatment delay eventually leads to significant periods of time without support or management.

Participants in our study reported with struggles at the start of their diagnostic journey and following their initial diagnosis of PCOS due to lack of information. Gibson-Helm et al's study show a similar finding, where 60% of patients said they were not given information on PCOS when diagnosed, and 20% felt the information given was inadequate (ME et al. 2014). Interestingly, most participants in our study demonstrated adequate knowledge regarding PCOS. However, they reported this information was rarely received from healthcare professionals, and instead a result of patients' own research.

Mental health is the most experienced symptom in those with PCOS across both non-white (90%) and White ethnicities (81.3%). Hillman et al reported 74.9% of women with PCOS reported poor mental health due to PCOS. Interestingly, they found women of white ethnic background discussed more about their mental health and subfertility (43.8% of White participants, compared to 0% non-white participants) than British Asian women. (SC et al. 2020). This may suggest an area to further explore, to ensure

women of all races have adequate healthcare support for mental health and subfertility issues. Additionally, mitigating communication barriers for non-white groups is important to ensure support reaches communities who need it most.

While similar studies have been done in the past, our work has several strengths that sets it apart. With more than 40 participants, this is a large qualitative study which gave us the strength to perform content analysis and delineate the differences in perception of women with PCOS across age and ethnicity. An average ~400 words per participant (16, 606 words in total) for the four open-ended questions in our survey depicts the long and in-depth answers from participants which adds to the strength of the findings in our study. Further, all participants in our study came from a verified source, thus confirming the diagnosis of PCOS.

A median 22 years since our participants were diagnosed with PCOS both serves as a strength and weakness to our work. While the lived experience with PCOS over time can help understand the spectrum of PCOS's impact across the lifespan, our findings may be limited by recall bias. We also did not have sufficient representation from all the major ethnic groups in the UK and hence our findings may not be extrapolated to all types of non-white women and further studies are needed to delineate the differences in experience and perception of PCOS.

5.5 Conclusion

With PCOS Pearls, we explored the feelings of people with PCOS to greater detail. People with PCOS were impacted significantly by their symptoms and many women feel dissatisfied with the support they receive from healthcare professionals. Educational resources regarding PCOS are vital to improve patients' knowledge and empower them to take an active role in the management of their condition. The detailed information about perceptions and experiences of people with PCOS from this study can be used to ensure future educational resources and diagnostic processes are built around end-user experience. We therefore propose future public and patient involvement (PPI) for people with PCOS to enable the co-creation of new resources informed by lived experience. These can help those newly diagnosed, gain a more comprehensive, authentic and true-to-life understanding of the condition. Furthermore, these resources should aim to include emotional wellbeing and peer-to-peer support in greater detail, as two priority themes highlighted from this study. We also propose to have greater involvement of people with PCOS while designing diagnostic and management pathways to ensure these are acceptable to those with the condition.

Table 13: Thematic data in epidemiological groups

		Group					
	Total (n=42)	**20-29 yrs (n=13)**	**30- 39 yrs (n=18)**	**40-49 yrs (n=6)**	**50-59 yrs (n=5)**	**Other races (n=10)**	**White (n=32)**
PCOS symptoms							
	504 references by 42 participants	180 references by 13 participants	215 references by 18 participants	41 references by 6 participants	68 references by 5 participants	108 references by 10 participants	396 references by 32 participants
Mental health	83.3%	92.3%	77.8%	66.7%	100.0%	90.0%	81.3%
Dermatological issues	81.0%	92.3%	72.2%	66.7%	100%	70%	84.4%

Menstrual issues	76.2%	76.9%	83.3%	50%	80%	60%	81.3%
Perception of symptoms	64.4%	76.9%	77.8%	50%	40.0%	70.0%	68.8%
Journey							
	421 references by 42 participants	156 references by 13 participants	175 references by 18 participants	45 references by 6 participants	45 references by 5 participants	93 references by 10 participants	328 references by 32 participants
Attitudes towards healthcare staff	88.1%	84.6%	88.9%	83.3%	100.0%	80.0%	90.6%
Diagnostic experience	71.4%	84.6%	72.2%	50.0%	60.0%	80.0%	68.8%
Management of PCOS	61.9%	53.8%	66.7%	66.7%	60.0%	50.0%	65.6%

Knowledge							
	197 references by 40 participants	88 references by 13 participants	80 references by 17 participants	20 references by 6 participants	9 references by 4 participants	60 references by 10 participants	137 references by 30 participants
Symptoms and signs	50.0%	61.5%	47.1%	50.0%	25.0%	40.0%	53.3%
Hormonal condition	45.0%	69.2%	23.5%	66.7%	25.0%	30.0%	50.0%
Medical terminology	37.5%	46.2%	29.4%	16.7%	75.0%	40.0%	36.7%
Heterogenous presentations	32.5%	46.2%	29.4%	33.3%	0%	50.0%	26.7%
Peer to peer advice							
	162 references by 41 participants	47 references by 12 participants	77 references by 18 participants	19 references by 6 participants	19 references by 5 participants	45 references by 10 participants	117 references by 31 participants

Being proactive in own care	48.8%	50.0%	38.9%	50.0%	80.0%	40.0%	51.6%
Becoming educated about PCOS	46.3%	58.3%	50.0%	33.3%	20.0%	70.0%	38.7%
Advice on mentality with a PCOS diagnosis	46.3%	58.3%	44.4%	33.3%	40.0%	70.0%	38.7%
Management of the condition	46.3%	33.3%	55.6%	66.7%	20.0%	70.0%	38.7%
Impact on social life							
	42 references by 19 participants	14 references by 6 participants	15 references by 7 participants	8 references by 3 participants	5 references by 3 participants	11 references by 4 participants	31 references by 15 participants

Societal expectations	52.6%	50.0%	57.1%	66.7%	33.3%	75.0%	46.7%
Everyday life	47.4%	33.3%	42.9%	66.7%	66.7%	50.0%	46.7%
Solidarity with women who have PCOS	42.1%	83.3%	28.6%	0%	33.3%	50.0%	40.0%

Table 14: Codes and example quotations for PCOS related symptoms theme in the PCOS Pearls survey.

Code	**Participant**	**Example Quotation**
Distressed by PCOS symptoms	19	"I stress myself out daily just looking at my knickers every time I go to the bathroom just hoping I've got a period. Knowing I'm not ovulating and don't have enough progesterone again makes me feel I'm not a woman and confirms my body is not healthy"
	35	"PCOS has destroyed my life, my confidence, my hopes and dreams and also has had a major effect on my physical and mental health."
Low mood/ depression	45	"I was deeply depressed."
	14	"The final symptom that really concerns me is my mental health. I'm a very anxious person and I definitely go through periods of very low mood. I don't feel that this could be categorised as depression because I'm still able to function at a basic level. But this can last for several days or weeks so it does impact my mood."
Lack of self-worth	15	"I feel rubbish every time I see myself in the mirror and I worry what other people think of me."

	19	“The lack of confidence and self esteem has never left me no matter how hard I try in altering my appearance, with weight loss.”
Hair related symptoms	40	“I grew a dark moustache at the age of eight.”
	9	“I have suffered from hirsutism for many years, it was this that was one of the first symptoms I experienced back in 2011. As time has progressed, the hair has become more of an issue with hair on my chin, chest and lower buttocks/top of thighs” “creating extra hair which will mean spending more time in the bathroom to get rid of them.”
Irregular menstruation	26	“I have really irregular periods”
	4	“periods can be erratic”

Table 15: Codes and example quotations for Patient Journey theme in the survey.

Code	**Participant**	**Quotations**
Contraception	36	“put on the pill (dianette).”
	6	“before I was on the combined pill I never had a regular cycle, I would go sometimes 8 months without a period and then bleed for a month or two until a doctor would give me medication to stop me bleeding.” “I then went on Yasmin, which didn't work well for me, then on Gedarel 30/150.”
Lifestyle changes	11	“I. kept on gaining weight again and again until I started to learn more about PCOS and insulin resistance, which made more sense to why I was not losing weight at the beginning. I started changing my methods, gaining gluten/dairy free and trying different alternative. I believe it helped a lot with my symptoms, especially for my gut health as. I used to get bloating very frequently after eating.”
	45	I feel like I have gone through some really necessary learning curves e..g diet management after having done all the stupid and dangerous extreme diets under the sun, before finding the safe and sustainable ways to manage things.

Management of dermatological symptoms	13	“I'd had excess hair on my face for years which got me really down. I wasn't given any advice and the only solutions given were some tablets to force an occasional bleed and to go private for any IPL if I wanted to.” “I always carried tweezers”
	15	“Acne was hard for my self esteem and made me feel low. I hated having to use strong creams and take tablets and found the visits to a dermatologist embarrassing.” “Again my skin is sensitive and attempts to remove the hair can make it look even worse. I can only realise use tweezers and that is time consuming. I end up spending ages in the bathroom and pretend to my family that I am on the toilet. If I have to see someone unexpectedly before I have used tweezers”
Lengthy diagnostic journey	21	“Terrible. I first went to the doctor about my periods when I was around 19, I had been in bed for a week because of the pain, I was prescribed painkillers but no further investigation was completed. I went again a couple of years later and was advised that my periods would probably be irregular until I had a baby. I was generally prescribed contraceptive medication without any follow up for the reasons for needing it. In 2018 I went to the doctor to advise that I had come of contraceptive pills and was having issues

		again with my periods and a GP advised that they suspected PCOS, it then took two years until I had a five minute appointment with a consultant that confirmed a. I had PCOS and b. There was nothing that I could be given to encourage me to ovulate as I was too fat.”
	5	“I first visited the doctors 3 years before getting diagnosed, and I visited several times in between for my irregular periods before they offered me blood tests and an ultrasound scan.”
Dissatisfaction with support from healthcare professionals	16	“Awful. No help, met with lose weight response.” “Now I’m at a healthy weight I’ve been told there’s nothing to do to help my symptoms. Very frustrated with specialists as you wait months for an appointment for them to not take into considerations my circumstances and only offer advice I could find online.”
	30	“I was given a generic leaflet about PCOS and no advice on how to manage my condition and what symptoms to look out for.” “I was not signposted to any services for support or ways to meet other people with PCOS so at the time I felt very much alone”

Table 16: Codes and example quotations for Knowledge of PCOS theme in the survey.

Code	**Participant**	**Quotations**
Description of PCOS: signs/ symptom terms	25	"Weight gain" "irregular periods" "your pcos makes it hard for you to lose weight but keep trying you will be ok." "Your mood swings and irritability and depression may well be caused by or effected by the syndrome that you have"
	7	"hair loss" "weight gain" "insulin resistance" "Finally I would say that although the condition involves my ovaries, and that there would be potential implication when trying to get pregnant"
Description of PCOS: hormonal condition	12	"PCOS is a misnomer - it has less to do with ovaries and more to do with hormones."

	31	“I would explain that PCOS is a complicated condition and that really it’s metabolic and hormonal”
Description of PCOS: constellation of symptoms and presentations	41	a lot of symptoms will come back to pcos .
	43	“‘PCOS is an endocrine disorder which is caused by hormonal balance and produces a number of symptoms. The cysts are not the condition, they are a symptom, and you don’t have to have all the symptoms to have PCOS’.”
Use of medical terminology	3	“Hirsutism” “insulin resistance”
	23	“androgenic alopecia”

Table 17: Codes and example quotations for Peer-to-peer advice theme in the survey.

