SUCCESS study: Development of a StructUred eduCation programme to improve Cardiovascular risk in womEn with polycyStic ovary Syndrome

Thesis for the degree of
Doctor of Philosophy
University of Leicester

By
Dr Hamidreza Mani

Supervised by
Professor Melanie Davies
Professor Kamlesh Khunti

NHS

UNIVERSITY *of*
Leicester

SUCCESS
Study

Development of a **S**truct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome

Thesis submitted for the degree of
Doctor of Philosophy
University of Leicester

By
Dr Hamidreza Mani
M.D.(Shiraz, Iran) MRCP (London)

Diabetes Research Centre
and
Cardiovascular Sciences
College of Medicine, Biological Sciences and Psychology

December 2013

Dedication

To the patients who shared their time and stories to make SUCCESS

Development of a structured education programme to improve

cardiovascular risk in women with polycystic ovary syndrome

Dr Hamidreza Mani

Abstract

Background: Polycystic ovary syndrome (PCOS) is a chronic condition with a reported prevalence of up to 18% and is associated with adverse long term outcomes. Structured education programmes have proved effective at optimising physical activity, biomedical outcomes and well-being of people with chronic conditions, however, pragmatic structured education interventions in women with PCOS are lacking.

Aim: To develop an evidence-based structured education programme for women with PCOS and increase their step-count.

Methods: Using a local multi-ethnic database, phenotypic presentation and long term cardiovascular outcomes of women with PCOS was determined. The attitudes of women with PCOS towards an education programme and their experience of living with PCOS was sought through qualitative interviews. A systematic review compared lifestyle interventions with insulin sensitizers in PCOS. Using the Medical Research Council's framework, the SUCCESS education programme was developed and tested in a randomised controlled trial.

Key Findings

- ➢ There are phenotypic differences in women with PCOS according to ethnicity or body weight.
- ➢ Overweight and obese women with PCOS have a high proportion of cardiovascular risk factors and higher age-specific rates of myocardial infarction as compared to general female population.
- ➢ In a meta-analysis, no statistical differences exist between the effect of lifestyle interventions and Metformin on BMI at six month.
- ➢ Women with PCOS welcome group education programmes. They have significant body image issues, which has an emotional impact.
- ➢ The SUCCESS education programme did not increase the step count at three month.

Conclusion:
This project established the high cardiovascular risk associated with PCOS. Although, the SUCCESS education programme did not show positive results at three months, it is the first pragmatic structured education programme tailored to women with PCOS. Outcomes at the final analysis in 12 months, will inform whether the programme should be implemented or adapted further and re-evaluated.

Disclaimer

Copyright

All text, images and artwork from the SUCCESS curriculum contained in this thesis are subject to copyright owned by the Leicester Diabetes Centre/University of Leicester.

Acknowledgment

The custom is to say "this is an original work of mine and I am grateful to A, B and C for their input in X, Y or Z parts of the thesis". I believe it would be difficult to do that for a project which comes out of the Leicester Diabetes Centre (LDC). This is an original work of mine, as original as it could be in the context of working within an amazing team. A list of people who have been involved in this project is presented in Appendix 1 (and I ask forgiveness from anyone whose name is missed from that list). That list, however, is not exclusive.

Here in LDC, the oxygen in "Air[1]" is mixed with education; it is only here that you can think of "developing a structured education programme" as your PhD project. Everyone is supportive. "I am happy to help" is in the nature of the team, even if it is only a pair of ears to listen to you at the end of a frustrating day, or some words of experience while making a cup of coffee.

The great artists responsible for building this beautiful team and creating such an inspiring atmosphere are my two supervisors: Melanie Davies and Kamlesh Khunti.

I have been brought up with the notion that "knowledge is an everlasting and priceless treasure". God knows how much I have learned from Melanie and Kamlesh. Besides, they have given me the most beautiful experience: "the opportunity to explore a research question".

I am always short of words when trying to express my feelings after viewing an impressive art exhibition. In the past few years, I have had the opportunity to live within the most beautiful collection of art! Words cannot describe my feelings and my gratitude to Melanie and Kamlesh and I will not try. Even thinking about that brings tears to my eyes and a lump to my throat. I am sure they know how much I respect them.

There would not be a SUCCESS without the "motherly", kind and caring inputs of Heather Daly; the guidance of Marian Carey; or thoughtful and experienced feedback of Jacqui Troughton and Margaret Stone. I am very grateful to them.