Code	**Participant**	**Quotations**

Advice: management of PCOS symptoms	18	“change diet accordingly”
	22	“I would say take care of yourself. I would say take care of your health overall, in terms of how you eat and try not to stress about weight, because developing an eating disorder is probably just gonna make it worse.”
Advice: becoming educated about PCOS	33	“The earlier you understand your PCOS, the types and how to manage it better, the better you will be in years to come.”
	42	“Try to find out as much as you can about it so that you can look after your health”
Advice: becoming proactive in own care	2	“To seek help early and not to be fobbed off by Doctors who dismiss or try to trivialise your requests for help/treatments.”
	31	“It would be to take a driving seat approach, and to put myself at the forefront when it comes to communicating with doctors or telling them what I think is going on with my body”

Advice: Staying positive	44	“Finding an enjoyable lifestyle is so important to help support PCOS symptoms and this is ultimately what will help to find an enjoyable state.” ‘Don’t be too harsh in yourself and strive for progress not perfection.”
	30	“Do not focus on the what ifs. Focus on the now and how you feel currently.”

Table 18: Codes and example quotations for Impact of PCOS on social aspects of life theme in the survey.

Code	**Participant**	**Quotations**
Impact on everyday life	34	“I suffered low moods and also was very isolated when my periods were heavy i tended not to go out much.”
	22	“the pain can sometimes be really unbearable, and sometimes like you know I’ve been off work because of it. I’ve also been off uni because of it and that’s really really impacted my wellbeing overall” “So I got my periods at around nine, and then I started experiencing like very very heavy periods beyond that, and I think I got to about thirteen or fourteen where it was really unbearable and I couldn’t even you know get through a day of school sometimes because you know I wouldn’t be allowed to go to the bathroom as often, and that, yeah it wasn’t great.”
Societal expectations of women	32	“My wellbeing has been impacted: I don't feel as "feminine " as perhaps I might have without the condition.”

	7	“I find that the pressures imposed by society on womxn to be thin and have beautiful hair are in direct opposition with the symptoms I have experienced as a result of PCOS.”
Solidarity with other women with PCOS	5	“And lots of my friends have PCOS, and lots of women worldwide have it too. So there shouldn’t be any shame in speaking up about it, about encouraging research into the area, and if anything I owe it to the women who don’t know or understand they have PCOS to speak up. So the biggest advice to my younger self would be don’t be afraid to talk about it, you’re not alone.”
	14	“Other women are an incredible help, reach out to people going through what you are. The condition is different for every single person but it’s great to get tips and support from others who understand what you’re going through.”

6 Including people with PCOS in designing and delivering education regarding the condition can help us reduce the gaps in knowledge, attitude, and practice of PCOS.

This chapter is addressed at two levels-first explaining the foundation of a simulation-based learning model that was developed to engage healthcare professionals and then explaining how people with PCOS were involved into this model to bridge the gaps in knowledge, attitude and practice of PCOS.

7 SIMBA: using Kolb's learning theory in simulation-based learning to improve participants' confidence

7.1 Introduction

Medical education has been evolving over the years, with digital advancement resulting in development of novel teaching methods. Technology assisted learning has become increasingly integral in contemporary medical education, where flexibility and learner-centred teaching methods take precedence, with e-learning being a major modality (J. Moran, Briscoe, and Peglow 2018; Ellaway and Masters 2008). E-learning refers to the use of the Internet to enhance knowledge and allows the learning process to transcend geographical boundaries (Ruiz, Mintzer, and Leipzig 2006). E-learning can be a strategy to deliver a simulation-based learning (SBL), designed to provide a learner with a concrete experience in a realistic and safe environment, followed by a debriefing to facilitate abstraction and conceptualisation (So et al. 2019; Okuda et al. 2009). SBL addresses two important ethical considerations in medical education: (i) replicates real-life scenarios for acquisition of necessary clinical skills and (ii) ensures patient safety (Lateef 2010). Contrary to the traditional approaches to medical education, such as lecture-based learning (LBL), SBL calls upon the learner's integrative capacity and trains learners to adapt to the dynamics of variation in the field (John Dent, Ronald Harden, and Dan Hunt 2007). Evidence has shown that SBL is

superior to LBL in teaching situation awareness (Chang et al. 2017) and acquisition of critical assessment and management skills (Steadman et al. 2006).

The benefits of SBL and the technologies it could employ are informed and shaped by the educational theories from domains closely related to them. One example is Kolb's experiential learning theory which is based on the theory of constructivism and states that knowledge results from the process of grasping and transforming experience; hence, each phase of the Kolb's cycle must be experienced for optimal learning (David A. Kolb 1984). This learning cycle consists of four phases: (a) concrete experience where the learner participates in an experience such as simulation, (b) reflection on the experience, (c) abstract conceptualisation where the learner considers thoughts and reflections to identify significance of the learning experience and considers what could have been done differently to enhance the outcome, and (d) active experimentation using what was learned to direct future practice (Poore, Cullen, and Schaar 2014). Constructivism supports the idea that learning is a social experience and requires reflection. Recently, social media has been increasingly used in medical education (Katz and Nandi 2021), evolving as a potent tool to deliver SBL and provide immediate feedback during SBL.

Simulation via Instant Messaging- Birmingham Advance (SIMBA) is an innovative teaching model designed to construct SBL through WhatsApp® (Melson et al. 2020a). With its concept, SIMBA is replicating the learning cycle proposed by Kolb's experiential learning theory. The online simulation is conducted via WhatsApp® and Zoom®. The session starts off by pairing and linking the participant and moderator on WhatsApp®. Both of them are introduced to each other with an ID to ensure anonymity, which we recommend maintaining throughout the session. The moderator starts the session by sending a pre-SIMBA survey. Upon confirmation of completion,

moderators initiate the first simulation by sending a set of instructions about how to go through the simulation as an image. This is followed by a volley of text exchange between participant and moderator to solve the case. Participants ask for information pertaining to the case and moderators send them the information as available on the pre-approved transcript. At the end of the online simulation, a discussion combined with Q&A takes place over Zoom® video-conferencing platform. SIMBA session is closed by a post-SIMBA survey shared by the moderator to the participant on WhatsApp® reflecting on the learners plans to bring changes to future practice based on the experience gained throughout the SIMBA session. The results from previous sessions have demonstrated that SIMBA is an effective teaching model to increase participants' confidence in managing various endocrine and diabetes simulated cases (Melson et al. 2020a).

The pandemic due to coronavirus (COVID-19) disrupted postgraduate teaching and learning significantly (Sen-Crowe, McKenney, and Elkbuli 2020). In our region, there was a complete halt of teaching with all available resources and personnel diverted to tackle the pandemic. To enable sustained training during the pandemic, SIMBA conducted its first international, completely virtual session on Adrenal pathologies. Originally, interactive sessions with an expert were delivered as face-to-face meetings. However, SIMBA switched to Zoom® platform to adjust to the pandemic.

In this study, we describe how Kolb's experiential learning theory is adapted in SIMBA by providing concrete experience and reflective observation throughout the session, and to evaluate the acceptance of the SIMBA and readiness of the participants to apply built on the knowledge gained.

7.2 Methods

The study was conducted in May 2020 by the SIMBA team with the support of the Institute of Metabolism and Systems Research at the University of Birmingham. The session was conducted over the course of four hours.

7.2.1.1 Preparation for the session

Standardised transcripts of five anonymised real-life adrenal cases were prepared for the following conditions: adrenal incidentaloma, adrenocortical carcinoma (ACC), Cushing's syndrome, Conn's syndrome, and COVID-19 infection in a patient with congenital adrenal hyperplasia (CAH). Each transcript included medical history, clinical examinations, investigation results, imaging studies, management and follow-up plan, and validated by an expert in adrenal pathologies to ensure accuracy of the real-life scenarios. Figure 21 describes in detail the steps building up to SIMBA session and on the day itself.

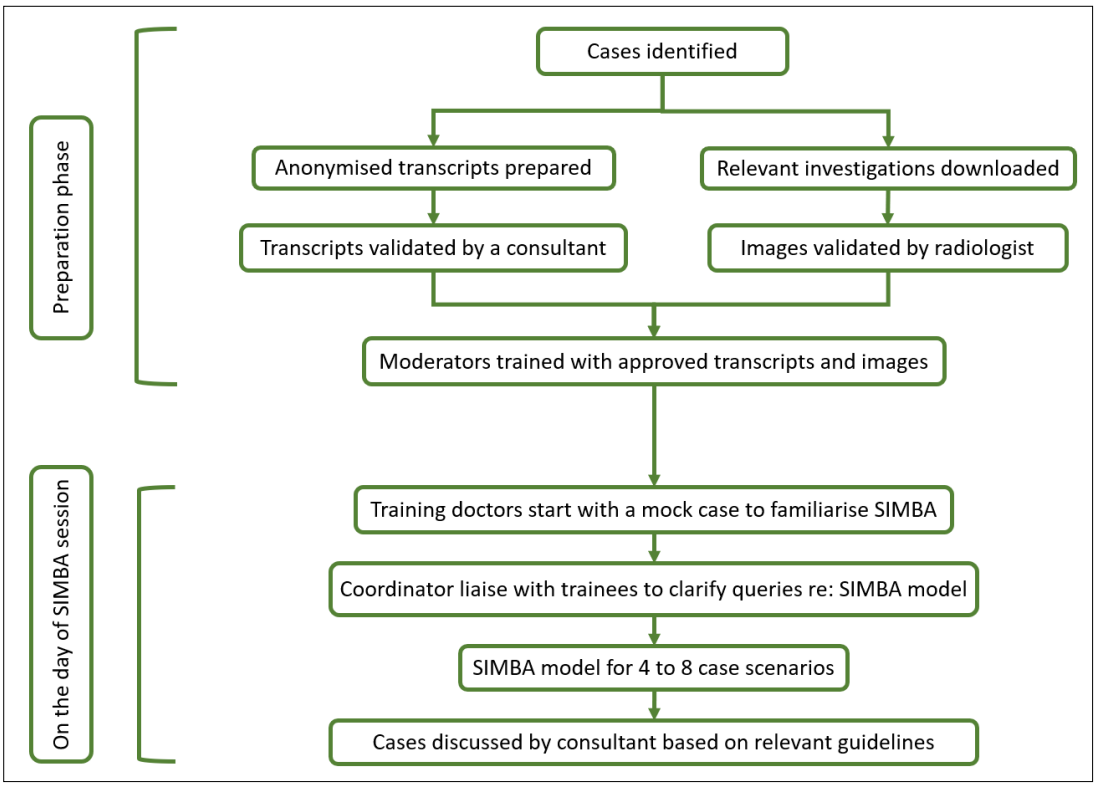


Figure 21. Flowchart of two stages—preparation and on-the-day—of the working model of SIMBA.

SIMBA session was facilitated by 29 medical students and 2 junior doctors who volunteered to be moderators for the session. Moderators interacted with the participants throughout the simulation and guided them to solve clinical scenarios. To ensure proficiency, prior to the actual session, all moderators were trained in six mock simulation sessions using the finalised transcripts.

The session was advertised on social media platforms (Facebook® and twitter®) by SIMBA and by endorsing organisations. Interested candidates registered for the session using Google forms. To keep the participants' identities anonymous, each participant was given a unique identification number (SIMBA ID). A couple of days before the session, participants were emailed their moderator's contact details and were asked to message their SIMBA ID to their assigned moderator in order to join the session and receive instructions throughout the session (links to pre- and post-SIMBA sessions, and Zoom®) as WhatsApp® was the only platform for communications. Furthermore, the participant must have messaged first in order to protect their personal information.

7.2.2 On the day of SIMBA adrenal session

7.2.2.1 Pre-SIMBA survey

Each participant was assigned to one moderator, whereas each moderator was guiding two to three participants through the online simulation. After the participants have contacted their moderator, they received a link to pre-SIMBA survey about their

socio-demographic information and self-reported confidence in managing various simulated and non-simulated adrenal cases. At this point, the participants were blinded as to which cases would be simulated. Once the submission of pre-SIMBA survey was confirmed by the moderator, simulation was initiated. The detailed description of the SIMBA session is described elsewhere (Melson et al. 2020a). The simulation provided participants with a concrete experience as per the first phase of the Kolb's learning cycle.

Following simulation, the participants were invited to a discussion and Q&A of simulated topics by expert endocrinologist with special interest in adrenal pathology via Zoom® to reflect on the concrete experience. The expert discussed the most suitable approach for each case including relevant investigations and management in the context of the most recent evidence-based international guidelines (Nieman et al. 2008; Lenders et al. 2014; Plouin et al. 2016; Nieman et al. 2015; Fassnacht et al. 2016; Bornstein et al. 2016; Funder et al. 2016; Fassnacht et al. 2018; Speiser et al. 2010; Wiebke Arlt et al. 2020). The expert highlighted the most important learning aspects for each case, after which the participants were given an opportunity to ask questions regarding simulated cases or similar clinical scenarios from their past experience.

7.2.2.2 Post-SIMBA survey

After the discussion, participants were invited to complete a post-SIMBA survey, same as the pre-SIMBA survey, but additionally including multiple choice questions (MCQs) related to simulated cases thus enabling abstraction of the knowledge received. To evaluate whether the participants would actively experiment in the future, the survey asked them an open-ended question regarding changes they intend to make in patient

care based on the experience gained during the session. Both surveys including the MCQs were developed by the SIMBA team without conducting reliability or validity testing.

7.2.3 Evaluation of SIMBA

The post-SIMBA evaluation form was designed to obtain feedback from participants regarding its impact. Kirkpatrick's training evaluation model was adopted, and two outcomes were identified (Kirkpatrick JD and Kirkpatrick WK 2016). Level 1 (reaction) was assessed with questions regarding engagement of the session. Level 2 (learning) involved acquiring self-perceived gain in core competencies and confidence levels in approaching various adrenal cases. Participants' attitude and self-reported confidence (Levels 1 and 2) were captured on 7-point Likert scale due to its simplicity to use and higher validity and reliability compared fewer response categories; additionally, respondents seem to find 7-point scale easier to complete (Preston and Colman 2000)Open-ended questions were also included in the surveys to explore participants' intentions to make behavioural changes in patient care following the session. Six domains of medical education based on the core competencies of Accreditation Council for Graduate Medical Education (ACGME) were also assessed using the question "Which of the following competency areas do you feel have been improved by today's teaching with SIMBA?", and participants were able to select as many competencies they found relevant (patient care, professionalism, knowledge on patient management, system-based practice, practice-based learning, communication skills).

7.2.4 Participants' assessment and feedback

7.2.4.1 SIMBA rating scale

Two SIMBA team members independently reviewed the WhatsApp® interaction between the moderator and the participant, and scored the participants' performance in each simulated case using an adapted version of the global rating scale (Figure 2) (Gerard et al. 2013). Seven items (history, examinations, initial investigations, diagnostic tests, imaging, clinical judgement, and management/follow-up) were assessed on a scale of 1 (not done) to 5 (excellent), giving a minimum score of 7 and maximum score of 35. Scores indicate relevance and accuracy of approach to the case in its various components (Figure 22). The assessment included written feedback for each case based on Pendleton's model of feedback (Pendleton D et al. 2003) and the scores were emailed to the participants on the following day of the session.

Score	1	2	3	4	5	Score
Eliciting history	Not done	25% of history	50% of history	75% of history	100% of history	**<<A>>**
Physical examination	Not done	25% of relevant and many irrelevant examinations	50% of relevant and some irrelevant examinations	75% of relevant and few irrelevant examinations	100% of relevant and very few to no irrelevant examinations	**<<B>>**
Initial investigations	Not done	25% of relevant and many irrelevant investigations	50% of relevant and some irrelevant investigations	75% of relevant and few irrelevant investigations	100% of relevant and very few to no irrelevant investigations	**<<C>>**
Diagnostic tests	Not done	25% of relevant and many irrelevant diagnostics	50% of relevant and some irrelevant diagnostics	75% of relevant and few irrelevant diagnostics	100% of relevant and very few to no irrelevant diagnostics	**<<D>>**
Imaging	Not done	25% of relevant and many irrelevant imaging	50% of relevant and some irrelevant imaging	75% of relevant and few irrelevant imaging	100% of relevant and very few to no irrelevant imaging	**<<E>>**
Clinical judgement	Not done	Inaccurate diagnosis and rationale	Accurate diagnosis with no rationale	Accurate diagnosis with incomplete rationale	Accurate diagnosis with complete rationale	**<<F>>**
Management and follow up	Not done	Inaccurate management plan	Accurate plan with no rationale	Accurate plan with incomplete rationale	Accurate plan with complete rationale	**<<G>>**

Figure 22. SIMBA rating scale, adapted from the Global Rating Scale by Gerard et al(Gerard et al. 2013).

7.2.5 Statistical analysis

To capture the differences in confidence levels and explore the impact of the SIMBA session, the adrenal cases included in the questionnaire were divided into two categories: (a) simulated: adrenal incidentaloma >4cm, ACC, Conn's syndrome, Cushing's syndrome, and COVID-19 infection in a patient with CAH; and (b) non-simulated: bilateral macronodular adrenal hyperplasia (BMNAH), Addison's disease, secondary adrenal insufficiency, androgen secreting adrenal tumours, adrenal incidentaloma <4cm, phaeochromocytoma, and adrenal metastases.

Using agree-disagree Likert scale, we aimed to capture the degree of participants' confidence. Hence, the data extracted from pre- and post-SIMBA survey were categorised into 3 groups: (i) confident: for those who responded with "strongly agree" and "agree"; (ii) unsure: for those who responded with "agree somewhat", "undecided", and "disagree somewhat"; (iii) not confident: for those who responded with "strongly disagree" and "disagree". Only those participants who completed both pre- and post-SIMBA evaluation forms were included. A Wilcoxon signed-rank test was used to statistically investigate differences in confidence levels between simulated and non-simulated cases of matched pairs pre- and post-SIMBA; performed using Stata (Stata/SE 16.0). Statistical significance was accepted at 95% confidence level (significance set at $p<0.05$). The change in confidence levels of managing cases pre- and post-SIMBA are reported as percentages and presented in bar charts.

Additionally, in the post-SIMBA evaluation form, participants were asked close- and open-ended questions for feedback and key takeaway from the SIMBA Adrenal session. Findings from close-ended responses are reported in frequencies and percentages. Material collected from open-ended questions were analysed using a

single coder using Braun and Clarke method of thematic analysis. Responses from the free text sections were first read and familiarised, systematically identifying main points of the text and attaching labels/codes to capture the main ideas. Relevant and recurrent codes were then collated into themes inductively (data-driven themes) and reviewed. All themes identified are presented in the table. Examples were chosen to encompass the various perspectives, leaving out repetition.

7.3 Ethics approval and consent to participate

The protocol was approved, and the study was conducted as part of specialist training improvement initiative commissioned by Health Education West Midlands Diabetes and Endocrinology specialist training committee. The specialist training committee, consisting of consultants, trainee representatives and other administrative staff from the deanery oversee the administration, management and delivery of training in our region for diabetes and endocrinology(Scobie 2012). Participation into this session was voluntary and all participants were informed using a General Data Protection Regulation (GDPR) statement during registration. A mandatory tick-box consenting to participation was included in registration form to ensure voluntary consent. All methods were carried out in accordance with relevant guidelines and regulations.

7.4 Results

Out of 40 participants, 33 (82.5%) completed both pre- and post-SIMBA surveys and were included in the analyses. This includes 18 (54.5%) participants from the UK (West Midlands (n=13), London (n=1), North West (n=2), and one participant did not complete specific location data), and 15 (45.5%) internationally (Bosnia and

Herzegovina (n=1), Cote d'Ivoire (n=2), Georgia (n=4), India (n=1), Ireland (n=2), Spain (n=2), Syria (n=1), Turkey (n=1), and Ukraine (n=1)). These participants comprise of consultants (n=6), specialist (n=1), senior residents/fellows (n=6), specialty trainee registrars (n=15), resident physicians (n=3), medical doctor (n=1), and currently out of training programme (n=1).

7.4.1 Participants' confidence levels

A Wilcoxon signed-rank test demonstrated SIMBA session elicited a statistically significant improvement in participants' self-reported confidence in their approach to simulated cases, as well as in non-simulated conditions (Table 19, Figure 23). No statistically significant improvement was observed when participants were assessed for their confidence in approach to Addison's disease (Z=1.414, p=0.2891).

Table 19: Changes in participants' confidence levels post-SIMBA session for approaching simulated and non-simulated cases with p values.

Case	**Confident**	**Unsure**	**Not confident**	**Significance**
Simulated cases				
Adrenal incidentaloma >4cm	+30.3%	-21.3%	-9.1%	Z=3.152, P=0.0020
ACC	+45.5%	-33.4%	-12.1%	Z=3.970, P<0.0001
Conn's syndrome	+36.3%	-27.3%	-9.0%	Z=3.873, P<0.0001

Cushing's syndrome	+39.3%	-36.3%	-3.0%	Z=3.742, P=0.0001
COVID-19 infection in a patient with CAH	+30.3%	-15.1%	-15.2%	Z=3.036, P=0.0029
Non-simulated cases				
BMNAH	+45.5%	-39.4%	-6.1%	Z=4.123, P<0.0001
Addison's disease	+12.1%	-12.1%	0.0%	Z=1.414, P=0.2891
Secondary adrenal insufficiency	+24.2%	-18.1%	-3.0%	Z=2.326, P=0.0332
Androgen secreting adrenal tumours	+39.3%	-24.2%	-15.2%	Z=3.847, P<0.0001
Adrenal incidentaloma <4cm	+30.3%	-21.3%	-9.1%	Z=3.152, P=0.0020
Phaeochromocytoma	+33.3%	-30.3%	-3.1%	Z=3.464, P=0.0005
Adrenal metastases	+33.3%	-15.1%	-18.2%	Z=3.989, P<0.0001

ACC, adrenocortical carcinoma; COVID-19, novel coronavirus disease; CAH, congenital adrenal hyperplasia; BMNAH, bilateral macronodular adrenal hyperplasia.