I have a great admiration for the meticulous and hard work of Janette Barnett. Janette's help in setting up the education programme and the many extra hours that she put into the work was priceless.

---

[1] Incidentally "Air" is the wing which hosts the patient education group in LDC.

Of course the "beautiful mind" of Mike Bonar, who pays attention to every detail, is not forgotten here. Mike's smile and his patience make it possible to go to him without the fear of being rejected; SUCCESS would not reach out for the stars without him (reference to the design of study logo).

I am very grateful for the statistical teaching I received through the course of this project from Laura Gray and Danielle Bodicoat, they both very patiently coped with my never-ending questions.

Miles Levy and Trevor Howlett, had key roles in the project and advised me through the steps especially in the part related to the database and I am very grateful to them.

Finally, my special thanks go to Denise Robinson and Raj Gill, PAs to Melanie and Kamlesh. They are like "gravity", the force which stops things from floating around! Their precious role in the life of a PhD student becomes very significant in the context of the very busy schedule that my two supervisors have. I am very grateful to them for being so friendly, lovely, patient and approachable.

A quick word about the indirect role of my family: I am lucky to have an understanding and supportive family (my parents, my brother and sister) who did whatever they could to ease my journey when I left Iran 9 years ago in pursue of my goals. The heaviest burden, however, was on my wife Bahar, who made every effort to be accommodating of all the collateral effects of a PhD study on our life. Her greatest art was entertaining our son Sina (who is now five years old), as the most difficult times of the past few months, while writing up this thesis, were the occasions that I had to refuse his invitations to play. At times his reaction to my refusal was a puzzled look and: "*You are a grown up! Why do you have homework?*"

Obviously English is not my first language and I therefore have to finish by mentioning my uncle Bahram, who has had the biggest contribution to my learning of English language and literature. I have been most fortunate to be able to enjoy his vast knowledge from the very first day I started the school.

In the above background; "this is my original work"!

Table of Contents

List of Figures

List of Tables

List of papers and presentations

Mani H, Khunti K, Levy MJ, Davies MJ. Diabetes advice for women with polycystic ovary syndrome; Prevention, Prevention, Prevention. Diabetes Management. 2013, 3(6), 1-14.

Mani H, Levy MJ, Davies MJ, Morris DH, Gray LJ, Bankart J, et al. Diabetes and cardiovascular events in women with polycystic ovary syndrome: a 20-year retrospective cohort study. Clin Endocrinol (Oxf) 2013 Jun;78(6):926-934

Abstracts and Conference presentation

Mani H, et al Effect of ethnicity on the clinical presentations of women with Polycystic Ovary Syndrome; a 20-year retrospective cohort study. Poster Presentation at BES, March 2013.
 Mani H, et al The development of a structured education programme to improve cardiovascular risk in women with Polycystic Ovary Syndrome (SUCCESS Study) Poster Presentation at BES, March 2013.
Mani H, et al. Diabetes and cardiovascular events in women with polycystic ovary syndrome; a 20 years retrospective cohort study.

- ➤ Poster competition; "Meeting for clinical scientists in training"; *Academy of Medical Sciences*; Feb 2013. Published in a special issue of Lancet.

- ➤ Oral presentation in East Midlands Endocrine Meeting; Nov 2012

- ➤ Oral Presentation British Endocrine Society meeting March/2012

Mani H, et al. Diabetes and polycystic ovary syndrome. Oral presentation in "30th North European Young Diabetologist" group; Amsterdam, August 2012.

Mani H, et al. Association of type 2 diabetes with Polycystic Ovary Syndrome; analysis of a large cohort of patients with Polycystic Ovary Syndrome. Poster Presentation in Diabetes UK March/2012.