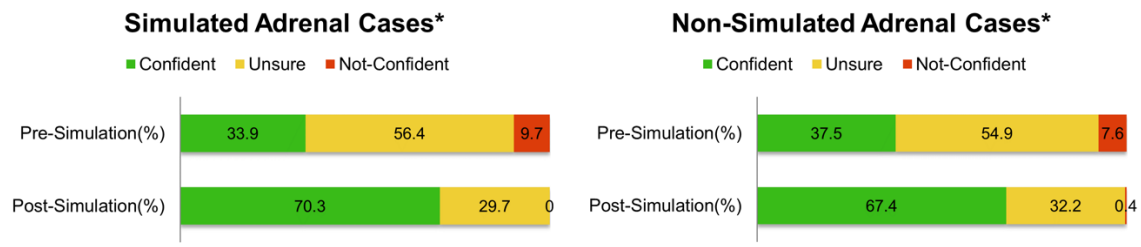


*Figure 23: Illustration of changes in participants' confidence levels for managing simulated vs. non-simulated adrenal cases. *p<0.0001.*

7.4.2 Participants' feedback/satisfaction and key takeaway

91.1% (n=30/33) strongly agreed/agreed the session was engaging. 84.9% (n=28/33) reported the session accommodated their personal learning style. 97.0% (n=32/33) agreed the chair provided balanced and evidence-based, where possible, approach to the cases. 93.9% (n=31/33) found the simulated topics applicable to their clinical practice, and the session impactful at a personal level. 97.0% (n=32/33) found the content of the session translatable to patient care. Six domains of medical education based on the core competencies by Accreditation Council for Graduate Medical Education (ACGME) were assessed and seen to improve: knowledge on patient management – 81.8% (n=27/33), practice-based learning – 75.8% (n=25/33), patient care – 45.5% (n=15/33), systems-based practice – 39.4% (n=13/33), professionalism – 30.3% (n=10/33), and communication skills – 12.1% (n=4/33) (Figure 24).

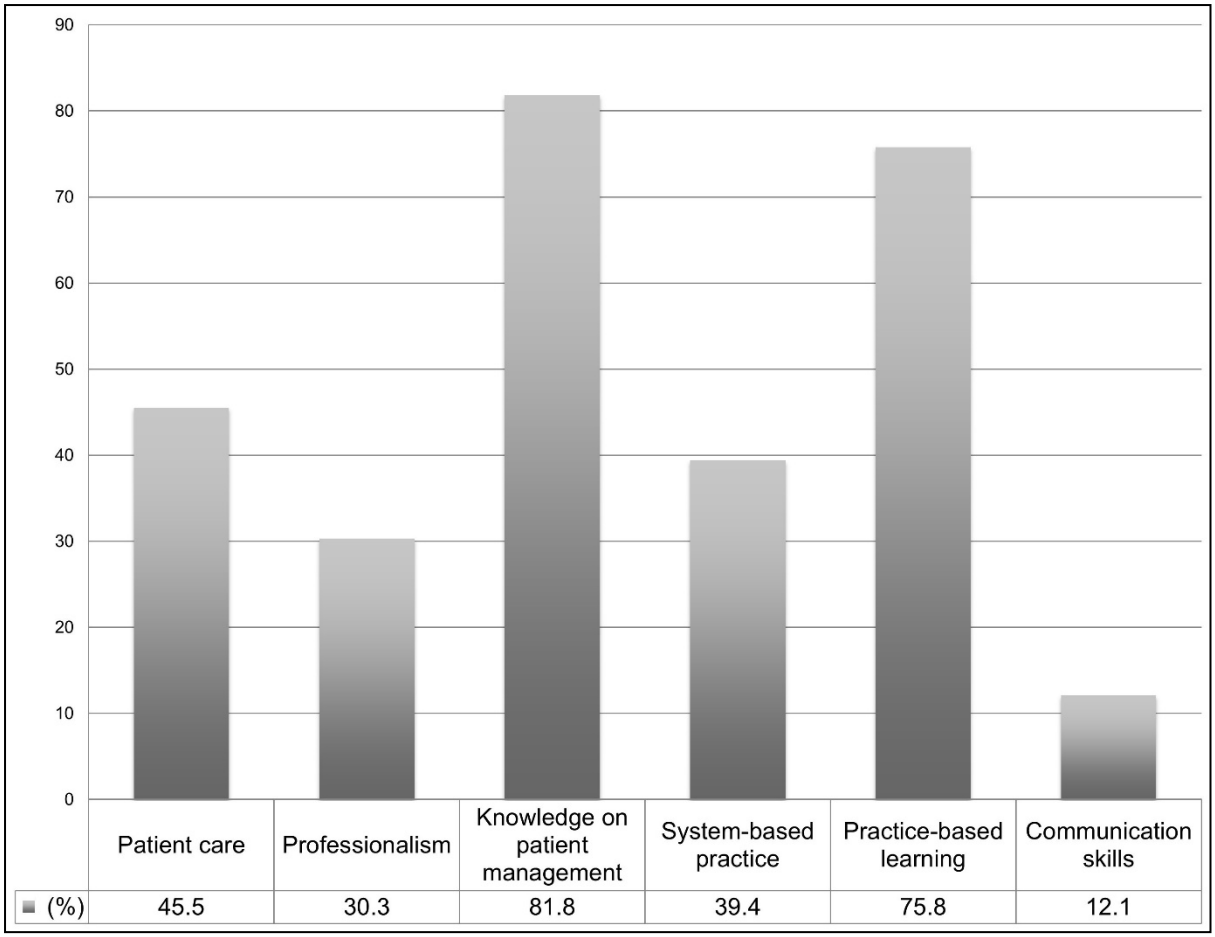


Figure 24: Illustration of changes in Six domains of medical education based on the core competencies proposed by Accreditation Council for Graduate Medical Education (ACGME).

7.4.3 Thematic Analysis of open-ended questions

Answers to the open questions were analysed to identify broad themes represented within them. 54.5% (n=18/33) provided a response to the question “as a result of what I have learned today, I intend to make the following changes to my practice that I believe will impact my patients’ care in a positive way”, suggesting a positive influence that can be translated to patient care (Figure 25A). 36.4% (n=12/33) responded to the open-ended section to provide “additional comments regarding the chair’s

contribution", and 8.3% (n=1/33) was negative, based on technical issues during the session, and the participant was unable to comment on the chair's contribution. The remaining 33.3% (n=11/33) responses were positive (Figure 25B).

A

Theme	Examples
Professional competence	*"Evidence based practice to include latest guidelines…"* *"Read more updated resources"* *"Better understanding of pathophysiology"*
Specific changes in clinical practice	*"COVID 19 and adrenal insufficiency treatment strategy…"* *"Radiology follow up in adrenocortical carcinoma"* *"Avoid unnecessary follow-up imaging…"* *"Request appropriate imaging for incidentaloma"* *"…unenhanced HU not useful in heterogeneous adrenal lesions"*
Personal behavioural changes	*"I am more confident in assessing patients…"* *"To practice more and attend MDT"* *"Because I am more confident, I am going to explore incidentalomas better"* *"…to improve my analytical methods and work on improving clinical acumen"*

B

Theme	Examples
Overall rating	"Great effort put in during difficult COVID period" *"Excellent discussion"* *"…so* knowledgeable, highly appreciated" *"Excellent, very encouraging"*
Evidence-based	*"Evidence-based"*
Delivery	**Positive** "Always a guide which likes to interact rather than giving only guidelines" *"Very professional"* *"Good and interesting case mix"* *"Highlighted important management steps"* **Negative** *"Audio (speakers and headphone) did not work at my end despite repeated attempts…"*

Figure 25: Thematic tabulation of responses to open-ended questions. (A) "as a result of what I have learned today, I intend to make the following changes to my practice that I believe will impact my patients' care in a positive way", and (B) "additional comments regarding chair's contribution".

7.5 Discussion

SIMBA was well received by the participants and proved to be an effective learning model to increase the self-reported confidence level in managing various cases on adrenal pathologies. During a pandemic, moving our SIMBA approach online, combining use of WhatsApp® and Zoom® to deliver the session, played a crucial role in the context of distance learning to provide sustained medical education. This is relevant for the ability of SIMBA to deliver enhanced training across the globe, with minimal resources and low cost.

The results provide insight into participants' perceived outcomes of the session, demonstrating the Kolb's 4-stage experiential learning cycle (David A. Kolb 1984), according to which the SIMBA model was constructed. This process begins with concrete experience—a SIMBA session conducted via WhatsApp®, where the participants were able to work through the motion of realistic case scenarios. Participants' satisfaction from this session was high, indicating that the model was well-received. Most participants found the SIMBA model engaging and accommodating to their personal learning style. This demonstrates that participants from various backgrounds were able to quickly familiarise themselves and adapt with the concept. SIMBA as a model combines e-learning and SBL and evolved with the learning preferences and strengths of the learners of this digital era. This is in line with suggestions to utilise instructions and environments learners are familiar with to improve responsiveness and enhance learning (Chapman and Calhoun 2006; Urick 2017). Further, studies have found that training professionals respond to different learning preferences between generational groups, with younger generations finding greater comfort in technology-based training (Urick 2017).

The second stage of the cycle—reflective observation—refers to the Zoom® discussion and Q&A session following the simulation. An expert discussed each case with evidence-based rationale. Participants were able to compare what was done differently, reflecting on their personal performance during the simulation. 97.0% of the respondents strongly agreed/agreed that the chair's contribution was evidence-based, and thematic analysis of feedback indicated positive overall rating. Overall, feedback regarding the delivery of the session demonstrated reflective observation where participants felt "important management steps" were addressed, and that the chair guided the participants through the case explaining current evidence, rather than spelling out the guidelines.

In the third stage of the Kolb's cycle of abstract conceptualisation, assimilation of the new information was facilitated by the post-SIMBA MCQs on the simulated cases. Throughout the session, participants were able to conceptualise the learnt key points and rationalise/make sense of them, to then add to their existing knowledge. Significant improvements in self-reported confidence levels of simulated cases were observed, and surprisingly, in non-simulated cases as well, likely due to the similarity in topics, requiring a similar approach. Additionally, topics such as phaeochromocytoma were reviewed during discussion which may have influenced participants' increased confidence levels for non-simulated case scenarios. Feedback on participants' performance was provided via the SIMBA assessment tool using an adapted Global Rating Scale and Pendleton's method to allow reflection.

In the fourth stage of the Kolb's learning cycle—active experimentation—the participant builds on the knowledge in their personal clinical practice. An important

finding from this session was the positive impact on participants' personal and professional learning, potentially translating to personal knowledge and patient care. This matches patient management and practice-based learning components of the ACGME's core competencies. Practice-based learning refers to achieving recertification following initial certification through continued education in the midst of daily clinical practice, taking into account the constantly evolving nature of the latter (Staton et al. 2007). This supports the aims of the SIMBA model, which employs the theory of connectivism, to disseminate latest evidence on the management of patients in the topic, while guiding participants through a scenario to allow subsequent self-appraisal according to scientific evidence, in a safe environment. Additionally, participants responded with intentions to improve aspects of their professional competence and to implement specific changes in clinical practice and personal behaviour. These can be anticipated to have long-term positive consequences in clinically-relevant settings, with a perceived ability to improve patient care.

7.5.1 Limitations and future research

While providing beneficial insight and supporting evidence, the study has certain limitations. While we were able to assess the effectiveness of SIMBA model using Kirkpatrick's levels 1 (reaction) and 2 (learning) in our pre- and post-SIMBA evaluation forms, levels 3 (behaviour) and level 4 (results/outcomes) translating to behavioural changes and longitudinal measurement of our model's impact remains a challenge. Our evaluation is currently limited to self-reported perceptions of improvement and willingness to apply the acquired knowledge and skills to the clinical practice. However, intentions may fail to be translated to actions due to intention-to-action gap (Desveaux et al. 2021). Another limitation of the study is that the measures used were researcher-developed, without evidence of validity and reliability, and dataset for

thematic analysis was small. Further longitudinal evaluation is needed to determine whether actual clinical competence is subsequently improved. Another potential line of research would be to investigate the cognitive outcomes such as knowledge and retention of information, in addition to the current non-cognitive outcomes evaluated (self-reported confidence levels, perceived impact, personal plans).

Furthermore, acceptance of the model may be biased, by attracting participants who were particularly intrigued by the unconventional method of delivery (WhatsApp®) offered by SIMBA and chose to participate. These participants might represent a population of learners who prefer the use of modern technology and are keen to participate in novel and innovative methods of learning. This sample selection bias may disproportionately tilt the positive response from respondents, leading to false belief of population acceptance of the model. Further research investigating how individual differences such as learning styles and personality play a role in acceptability and preference for the model would be interesting. Nevertheless, the results demonstrate participants' satisfaction with the session.

7.6 Conclusion

The SIMBA model mirrors the Kolb's experiential learning theory from practical point of view. The results demonstrate the positive reception of SIMBA highlighting the advantages of utilising social media as a platform for medical education. Improvements in confidence levels and core competencies using existing freeware social media software paves way for such sessions to be conducted at a low cost internationally.

7.7 Future of SIMBA

The results from this SIMBA Adrenal session provide evidence that the delivery of SBL via social media is a promising strategy, with a potential of engaging healthcare professionals worldwide. We aim to further expand the reach of SIMBA with more frequent sessions to encourage globalisation and bridge existing gaps in healthcare. Additionally, SIMBA may be used in future credentialing and assessment processes. Thus, our vision is to achieve low-cost teaching delivery, with minimal resources required to organise each session.

8 Simulation via Instant Messaging - Birmingham Advance helps to narrow knowledge and expectations gap between clinicians and women with polycystic ovary syndrome: SIMBA-PCOS

8.1 Introduction

Patient and public involvement (PPI) is important to drive towards an equal partnership in clinical decision making and patient-centred care (Howe and Anderson 2003; S. W. Dijk, Duijzer, and Wienold 2020). The General Medical Council (GMC) first highlighted its importance in the standards for undergraduate education in “Tomorrow’s Doctors” published in 2009 and later in the postgraduate ‘Standard for Deaneries’ calling for deaneries to ensure active and meaningful involvement of patients and public in doctors’ training (General Medical Council 2009)(Medical Council 2015). Up until then, patients’ role in education was indirect or passive with limited contribution to curriculum development and its delivery, as well as student assessment (“Oxford Textbook of Medical Education” 2014). More active roles are seen in nursing and social work education including patients’ storytelling, teaching in clinical and communication skills, co-teaching with faculty and mentoring programmes.

Polycystic ovary syndrome (PCOS) is a common condition affecting about 10-20% of women worldwide (WA et al. 2010). Following the diagnosis, women with PCOS are often left with unmet information needs which can further impact their mental health (Gibson-Helm et al. 2017). This is probably due to the diverse symptoms of PCOS and a lack of awareness amongst Healthcare Professionals (HCPs) (and patients) regarding the international consensus guidelines for managing women with PCOS (Teede, Misso, Costello, Dokras, Laven, Moran, et al. 2018a). Further, current educational interventions towards improving knowledge, attitude and practices of PCOS amongst HCPs has limited patient and public involvement (PPI). Therefore, there is an urgent need to establish an effective educational intervention for both HCPs and women with PCOS to improve patient and public experience on the diagnosis and management of PCOS.

Simulation via Instant Messaging - Birmingham Advanced (SIMBA) is a virtual simulation platform that has been successfully used in postgraduate medical education (Melson E et al. 2020a). In SIMBA, learners undergo simulation-based learning through WhatsApp managing various real-life cases from a patient presentation to their management and follow-up. This model has been proven to increase learners' confidence in their approach to the simulated cases with a good acceptance rate and reproducibility (Melson et al. 2021; M. G et al. 2021a; E. N et al. 2021; Melson E et al. 2020b). However, previous SIMBA sessions have been limited to HCPs. The aim of this study was to evaluate the effectiveness of SIMBA as an educational intervention for PCOS in both HCPs and people with PCOS. Additionally, we aimed to identify gaps in knowledge and expectations between women with PCOS and HCPs involved in their care.

8.2 Methods

We designed an educational intervention for both HCPs and women with PCOS using SIMBA. A mixed-method research design was used to answer our research questions. The study is divided into two arms: one focussed on HCPs (SIMBA-HCP) and another arm involving people with PCOS (SIMBA-PCOS). While HCPs underwent simulation-based learning focusing on four case scenarios of PCOS (PCOS and skin, PCOS and weight excess, PCOS and fertility, and PCOS and menstrual irregularities), people with PCOS underwent with workshop-style learning in parallel, using identical cases. Both groups then came together for discussion of the cases with the experts via Zoom (Figure 26). These cases are designed based on PCOS clinical guidelines as well as previous study on learning needs of both women with PCOS and HCPs (M et al. 2018; Teede, Misso, Costello, Dokras, Laven, Moran, et al. 2018b). With assistance from specialist endocrinologists and gynaecologists, these scenarios were developed into anonymised transcripts which included information on past medical history, clinical examinations, laboratory investigations and imaging results. Moderators for WhatsApp were recruited through advertisements, trained in each of the simulated scenarios and interacted with HCPs as moderators on the day of the simulation. Details for each arm of the session are outlined below.

8.2.1 SIMBA-HCP

HCPs interacted with moderators on WhatsApp simulating the cases presented to them. They were expected to take a history, request relevant investigations, and arrive at a diagnosis and management plan for the cases. The information requested by the HCPs through WhatsApp will be copied and pasted by the moderators from the pre-prepared transcripts. If the requested information was not available in transcripts, the moderator replied with ‘information requested is not available’. After completing all the simulated cases, they were invited for a discussion and Q&A session. We have published a detailed description of various steps involved in the process previously (Melson et al. 2020c).

8.2.2 SIMBA-PCOS

In parallel, people with PCOS were invited to participate in a workshop-style learning. Here, the same transcripts of cases used in SIMBA-HCP were presented to participants sharing information on how people with PCOS are managed in real-life. This was followed with a discussion of the cases concentrating on ‘what was done well’, ‘what could be done better’, and ‘what was not covered’ during the case management. A participant was invited to volunteer and summarise the discussions of each case which was then presented to the audience during discussion.

8.2.3 Case discussion with Q&A

This session brought together HCPs and women with PCOS to discuss the cases in detail. 30 minutes were allocated per case. In the first 5 minutes, experts presented the case to the group. This was followed by discussion of the cases with reference to evidence-based guidelines (5 minutes). In the following five minutes, HCPs who participated in the simulation asked their queries on the cases. The participant from SIMBA-PCOS group who summarised the discussions shared their findings on that case for five minutes. Each session ended after a 10-minute discussion on challenges of managing the cases to identify the gap in knowledge and expectations between women with PCOS and their HCPs.

A mixed quantitative and qualitative research methods was used to answer our research questions. Data were extracted from the pre- and post-SIMBA surveys. Participants who completed both pre- and post-SIMBA surveys were included in the analysis. For SIMBA-HCP, baseline characteristics including location and level of training were measured. Pre- and post-SIMBA questionnaires were used to evaluate the effectiveness. Participants' self-reported confidence levels in managing each case were measured using a Likert scale in investigation and management of fertility, skin, weight, menstrual irregularities, mental health, weight, and endometrial cancer. Six domains of medical education based on the core competencies of Accreditation Council for Graduate Medical Education (ACGME) were also assessed (Staton et al. 2007). Participants were able to select as many competencies as they found relevant to the session including patient care, professionalism, knowledge on patient management, system-based practice, practice-based learning, communication skills. For SIMBA-PCOS, demographic information including age, ethnicity, location, and years since

diagnosis were identified. Effectiveness of SIMBA in increasing knowledge on PCOS for women were explored through a series of questions and measured using a 5-point Likert scale. Pre- and post-SIMBA questionnaires were used to evaluate the effectiveness. These consisted of questions on knowledge regarding the conditions pre- and post-simulation. The workshop for SIMBA-PCOS and discussion sessions were recorded by Zoom and transcribed. Thematic analyses were used to analyse the data obtained from the session's recording to help answer our research question.

8.2.4 Statistical analyses

Participants' confidence was measured using a 7-point Likert scale (Strongly agree to strongly disagree) within three domains: clinicians were assessed on their confidence in managing PCOS-related issues, and patients were asked for their confidence in clinicians' management approaches for PCOS-related issues. This data was recoded into three categories: Confident: strongly agree, and agree; Unsure: agree somewhat, undecided, and disagree somewhat; and Not Confident: strongly disagree and disagree.

Participants who completed both pre- and post-SIMBA questionnaires were included in the analysis. Statistical analysis of quantitative data was performed using STATA (STATA/SE 17.0 for Mac). Confidence levels are reported in frequencies and percentages and are presented as bar charts. The Wilcoxon Signed-Rank test was used to compare pre- and post-SIMBA self-reported confidence levels. Statistical significance was accepted at a 95% confidence level. Significant results are highlighted using an asterisk. In addition, improvement in participants' confidence levels of simulated cases (Skin, Weight, Fertility and Menstruation-related issues) compared

to non-simulated cases (Menopause, Diabetes, Mental health, Endometrial cancer-related issues), followed by all sessions combined was included in comparison and reported as above.

Post-SIMBA questionnaires also included open-ended questions regarding overall feedback of the session. The responses were reviewed and combined in an inductive thematic analysis approach to identify common themes of feedback.

8.3 Results

8.3.1 SIMBA-HCP (HCP)

25 participants completed both pre- and post-SIMBA questionnaires. Characteristics of participants are described in

Table 20. Feedback on the SIMBA model highlighted clinicians' improved competence in patient care (64%), professionalism (28.0%), knowledge of patient management (72.0%), system-based practice (32.0%), practice-based learning (60%) and communication skills (40%). In addition, 88.0% strongly agreed/agreed that simulated topics were applicable to their practice, and 100% of participants would attend similar SIMBA sessions in the future.

Clinician's confidence in managing PCOS-related issues increased post-SIMBA for all eight domains of PCOS measured in this session (skin, weight, fertility, menstruation, menopause, diabetes, mental health, and endometrial cancer). Simulated cases and non-simulated cases showed a 41.0% and 40.0% increase in confidence respectively ($p<0.001$), with all cases combined showing 40.5% increase in confidence ($p<0.001$) (Figure 27A).