Abbreviations

Abbreviation	Full text
AN	Acanthosis Nigricans
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CLAHRC	Collaboration for Leadership in Applied Health Research and Care
CV	Cardiovascular
CVD	Cardiovascular Disease
FSH	Follicle Stimulating Hormone
HDL-C	High Density Lipo-protein Cholesterol
HF	Heart Failure
HIS	Health Informatics Service
HRQoL	Health Related Quality of Life
IGT	Impaired Glucose Tolerance
IMD	Index of Multiple Deprivations
LCW	Leicester Clinical Workstation
LDL-C	Low Density Lipo-protein Cholesterol
LDRC	Leicester Diabetes Research Centre
LH	Luteinizing Hormone
LRI	Leicester Royal Infirmary
MI	Myocardial Infarction
MRC	Medical Research Council
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatosis-Hepatitis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
PCO	Polycystic Ovary
PCOS	Polycystic Ovary Syndrome
RCT	Randomised Controlled Trial
RR	Relative Risk
SA	South Asian
SD	Standard Deviation
SEM	Standard Error of Mean
SHBG	Sex Hormone Binding Globulin
SUCCESS	**S**truct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome
T2DM	Type 2 Diabetes Mellitus
TG	Triglyceride
UHL	University Hospitals of Leicester
USS	Ultrasound Scan

Introduction to this thesis: a guide to SUCCESS

SUCCESS: Struct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome

Possibly the best introduction might be to explain how SUCCESS happened.

It all started with a research question: "Do women with polycystic ovary syndrome (PCOS) have higher rates of cardiovascular diseases than the general female population?" A database was available to explore this question. However, that could not be the end of the research. What if the answer was "yes"? We already knew from previous studies that women with PCOS were at high risk of diabetes and therefore, besides knowing their risk of cardiovascular diseases, there needed to be a proposal for a risk reduction intervention. In other words, confirming their high risk status was important, but it was more important to be able to offer a practical and pragmatic solution to the problem. The concept of risk reduction and prevention is the future of medicine (1). One plausible solution was a structured education programme to empower these women with the knowledge they need to influence their modifiable risk factors and reduce their diabetes risk (2). However, the success of a structured education programme lies in the behaviour change of the subjects (3) and the behaviour is defined within the context of the person's "structural, social and economic context" (3) and consequently "personal relevance" is a mandatory element for the application of any education programme (3). A woman with PCOS faces a wide range of issues in addition to her high risk status: possible body image issues (excess hair or obesity), increased risk for infertility, dysfunctional uterine bleeding, obstructive sleep apnoea and even higher possibilities of cancer (4,5). Therefore the available prevention programmes (6,7) might not have the "personal relevance" for these women and the previous lifestyle studies in this population (8) did not seem to be pragmatic. Therefore a pragmatic structured education programme tailored to the needs of women with PCOS was needed. Thus, the initial question turned into a quest to develop and test an education programme tailored to the needs of women with PCOS.

The Leicester Diabetes Centre, with more than a decade of experience in developing structured education programmes, was the ideal host to nurture this project.

This thesis, which is structured in 10 chapters, is the report of this work. Here is the summary of these chapters:

Chapter 1: Polycystic Ovary Syndrome (PCOS), a common chronic disease with long term health consequences: This chapter describes the epidemiology of PCOS, the links to insulin resistance and its long term health complications.

Chapter 2: Phenotypic analysis and cardiovascular outcomes in a multi-ethnic cohort of women with PCOS: This chapter is the phenotypic description of a multi-ethnic cohort of women with PCOS as well as the long term CV outcomes in this population as compared to the local general female population.

Chapter 3: A systematic review and meta-analysis comparing the effect of pharmacotherapy (insulin sensitizers or incretin based therapies) to lifestyle management on body mass index in women with polycystic ovary syndrome; following the review of the available interventions to improve weight as surrogate marker of the metabolic risk status in women with PCOS, in this chapter a comparison is made between pharmacological and lifestyle interventions.

Chapter 4: Rational and structure of SUCCESS: This chapter reviews the principles of developing an education programme and the learning theories underpinning the SUCCESS education programme.

Chapter 5: Development of the education programme: The results of qualitative interviews with a representative sample of women with PCOS are presented, followed by a detailed description of the steps taken in developing the curriculum for the SUCCESS education programme.

Chapter 6: A randomised controlled trial to assess the effect of SUCCESS education on increasing walking steps in women with PCOS; design and

methods: The design of the SUCCESS-RCT, and the primary and secondary outcomes, which are set to be evaluated after 12 months, are reviewed.

Chapter 7: High rates of risk factors for cardiovascular diseases in overweight and obese women with PCOS, Baseline characteristics of the SUCCESS-RCT cohort: This chapter is the analysis of the baseline characteristics of the patients recruited to SUCCESS-RCT and explores the cardiovascular risk factors in this cohort.

Chapter 8: Health related quality of life, illness perception and the lived experience with PCOS. Baseline data from the SUCCESS-RCT: Description of the baseline characteristics of the SUCCESS cohort continues in this chapter in view of their health related quality of life, illness perception and also their view on their experience of living with PCOS as expressed during the education programme. Participants' feedback on the education intervention is also described.

Chapter 9: Effects of a structured education programme in women with polycystic ovary syndrome on step counts, 3 months interim analysis of the SUCCESS-RCT: The effects of the SUCCESS education programme on increasing walking steps, other indices of physical activity, blood pressure, and health related quality of life in a three months interim analysis are described in this chapter.

Chapter 10: Discussion The final chapter of this thesis reviews the findings from each chapter with their implications, and presents the future directions for this programme of research.

You will notice through the chapters that this project has had multiple steps using a wide range of data and methodologies; from simple quantitative methods to meta-analysis and also some qualitative data. I have done my best to safeguard the concept of the "originality" of the work and lead the work and perform the analyses where possible. However, some parts needed input from experts. For

these parts, I have done my best to understand the principles of the methodologies but obviously I could not have mastered all of them. Through the course of writing, I have therefore acknowledged the input of others where appropriate.

Chapter 1 : Polycystic Ovary Syndrome, a common chronic disease with long term health consequences

The ultimate aim of this project was to develop an evidence-based structured education programme for lifestyle change tailored to the needs of women with PCOS. In order to develop a comprehensive programme, it was necessary to understand PCOS.

In this chapter, the diagnosis, epidemiology, the underlying insulin resistance in PCOS and the complications of this condition are reviewed.

1.1 Introduction

Women with PCOS are often young (4,5) and emotionally distressed by their condition (9). Although all these presenting symptoms are important and need addressing, the diagnosis of PCOS has a much greater and more lasting impact on a woman's life; with higher risk of impaired glucose tolerance (IGT) [where IGT is defined as blood glucose ≥ 7.8 mmol/l and less than 11.1 mmol/l 2 hours after a 75 gram load of glucose (10)], type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome, fatty liver disease, hypertension, dyslipidemia, cardiovascular diseases, sleep apnoea, gestational problems, as well as depression (4,5,9,11-20). These metabolic complications and the long term health risks attached to them need to be monitored and treated in these patients, as well as their presenting problems. A cost analysis in America estimated an overall cost of $4.36 billion in 2005 equal to 20% of the cost of diabetes for patients in an equivalent age group. (21) Although about 40% of the associated cost was reported to be related to T2DM, this cost did not include some of the other long term complications associated with PCOS and therefore has to be a gross under-estimation (14). It is therefore important to understand PCOS and its long term adverse effects on health in more detail.

1.2 Diagnosis of PCOS

Possibly the first descriptions of PCOS were around 2,500 years ago by Hippocrates in his notes on the "diseases of women" where he described "young women who do not become fertile despite having menstruation" and also attributed "general ill health" to the women who did not have any menstruation at all (22). In the nineteenth century, Rokitanski gave a detailed description of the anatomical and morphological changes which happened in an ovary affected by multiple cysts and described it as an "anomaly of texture" (23). Some of the hyperandrogenic signs were later described in the early 20th century (24). It was finally Stein and Leventhal who combined the ovarian morphology and the signs to form the diagnosis of "Stein-Leventhal syndrome" (25). Over the next 70 years the diagnosis of PCOS has been through multiple consultations (5,26,27) to eventually settle on the presence of two out of three major criteria (4,14);

1) Clinical or biochemical hyperandrogenism*; this includes evidence of hirsutism, acne or androgenic alopecia or higher than normal levels of free testosterone or free androgen index.

2) Anovulation* (chronic or oligo) which is defined as having less than 10 menstruation in a year (> 35 days intervals between menstruations) or evidence of the lack of ovulation despite regular menstruation.

3) Polycystic ovaries on ultrasound which is defined as the presence of 12 or more follicles measuring 2-9 mm in each ovary and / or increased ovarian volume of more than 10 ml.