Thematic analysis of feedback from participants to open-ended questions (n=13, 52%) showed positive rating for the session with some constructive comments for future sessions. Suggestions focused on three themes: time considerations, Q&A discussion format, and session content. Participants reflected on needing more time for cases and discussion to allow for more questions to be answered. There was a call for a more focus on assessment and management of the cases during the Q&A discussion.

8.3.2 SIMBA-PCOS (women with PCOS)

Fifteen women with PCOS attended the session. 12 completed both pre- and post-session surveys. Table 21 shows the demographics of women with PCOS who attended the session. The median age of PCOS diagnosis (n=10) were 20.5 (IQR 19-25). 83.3% (n=10) of people were aware of the criteria for diagnosis of PCOS, and no significant difference after the session was noted (p=1.000).

90% HCPs strongly agreed/agreed that SIMBA-PCOS benefits people with PCOS to understand better about their condition and understand clinician's perspectives on the diagnosis and management of PCOS. In addition, 100% strongly agreed/agreed SIMBA-PCOS benefits clinicians to understand patients' perspectives on the diagnosis and management of PCOS.

PPI participants' confidence in HCPs to manage PCOS-related issues was not different after the session when examining each of the eight PCOS domains covered. However, we saw 6.25% increase in confidence when all responses combined (p=0.0141) (Figure 27B). Similarly, PPI participants' confidence in HCPs' awareness of options available for the management of PCOS-related issues increased in for simulated cases (+16.6%, p=0.02), non-simulated cases (18.8%, p=0.006), and for all cases (+17.7%, p=0.0002) (Figure 27C).

We identified four themes from the recordings that summarised participants' experience on their diagnosis and management of PCOS. Firstly, the delay in diagnosis of PCOS was also commonly mentioned in the discussion. Secondly, people with PCOS felt they were not given sufficient information upon the diagnosis of PCOS including the potential of developing other symptoms and complications of PCOS. Thirdly, they thought clinicians focussed on one symptom of PCOS and not address other co-morbidities, especially mental health issues associated with PCOS. Finally, patient-centred care was below par in the management of PCOS, such as not giving enough information regarding prescribed drugs and their side effects. Table 22 summarises the thematic analysis from the workshop involving women with PCOS.

Thematic analysis of feedback from the questionnaire for patients revealed positive and constructive feedback. 83.3% responded positively, reviewing the workshop with

recurring feedback themes referencing informative, engaging discussion and organised structure. Suggestions for improvement for future sessions centred around the format of the session advising breaking down the cases over sessions or reducing the number of cases to allow for future exploration of cases, together with organising structured feedback for future session discussions allowing the equal contribution of all participants and representation from a wider range of patient groups.

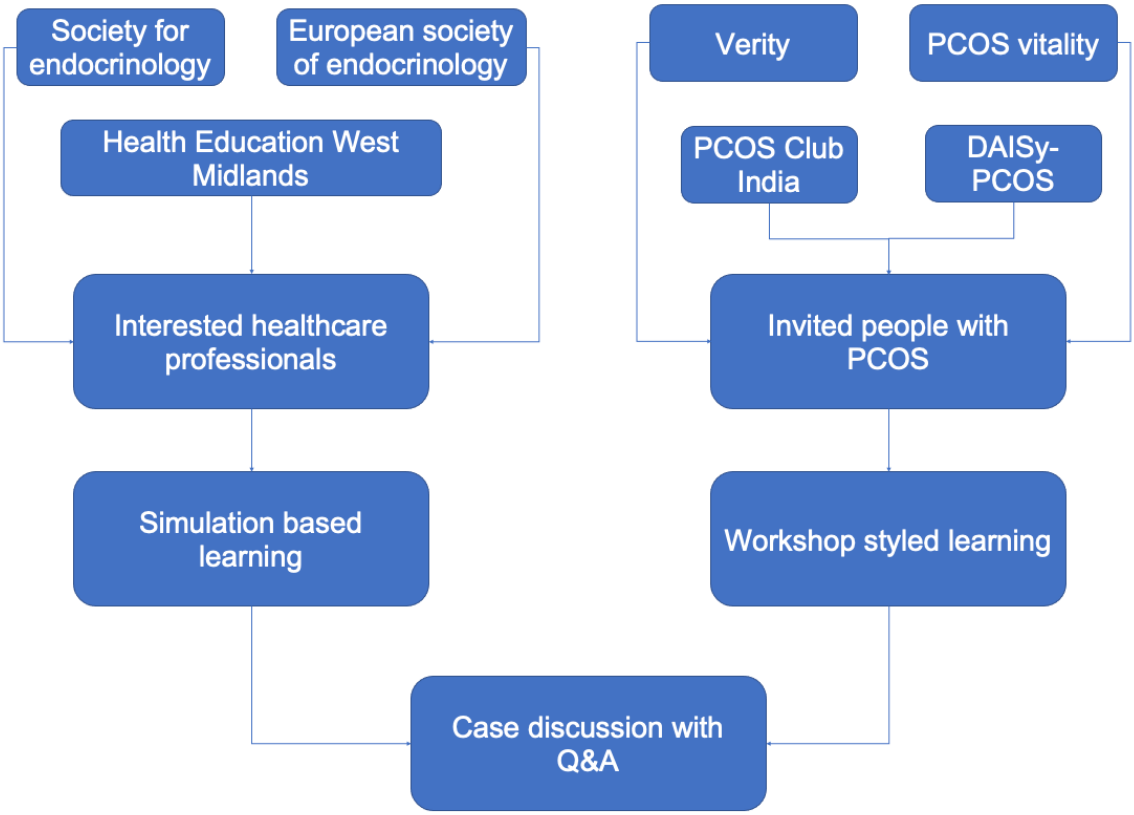
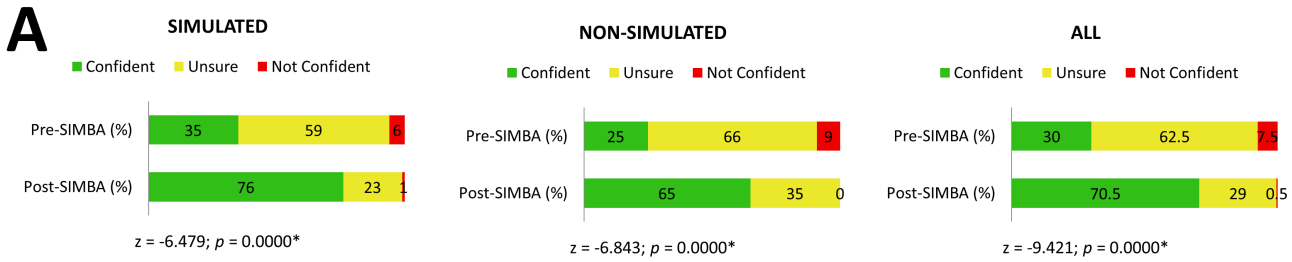
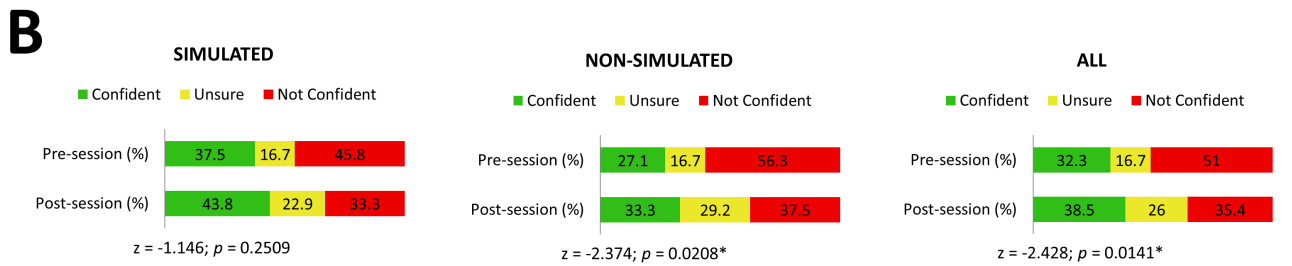


Figure 26: Overview of SIMBA-PCOS session


A
SIMULATED
Confident
Unsure
Not Confident
Pre-SIMBA (%)
35
59
6
Post-SIMBA (%)
76
23
1
z = -6.479; p = 0.0000*
NON-SIMULATED
Confident
Unsure
Not Confident
Pre-SIMBA (%)
25
66
9
Post-SIMBA (%)
65
35
0
z = -6.843; p = 0.0000*
ALL
Confident
Unsure
Not Confident
Pre-SIMBA (%)
30
62.5
7.5
Post-SIMBA (%)
70.5
29
0.5
z = -9.421; p = 0.0000*


B
SIMULATED
Confident
Unsure
Not Confident
Pre-session (%)
37.5
16.7
45.8
Post-session (%)
43.8
22.9
33.3
z = -1.146; p = 0.2509
NON-SIMULATED
Confident
Unsure
Not Confident
Pre-session (%)
27.1
16.7
56.3
Post-session (%)
33.3
29.2
37.5
z = -2.374; p = 0.0208*
ALL
Confident
Unsure
Not Confident
Pre-session (%)
32.3
16.7
51
Post-session (%)
38.5
26
35.4
z = -2.428; p = 0.0141*

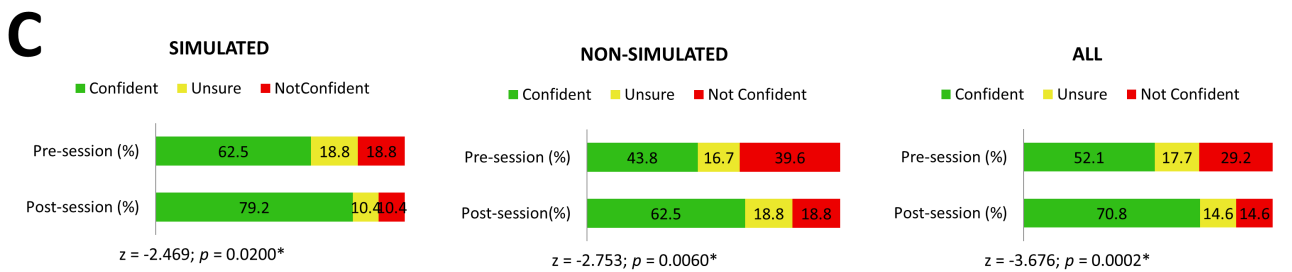

C
SIMULATED
Confident
Unsure
NotConfident
Pre-session (%)
62.5
18.8
18.8
Post-session (%)
79.2
10.4
10.4
z = -2.469; p = 0.0200*
NON-SIMULATED
Confident
Unsure
Not Confident
Pre-session (%)
43.8
16.7
39.6
Post-session(%)
62.5
18.8
18.8
z = -2.753; p = 0.0060*
ALL
Confident
Unsure
Not Confident
Pre-session (%)
52.1
17.7
29.2
Post-session (%)
70.8
14.6
14.6
z = -3.676; p = 0.0002*

Figure 27: ***A)*** *Illustration of changes in healthcare professionals' confidence levels for managing simulated vs non-simulated cases.* ***B)*** *Illustration of changes in confidence levels of women with PCOS for their confidence in HCPs to manage simulated vs non-simulated PCOS-related issues.* ***C)*** *Illustration of changes in confidence levels of women with PCOS for their confidence in HCPs' awareness of options available for the management of simulated vs non-simulated PCOS-related issues.*

Table 20: Demographics of HCPs attending SIMBA-PCOS.