*(When other possible causes for 1 and 2 have been ruled out)

In the early 1990s the National Institute of Health (NIH) accepted the combination of criteria 1 and 2 (26). The Rotterdam criteria (27) were accepted in 2003 as any combination of at least two of the above criteria. In 2009 the Androgen Excess Society (AES) declared the presence of hyperandrogenaemia as being mandatory which could be combined with either criterion two or three (5). The Rotterdam criteria have recently been endorsed again in 2012 (4,14). The combination of these signs and symptoms produces a variety of phenotypes in women with PCOS as shown in Table 1.1 together with the diagnostic criteria in which they fit.

Table 1.1 Four Possible phenotypes of PCOS

Features	A	B	D	E
Hyperandrogenism	+	+	+	-
Oligo-anovulation	+	+	-	+
Polycystic Ovaries	+	-	+	+
NIH 1990 Criteria	√	√	X	X
Rotterdam 2003 Criteria	√	√	√	√
Androgen Excess Society (AES)	√	√	√	X

√ Diagnosed with the criteria   X not diagnosed by the criteria.

1.3 Epidemiology

The reported prevalence of PCOS ranges from 3.4% (28) to 17.8% (29) depending on the criteria used for the diagnosis or the studied population. Table

1.2 summarises the studies which have reported the prevalence of PCOS and the diagnostic criteria used in their study. Some of these studies are population based screening studies and have been able to report an estimate of undiagnosed PCOS patients in the study (patients who were diagnosed for the first time during that study); ranging from more than a third in Iran (30,31) to 69% in Australia (29) and 89% in Sri-Lanka (32).

There are other reports of the prevalence of PCOS from around 1.6% (33) to 26% (34). However, they are not considered reliable; because the former is an insurance database and the latter is based on a diagnosis guideline which was never internationally approved.

Table 1.2 Summary of the studies reporting the prevalence of PCOS† (Foot notes on page 10)

Author	Place of study	Population	Population described	Criteria	Prevalence
Asuncion (35)	Spain	154	Volunteer blood donors	NIH	6.5%
Azziz (36)	USA	400	University employees	NIH	6.6%
Chen (37)	China	915	Women attending their annual routine check	Rotterdam	2.4%
Chen (37)	China	915	Women attending their annual routine check	NIH	2.2%
Chen (37)	China	915	Women attending their annual routine check	AES	2.2%
Diamanti-Kandarakis (38)	Greece	192	Open invitation to reproductive age women	NIH	6.77%
Gabrielli (39)	Brazil	859	Women attending for cervical screening	Rotterdam	8.5%
Knochenhauer (28)	USA	369	University employees	NIH	4.0% total; 3.4% Black, 4.7% white
Kumarapeli (32)	Sri-Lanka	3030	Cluster random sampling of population	Rotterdam	6.3%
Lindholm (40)	Sweden	267	Part of community screening for high risk cardiovascular disease and diabetes	NIH	4.8%
March (29)	Adelaide, Australia	728	All female babies born 30 years before the study were approached	Rotterdam	11.9%
March (29)	Adelaide, Australia	728	All female babies born 30 years before the study were approached	Rotterdam	17.8%**
March (29)	Adelaide, Australia	728	All female babies born 30 years before the study were approached	NIH	8.7%

Author	Place of study	Population	Population described	Criteria	Prevalence
Moran (41)	Mexico	150	20-45 years volunteers	Rotterdam	6.6%
Moran (41)	Mexico	150	20-45 years volunteers	NIH	6.0%
Nidhi (42)	India	460	College students	Rotterdam	9.1%
Tehrani (30)	Iran	1002	Random selection from a larger population screening for Hyperlipidemia	NIH	8.5%
Tehrani (31)	Iran	1126	Cluster random sampling of general population	Rotterdam	14.6%
Tehrani (31)	Iran	1126	Cluster random sampling of general population	NIH	7.1%
Tehrani (31)	Iran	1126	Cluster random sampling of general population	AES	11.7%

USA = United States of America, NIH = National Institute of Health, AES = Androgen Excess Society,
*Year published,
** This is if they imputed data for those who did not complete ultrasound exam or blood test.
†Some of the studies (29,31,37,41) have reported the prevalence based on different diagnostic criteria and these reports are separated in different rows.

When looking at the Table 1.2 it is immediately noticeable that the prevalence changes with the diagnostic criteria and the studied population. This is likely to be a reflection of the varying prevalence of signs and symptoms of PCOS in different populations.

1.3.1 Prevalence of signs and symptoms of PCOS

The prevalence of these signs and symptoms may vary according to the ethnicity, age and/or the BMI of the studied population and this will be explored further in Chapter 2.

1.3.1.1 Clinical or biochemical evidence of hyperandrogenism

Hirsutism is the most common symptom of hyperandrogenism with a prevalence of up to 78% (4,5,43,44). Acne and androgenic alopecia are much less prevalent; 20% to 40% of patients with acne may suffer from PCOS and 10% of those with alopecia (5). Hirsutism appears to be more common amongst the south Asians (SA) as compared to the white population (45) and is less prevalent in the Far East Asian population (46).

1.3.1.2 Oligo or Anovulation

This is the most common criteria and up to 95% of the women with PCOS are reported to have oligo-amenorrhoea (4,32).

It seems that with moving from regular menstruation to amenorrhoea in women with PCOS the extent of hyperandrogenism and antral follicles increase (4,47). In other words the more severe the menstrual problem the more severe is the PCOS phenotype (4).

1.3.1.3 Polycystic ovaries

Polycystic ovaries are very common in women with a prevalence of about 20-30% (5,43,48). They are reported to be as high as 52% in south Asians (49). The number of the follicles, and consequently the prevalence, decreases by

advancing age (5,50). It is estimated that up to 20% of women with polycystic ovaries will have the syndrome (5).

1.4 Pathophysiology

The specific pathology underlying PCOS remains uncertain. It has a multifactorial and heterogeneous pathophysiology with possible genetic and environmental elements (4,14,17,51). Although in most cases the diagnosis of PCOS is made after menarche, the origin is believed to have started in childhood or even fetal life (17,51-55). Besides, the evidence of familial clustering of the syndrome (51,56,57) and the genetic associations (17,51,58) indicate that some women have a predisposition for PCOS. Nevertheless it seems that epigenetic and environmental factors in the form of hyperandrogenism and insulin resistance play a significant role (17,51,54).

The association between hyperandrogenism and disordered carbohydrate metabolism was initially described in 1921 as "the diabetes of bearded women (diabète des femmes à barbe)" or Achard-Thiers syndrome (17,24). A few decades later Berghen et al (59), showed that women with PCOS have associated hyperinsulinemia independent of their body mass index (BMI). Further studies have confirmed the presence of insulin resistance independent of BMI, age or ethnicity in PCOS (17,51,54,60-63).

It is clear that insulin resistance plays a major pathologic role in this condition and explains the multi-organ involvement in PCOS (14,16,54). Nevertheless, some of the phenotypes are more strongly associated with insulin resistance and consequently an abnormal metabolic profile. The classic phenotype of anovulatory-hyperandrogenic women with PCOS described by the National Institute of Health (NIH) 1990 criteria (26) are much more likely to show evidence of insulin resistance (17,64,65). Two of the distinctive Rotterdam (27) phenotypes including ovulatory women with hyperandrogenism or with polycystic ovaries are shown to have normal insulin sensitivity (17,64,65). Conditions which lead to increased insulin resistance like obesity may convert these metabolically benign

phenotypes to the classic anovulatory PCOS (12,17). Insulin stimulates ovarian androgen production (66-69) and reduces the hepatic production of sex hormone binding globulin (68,70,71) and therefore hyperinsulinemia resulting from insulin resistance contributes to the development of signs and symptoms of PCOS. Besides, there are insulin receptors on normal and PCOS ovaries and it seems that insulin as well as stimulating androgen production induces the Luteinizing hormone (LH) effect on androgen production. Androgen has a feedback effect on hypothalamus to stimulate the gonadotropin releasing hormone (GnRH) release which, in turn, stimulates the pituitary to increase the LH and reduces follicular stimulating hormone (FSH) secretion (72). This can cause follicular arrest and anovulation (72). Consequently there is a cyclic interaction between insulin resistance, hyperandrogenism and anovulation; each contributing to the progress of the condition. In addition, the intrinsic contribution of PCOS to the insulin resistance disregarding the underlying BMI should not be ignored as shown in numerous studies (17,54,62). It appears that the resistance to the peripheral uptake of glucose is a dominant mechanism for insulin resistance in PCOS (17,54,73,74) with a sub-receptor defect (17,54,75-77), which is slightly different in nature to other insulin resistance status such as obesity and T2DM (17,54,75,78). It is also shown that the underlying mechanism and contribution of different tissues (muscle, fat, and liver) are different to the overall insulin resistance in women with PCOS (17,54,73). Some degrees of β cell dysfunction (17,54,79-81) have also been reported in the spectrum of disease. However glucose levels may remain normal in some of these patients as a result of the compensatory hyperinsulinemia secondary to increased β-cell function (54). Dominant peripheral insulin resistance explains why women with PCOS tend to demonstrate a normal fasting glucose and abnormal post-prandial status (82-85).