	Frequency, n (%)
Country of origin	
UK	13 (52%)
Non-UK	12 (48%)
Training level	
Specialist	2 (8)
Specialist in training	15 (60)
Non-specialist	6 (24)
Other	2 (8)

Table 21: Demographics of women with PCOS attending SIMBA-PCOS.

	Frequency, n/N
Country of origin	
UK	9/15
Non-UK	6/15
Ethnicity	
White	9/15
Asian	5/15
Black	1/15

Table 22: Themes identified from the workshop involving women with PCOS.

Themes	Quotes
Diagnosis experience of PCOS	"sort of like the mental health side of things, with a PCOS and that is diagnosis and university or, at any age is something which was neglected. My diagnosis and something which has been the most difficult part and having being somewhat of a history of an eating disorder which i'm very open about it was a massive massive trigger " "I actually think it's really quite relevant to make clinicians aware that PCOS doesn't have to just be. sort of it can happen anytime it doesn't you know our people may become more aware of it at different times you know, like we, you know as women, a lot of us do end up tend to be on contraceptive" "they've had one child, but then they develop PCOS you are the only find that there's an issue going up to the second child or sort of later on, was something that I wanted to mention" "10 years ago was considered something (PCOS) that you, you get when you're an adolescent" (from clinican)

Clinicians seem to focus only on one symptom but not addressing other comorbidities	"No real discussion about obesity" "…support herself and clearly a mom sister has had sorts of history there, but I think it's the idea of treating the patient as a whole needs to come across the soul being" "As well as emotional support we're having to deal with all of these diagnoses at the age of 18 and potentially off in university by yourself, without a network" "…the thing that jumped out to me is that the patient originally presented with unexplained weight loss and yet, at the end of her diagnosis" "That when it's kind of brushed off as like oh yeah it's hair loss. Sometimes it feels almost like a cosmetic thing but it's so much more than a cosmetic thing, and so I would have liked to have seen a bit more about that.." "So what was done well and people did like that the blood tests included lots of other conditions, and they also thought it was good that the patient was referred to other speciality is like the diabetic team and for management of their diabetes" (on clinicians' approach in the transcript)

	“And so I think that's really important but that was done very well, because at 18 she might not need to consider the fertility side, but the hair access hair and weight gain and all of that and metabolic aspects are important to be addressed” (on clinicians’ approach in the transcript) “I actually had to cry out to my GP be like I need mental health support and this time because. I like the kind of the fertility issues don't bother me their regular periods I don't care about that, but actually trying to navigate with my mental health and weight gain and not having any support in that I can't do that online” “And you know the irregular periods oh you've not had them for months have you had a stressful stress in your life are you doing exams, whatever that can really be brushed off in that way. And the weight gains gone up and again there's can sometimes be stigma around oh you're just being a lazy patient and stuff so it's more it's more of this, the subtle PCOS presentation and maybe isn't obvious to someone who doesn't specialize in the condition” “But it's that patient having the knowledge to actually going through this treatment they need to look at the whole self that they're dealing with and that the fertility issues may then cause other issues and not be afraid to actually go and speak to the GP”

	“Some will say when you're trying to get pregnant come back”
Adequacy of the information on PCOS given at diagnosis	“...explaining why the hairs excess, you know the sequence of events that leads to that and would help, and do you think it's unfortunate that someone has to become, and you know have problems with pre diabetes” “I just thought because she's so young she's at and it be helpful to explain that it's a lifelong condition and that the symptoms can be our spectrum and they look different in different people” “…doctors have been very dismissive and have just said, oh come back to us when you want to get pregnant” “But I think, as someone with PCOS, I would like to know if I was in that pre-diabetes sort of around which this patient was in. more likely to stick to their medication if they understand why they've been put on it so just I think just knowledge is power and telling the patient that” “Just think it's quite important (giving adequate information), because fertility seems to be quite a gateway for a lot of doctors and clinicians dealing with patients”

	“Medical professionals should be sort of more aware of so like I was told to go away and lose weight and come back when I want children, but what if. I don't want you to I mean like what if I don't want children, I think it's probably just my comment for people to sort of be aware of potentially”
Patient centredness in the management of PCOS	“A lot of consideration of side effects are important to us” “Really that you've already got a weight issue there and really I would have liked to have seen better support in a haze approach and instructing on how to balance her insulin levels for a health based thing rather than focusing on the weight as an issue” “Just do it, but there's no actual follow through of how we can lose away and especially with this uphill battle of PCs which has this metabolic aspect, how can we lose weight for someone who has PCOS specifically” “Maybe taken into account and that's kind of what happened on my end and my experience is that by the time we started trying to address my hair loss it had progressed so far” “And just from a patient perspective that makes like me feel very unseen when that happens in an appointment because hair loss to me is such a huge issue”

	“Knowing how long you're going to be on medication, and it is going to be successful, just explaining that there might be other options if it doesn't work could be something that might help with a bit of comfort, I think” “I think the medication side of things, seems to be done, really, really well and from my experience I wasn't offered anything other than the pill so i'm seeing how many options kind were of provided is it's quite cool” “Maybe that's not side effects of stuff to look out for, so I think it would have just been helpful at the end to be like if you're going to be metformin will make sure that we (are given enough information)” “Embryo transfer, whatever that she was having done so, I think, just like I guess an explanation of you know, telling the patient that she's likely to get better or you know that it's not likely to impact on her fertility long term is really important” “about bariatric surgery I think it's just it's something that's nice to pick up with, and as though it's not. We should just be handed up bariatric surgery to everyone and everybody and that it's you know the fix all for the obesity crisis and things like that I think it's it's Nice that it's there as a. You know, as a treatment option, you know if somebody has tried to lose weight and they haven't done so successfully. bariatric surgery has

	a time and a place, providing that that person is aware of the we could go on for hours about this around the issues around bariatric surgery….that is just something else for clinicians to be aware of as a line of treatment”

8.4 Discussion

SIMBA-PCOS was effective in improving clinicians' confidence in managing PCOS-related issues. Most PPI participants agreed that SIMBA-PCOS session benefits women with PCOS in understanding more about their condition and understanding clinicians' perspectives on diagnosis and management of PCOS. All PPI participants also agreed the session helps clinicians better understand patients' perspectives about the diagnosis and management of PCOS. Women's confidence in clinicians' management approach of PCOS were improved post-session. Overall, our findings suggest there is a gap in knowledge and expectations between people with PCOS and HCPs involved in their care, and this gap can be reduced by attending SIMBA session involving both PPI and HCPs.

To the best of our knowledge, this is the first virtual educational activity that had PPI with the aim of identifying and closing the gap of knowledge between women with PCOS and HCPs. The effectiveness of SIMBA as an educational tool in improving clinicians' confidence in managing simulated cases compared to non-simulated cases, with high acceptance rate, is consistent with our previous SIMBA sessions (Melson E et al. 2020b; M. G et al. 2021b). While patients' confidence in HCP's approach to PCOS-related symptoms and their awareness of options available for the management of PCOS-related issues were not significantly different in each domain, an overall improvement was noted suggesting cross-over learning with each case discussion adding to the next to improve the knowledge.

Several studies have highlighted the gap in knowledge, attitude, and perception of clinical care between people with PCOS and HCPs. Delay in diagnoses of PCOS and inadequate information given to patients on diagnoses have reported from across the

world (ME et al. 2014; M et al. 2017; S. Hillman, Dale, and Bryce 2019a) While there was a lack of understanding about PCOS as a metabolic disease with an increased risk of endometrial cancer by affected people, patients reported their weight not being addressed by their HCPs despite being overweight or having obesity (S. Hillman, Dale, and Bryce 2019b). Similarly, their frustrations about the delay in diagnosis and lack of information given to them about PCOS were also voiced out (S. C. Hillman et al. 2020). A more in-depth interview later showed that clinicians seem to focus on one symptom, usually symptom that triggered the consultation, of PCOS (e.g., fertility) and did not explore the condition holistically, a finding that is similar to this study.

Poor experiences with diagnosis and management of PCOS have been associated with increased anxiety and depression (AA et al. 2011) further impacting self-management (K et al. 2010; JC and AJ 2007b). This has led to patients and their carers relying on mostly non-evidence based information online (JC and AJ 2007c). Furthermore, HCPs, when not well-informed, are limited on what they can prescribe for people with PCOS (JC and AJ 2007c). Therefore, it is important for HCPs to work closely with people with PCOS to provide adequate information as well as address all the questions and expectations they may have. We think that SIMBA-PCOS could be an important tool to address the abovementioned gap. This type of educational events for patients can also help them understand evidenced based strategies that is currently available for PCOS with limitations faced by the clinicians. This may potentially reduce any unrealistic expectation of the patients and reduce the gap in knowledge and expectations between women with PCOS and HCPs.

While the study has several strengths in the design and outcomes, we acknowledge there are some factors which may limit the generalisability of our findings. Our PPI

participants were invited through PCOS charities who were interviewed by the charities for their interest in participating. This may be a potential selection bias. However, the interview was necessary to ensure their engagement for the full duration of our session. In addition, our small sample size may also impact on our results. However, applying a mixed-method approach helped consolidating the findings from the study.

8.5 Conclusion

SIMBA-PCOS is an effective learning tool for both people with PCOS and their healthcare professionals to enhance their understanding of the condition. The model also helped identify and reduce gaps in knowledge and expectations between people with PCOS and HCPs. Future large scale studies over period of time are needed to study the long term impact on clinical practice and patient-reported outcome measures.

9 Synopsis and future directions

My work with healthy volunteer blood samples confirmed that 11-oxygenated androgens form a stable circulating pool of androgens during adulthood, while classic androgens decline with age and are subject to menstrual cycle-dependent variation. Although the initial plans were to compare these results to women with PCOS, COVID pandemic limited our sample collection. However, these results forms the first half of the project, and we are currently working on the second half of the project to collect samples from women with PCOS. BMI is a factor in the regulation of 11-oxygenated androgen metabolism in peripheral tissues, that warrants further investigation. These findings can have important implications in the future to establish the role of androgens, both classic and 11-oxygenated in various pathologies, but importantly, the findings in the female cohort represent the comparator cohort for the ongoing studies by our group on androgen excess phenotypes and metabolic risk in women with PCOS.

The results of Blue Morpho study showcase the need for a tailored, multidisciplinary approach to the management of people with PCOS in the community and improving awareness amongst primary healthcare to improve patient care. The overall high rate of emotional and psychosocial distress highlights the need for regular in-depth screening of those living with PCOS across the globe and the role of psychologists in the PCOS care team to provide comprehensive care further. In addition, the emotional and psychosexual wellbeing of people with PCOS in the community needs to be identified, mainly focusing on poor body image, weight stigma and sexual dysfunction.

With PCOS Pearls, we explored the feelings of people with PCOS to greater detail. People with PCOS were impacted significantly by their symptoms and many women feel dissatisfied with the support they receive from healthcare professionals. Educational resources regarding PCOS are vital to improve patients' knowledge and empower them to take an active role in the management of their condition. The detailed information about perceptions and experiences of people with PCOS from this study can be used to ensure future educational resources and diagnostic processes are built around end-user experience. We therefore propose future public and patient involvement (PPI) for people with PCOS to enable the co-creation of new resources informed by lived experience. These can help those newly diagnosed, gain a more comprehensive, authentic and true-to-life understanding of the condition. Furthermore, these resources should aim to include emotional wellbeing and peer-to-peer support in greater detail, as two priority themes highlighted from this study. We also propose to have greater involvement of people with PCOS while designing diagnostic and management pathways to ensure these are acceptable to those with the condition.