1.5 Long term health risks associated with PCOS

One of the implications of the underlying insulin resistance in PCOS is the involvement of multiple systems in the body (4,17,54). Additionally, PCOS starts at a very young age (4,14,55) and while some of the symptoms like irregular menstruations attenuate by age (86,87), others like alopecia and hirsutism may become more prominent (4). The metabolic impact associated with insulin resistance is likely to be carried forward to the post-menopausal state and the later life (4,14,87). PCOS also has an impact on the quality of life and is associated with depression and anxiety (88-90).

The next section reviews the long term consequences of PCOS in three broad categories of "metabolic", "mental health" and "cancer".

1.5.1 Metabolic complications

These include a number of complications which are generally associated with insulin resistance.

1.5.1.1 Obesity and PCOS

The association of PCOS and obesity is well known while their causal relationship is still a point of debate (68,91). It is interesting that PCOS is more associated with obesity (BMI≥30 kg/m^2) than being overweight (25 kg/m^2 < BMI < 30 kg/m^2). In some studies up to 76% of the patients have been obese (92,93) while only around 20% are overweight (4). In comparison to the non-PCOS population they also have higher rates of overweight, obesity and central obesity with respective Relative Risk (95% Confidence Interval) of 1.9 (1.5, 2.5), 2.8 (1.9, 4.1) and 1.7 (1.3, 2.3) (18). However, there are notable ethnic differences for this association; western studies report much higher rates (up to 90%) (93) for overweight and obesity as compared with far east Asia (20%) (94,95) even adjusting for ethnic specific cut off points (BMI > 23 kg/m^2) only increased the prevalence to 35% (94).

Obesity is associated with insulin resistance (96) with a slightly different mechanism as compared to PCOS (17,54), with obese women with PCOS having greater insulin resistance as compared to lean PCOS women (12,17,81).

Excess body weight decreases the SHBG and consequently increases free or total testosterone (4,12). It is expected that the excess adiposity exacerbates the associated reproductive and metabolic consequences of PCOS (5,12,68), however, there are few studies looking specifically at the effects of weight or characteristics, signs and symptoms of obese PCOS patients (4).

1.5.1.2 Diabetes

The prevalence of impaired glucose tolerance (IGT) and T2DM in women with PCOS has been reported to be as high as 35% and 10% respectively (4,17,63,82,84,97). In comparison with the control group or general female population, the overall prevalence of diabetes has been reported to be 2-3 times higher in women with PCOS (13,17,98,99). A recent meta-analysis of the epidemiological studies reported that women with PCOS had an increased prevalence of IGT (OR 2.48, 95% CI 1.63, 3.77) and T2DM (OR 4.43, 95% CI 4.06, 4.82) even after adjustment for BMI (13). The increased risk of diabetes has been shown in post-menopausal women with PCOS (100-102) as well as adolescents (103,104). Women with PCOS have a much higher chance of gestational diabetes and other gestational complications associated with insulin resistance such as spontaneous abortion (4,16,17,105,106) and they carry a higher risk of abnormal glucose metabolism after the pregnancy and gestational diabetes (107). In other words, there is a lifetime high risk status for T2DM in women with PCOS starting from adolescence to the post-menopausal period.

There have been some attempts to calculate the conversion rate from normal to IGT or to T2DM in this patient population (summarised in Table 1.3). However, most of these studies have either a short follow up period or include a very small number of women with PCOS (maximum number is 83 women) and in the case of the last study (108) the baseline status of patients is not clear. Therefore more studies with larger cohorts are required (13).