Our work with SIMBA model mirrors the Kolb's experiential learning theory from practical point of view. The results demonstrate the positive reception of SIMBA highlighting the advantages of utilising social media as a platform for medical education. Improvements in confidence levels and core competencies using existing freeware social media software paves way for such sessions to be conducted at a low cost internationally. And a step further is SIMBA-PCOS, proving to be an effective learning tool for both people with PCOS and their healthcare professionals to enhance their understanding of the condition. The model also helped identify and reduce gaps in knowledge and expectations between people with PCOS and HCPs. Future large-

scale studies are needed to study the long-term impact on clinical practice and patient-reported outcome measures.

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11 List of my publications

Those included in this PhD have been highlighted in bold

11.1 Original articles

11.1.1 Pubmed indexed

During PhD

1. Kempegowda, P., Robbins, T. D., Boelaert, K., Arlt, W., Ayuk, J., Sankar, S., & Karamat, M. A. (2021). Improving diabetes and endocrinology specialty training with modest resources: the Health Education West Midlands model. *Future Healthc J*, *8*(3), e644–e647. https://doi.org/10.7861/FHJ.2020-0091
2. Ooi, E., Nash, K., Rengarajan, L., Melson, E., Thomas, L., Johnson, A., Zhou, D., Wallett, L., Ghosh, S., Narendran, P., & Kempegowda, P. (2021). Clinical and biochemical profile of 786 sequential episodes of diabetic ketoacidosis in adults with type 1 and type 2 diabetes mellitus. *BMJ Open Diabetes Research and Care*, *9*(2), e002451. https://doi.org/10.1136/BMJDRC-2021-002451
3. Schiffer, Lina, Alicia Bossey, Punith Kempegowda, Angela E Taylor, Ildem Akerman, Dagmar Scheel-Toellner, Karl-Heinz Storbeck, and Wiebke Arlt. 2021. “Peripheral Blood Mononuclear Cells Preferentially Activate 11-Oxygenated Androgens.” *European Journal of Endocrinology* 184 (3). https://doi.org/10.1530/eje-20-1077.
4. Morgan, Georgia, Eka Melson, Meri Davitadze, Emma Ooi, Dengyi Zhou, Thia Hanania, Wentin Chen, et al. 2021. “Utility of Simulation via Instant Messaging – Birmingham Advance (SIMBA) in Medical Education during COVID-19

Pandemic." *Journal of the Royal College of Physicians of Edinburgh* 51 (1): 168–72. https://doi.org/10.4997/JRCPE.2021.218.

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8. Kempegowda, Punith, Eka Melson, Agnes Johnson, Lucy Wallett, Lucretia Thomas, Dengyi Zhou, Catherine Holmes, et al. 2021. "Effect of Covid-19 on the Clinical Course of Diabetic Ketoacidosis (Dka) in People with Type 1 and Type 2 Diabetes." *Endocrine Connections* 10 (4): 371–77. https://doi.org/10.1530/EC-20-0567.

9. Kempegowda, Punith, Lauren M. Quinn, Joht Singh Chandan, Lisa Shepherd, Samina Kauser, Asad Rahim, and Andrew Bates. 2020. “Long-term Testosterone Undecanoate Replacement Therapy: Impact of Ethnicity.” *Clinical Endocrinology*, January, cen.14157. https://doi.org/10.1111/cen.14157.
10. Kempegowda, P., H. Sunsoa, J.S. Chandan, L.M. Quinn, P.M. Amrelia, S.N. Atta, S. Amir, et al. 2020. “Retinopathy and Microalbuminuria Are Common Microvascular Complications in Cystic Fibrosis-Related Diabetes.” *Therapeutic Advances in Endocrinology and Metabolism* 11. https://doi.org/10.1177/2042018820966428.
11. **Melson, Eka, Meri Davitadze, Manal Aftab, Cai Ying Ng, Emma Ooi, Parisha Blaggan, Wentin Chen, et al. 2020. “Simulation via Instant Messaging-Birmingham Advance (SIMBA) Model Helped Improve Clinicians’ Confidence to Manage Cases in Diabetes and Endocrinology.” *BMC Medical Education* 20 (1): 274. https://doi.org/10.1186/s12909-020-02190-6.**

Pre-PhD

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Year Study." *BMJ Open Diabetes Research and Care* 7 (1). https://doi.org/10.1136/bmjdrc-2019-000695.

14. Kempegowda, Punith, Alana C Livesey, Laura McFarlane-Majeed, Joht Singh Chandan, Theresa Smyth, Martha Stewart, Karen Blackwood, et al. 2018. "Are They High on Steroids? Tailored Interventions Help Improve Screening for Steroid-Induced Hyperglycaemia in Hospitalised Patients." *BMJ Open Quality* 7 (1): e000238. https://doi.org/10.1136/bmjoq-2017-000238.
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18. O'Reilly, M.W., P. Kempegowda, M. Walsh, A.E. Taylor, K.N. Manolopoulos, J.W. Allwood, R.K. Semple, et al. 2017. "AKR1C3-Mediated Adipose Androgen Generation Drives Lipotoxicity in Women With Polycystic Ovary Syndrome."

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22. Kempegowda, Punith, Sara Rani Marcus, Priyank Solanki, Rashmi S. Reddy, Nandini D. R., and Mala Dharmalingam. 2011. "Prevalence of the Metabolic Syndrome in Rural India—a Disparity in Definitions." *International Journal of Diabetes in Developing Countries* 31 (4): 188–93. https://doi.org/10.1007/s13410-011-0046-y.
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31. Kumar, Anil T, U Sudhir, Gita Srinivasan, and Punith Kempegowda. 2008. “Association of Body Mass Index with Blood Pressure in the Elderly.” *JIACM* 9 (4): 274–76. http://medind.nic.in/jac/t08/i4/jact08i4p274.pdf.

32. Kempegowda, Punith, Lalitha Krishnappa, G Suman, BS Pradeep, and Jayanth Kumar. 2008. “Evaluation of Primary Immunization Coverage of Infants Under Universal Immunization Programme in an Urban Area of Bangalore City Using Cluster Sampling and Lot Quality Assurance Sampling Techniques.” *Indian Journal of Community Medicine* 33 (3): 151–55.
33. Umesh, L, E Mahesh, Anil Alind Kumar, K Lalitha, G Suman, and K Punith. 2007. “Infections in Renal Transplant Recipients.” *Journal, Indian Academy of Clincial Medicine* 8 (4): 315–23. http://medind.nic.in/jac/t07/i4/jact07i4p316.pdf.

11.1.2 Peer-reviewed and non-PUBMED indexed original articles

Pre-PhD

34. Kumar, Anil, Jeetendra Kumar, Balakrisnan Iyer, Sanjeev Kumar, and Punith Kempegowda. 2014. “Impact of Pill Burden and Socio-Economic Status of Patients on Adherence to Pharmacologic Therapy in Elderly.” *West London Medical Journal*. http://bjll.org/index.php/wlmj/article/view/629.
35. Narayan, Arun, Sanjay Kulkarni, Rahul Kothari, Telugu Seetharam Deepak, and Punith Kempegowda. 2014. “Association between Plasma Adiponectin and Risk of Myocardial Infarction in Asian Indian Patient with Diabetes.” *British Journal of Medical Practitioners* 7 (4): a729. http://www.bjmp.org/content/association-between-plasma-adiponectin-and-risk-myocardial-infarction-asian-indian-patient-diabetes.
36. Mahesh, E, Medha Y Rao, VA Indumathi, Prithvi S Kumar, Mohammed Wasim Khan, and Punith Kempegowda. 2011. “Community-Acquired Urinary Tract Infection in the Elderly | British Journal of Medical Practitioners.” *BJMP* 4 (1):

a406. http://www.bjmp.org/content/community-acquired-urinary-tract-infection-elderly.

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11.2 Reviews

During PhD

38. **Kempegowda, Punith, Eka Melson, Konstantinos N Manolopoulos, Wiebke Arlt, and Michael W O’Reilly. 2020. “Implicating Androgen Excess in Propagating Metabolic Disease in Polycystic Ovary Syndrome.” *Therapeutic Advances in Endocrinology and Metabolism* 11 (January): 2042018820934319. https://doi.org/10.1177/2042018820934319.**

Pre-PhD

39. Schiffer, Lina, Punith Kempegowda, Wiebke Arlt, and Michael W M.W. O’Reilly. 2017. “MECHANISMS IN ENDOCRINOLOGY: The Sexually Dimorphic Role of Androgens in Human Metabolic Disease.” *European Journal of Endocrinology* 177 (3): EJE-17-0124. https://doi.org/10.1530/EJE-17-0124.

11.3 Letters and other article types

During PhD

40. Ng, C. Y., Allison, I., Ooi, E., Davitadze, M., Melson, E., & Kempegowda, P. (2021). Medical students’ and junior doctors’ leadership and teamwork skills

improved after involvement with Simulation via Instant Messaging-Birmingham Advance (SIMBA). *BMJ Leader*, leader-2021-000486. https://doi.org/10.1136/LEADER-2021-000486

41. **Melson, Eka, Wentin Chen, Dengyi Zhou, Emma Ooi, Nia Evans, Dwi Delson, Meri Davitadze, and Punith Kempegowda. 2021. "Adaptation and Use of Media in an Innovative Simulation-Based Clinician Training Programme."** ***BMJ Simulation and Technology Enhanced Learning*** **0 (June): bmjstel-2020-000808. https://doi.org/10.1136/bmjstel-2020-000808.**

Pre-PhD

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43. Kempegowda, Punith. 2014. "Cyanamide." In *Encyclopedia of Toxicology*, edited by Philip Wexler, 3rd ed., 1091–92. New York: Elsevier Ltd. https://doi.org/10.1016/B978-0-12-386454-3.00483-8.

12 Appendix A

Survey content

1. I read and understand the survey's information and privacy statement. And I consent to take part in the survey.
2. What is your year of birth?
3. In order to monitor and improve our diversity, please tell us which gender you identify with?
4. In order to monitor and improve our diversity, please tell us which ethnicity you identify with?
5. Are you based in the UK?
6. Where in the UK are you based?
7. Which country do you live in?
8. Have you been formally diagnosed with PCOS?
9. In which year were you diagnosed with PCOS? (YYYY format)
10. In which year did you first notice the symptoms of PCOS? (YYYY format)
11. I read and understand the instructions for the survey
12. In what format would you like to provide your responses
13. What is your mobile number including the international dialling code on which we can WhatsApp you? (we will delete the number from our records once we received your response to the survey)

14. What is your experience till date with the symptoms of PCOS, including their impact on your mood and wellbeing?
15. What was your experience till date with the process of being diagnosed with PCOS?
16. Imagine your current self meets your younger self (at the time you first experienced symptoms of PCOS), how would you explain to your younger self what PCOS is?
17. What advice would you give to this younger self about PCOS, knowing what you know now?