Table 1.3 Annual conversion rates to IGR and T2DM in PCOS populations (Summary of studies)

Name	No	Follow up (years)	NGR to IGR	NGR to T2DM	IGR to T2DM
Pesant (109) †	83	3	6.8%	2.0%	Not reported
Legro (110)	71	2.5	16%	Not reported	2%
Norman (111)	67	6.2	1.5%	1.3%	9%
Ehrmann (97)	25	2.4	28.2%	5.6%	37.2%
Hudecova (108)	49	13.9	It is not clear whether they had NGR or IGR at baseline. 16.3% IGR and 8.3% T2DM at the follow up visit		

NGR = Normal Glucose Regulation, IGR = Impaired Glucose Regulation (Impaired fasting glucose or impaired glucose tolerance), T2DM = Type 2 diabetes mellitus.

†It is worth noting that 59% of the population in this study were on insulin sensitizers [not specified which insulin sensitizer] when they had their second OGTT.

These reported conversion rates are not very different from the high risk groups in the general population. Evidence from a screening study in the general population shows a conversion rate of 17.0 and 11.8 per 100 person years respectively for IGT and Impaired fasting glucose (= IFG is defined as fasting glucose ≥ 6.1 mmol/l and less than 7 mmol/l) (112). In a multi-ethnic population, 4.7% of those with normal glucose tolerance developed T2DM after 5 years while 20.8% of those with IGT and 21.6% of those with IFG during the same period developed T2DM (113). A meta-analysis of prospective cohort studies reported that compared to the normoglycaemic people, those with IGT had a relative risk of 6.4 (4.9–7.8) of conversion to T2DM (114).

1.5.1.3 Hypertension

Women with PCOS also have evidence of altered vascular function (115-117) and labile day time blood pressure (BP) (118) which are suggestive of the presence of hypertension. However, epidemiologic data is inconclusive (100,102,119-121). Higher rates of the hypertension reported in a Dutch study were thought to be associated with BMI and not PCOS per se (98,122). However,

in another study, age and BMI adjustment did not change the results and women with PCOS had higher systolic BP as compared to the non-PCOS controls (123). In conclusion, although there remains a need for further long term follow up studies, it is plausible to consider these patients at high risk of hypertension (16).

1.5.1.4 Dyslipidaemia

Dyslipidaemia is one of the most common metabolic abnormalities in women with PCOS (5,16,124) with a reported prevalence of up to 70% (125). In one study, in comparison to the non-PCOS control group, higher levels of low density lipo-protein cholesterol (LDL-C) in women with PCOS were independent of age, BMI, exercise, and alcohol intake (125). The reported pattern of dyslipidaemia is generally consistent with the expected pattern in insulin resistance status; high LDL-C and Triglyceride (TG) and low high density lipo-protein cholesterol (HDL-C) (5). A systematic review and meta-analysis of these observational studies reported that in women with PCOS TG, LDL-C and non-HDL-C were higher by 0.29mmol/L (95% CI 0.19-0.39), 0.31 mmol/L (95% CI 0.26-0.41) and 0.49mmol/L (95% CI 0.41-0.57), respectively while HDL-C was lower by 0.15mmolL (95% CI 0.10-0.23)[2] (126). After matching for BMI, LDL-C and non-HDL-C cholesterol levels were still higher in women with PCOS (126). In a meta-analysis the classic phenotype, anovulatory hyperandrogenic PCOS, (26) had the worst lipid profile (126).
High levels of LDL-C appear to stay significantly higher in women with PCOS even after the menopause (127,128).

1.5.1.5 Cardiovascular disease

Evidence suggests that women with PCOS might be at increased risk of cardiovascular diseases (CVD). As discussed above, they have higher prevalence of dyslipidaemia, hypertension, T2DM, IGR, and obesity. Despite

---

[2] These numbers are converted from mg/dl to mmol/L for the purpose of this thesis. The actual report in the paper is in mg/dl and the numbers for the 4 above variable are 26mg/dl (95% CI 17-35), 12 mg/dL (95% CI 10-16) and 19 mg/dL (95% CI 16-22), 6 mg/dL (95% CI 4-9) respectively.

PCOS being associated with these established cardiovascular (CV) risk factors, published data to date have not confirmed a link with hard CV outcomes (4,91,129). PCOS is the most common cause of unexplained oligo-amenorrhoea (5) and studies have reported a significant correlation of menstrual dysregulation with CVD even after adjustment for BMI and other confounders (130). In addition, women with menstrual irregularity have a higher prevalence of angiographic abnormalities (131). However, PCOS patients in the Dallas Heart Study did not have a higher rate of coronary artery calcification (132). A long term retrospective cohort study reported no differences in myocardial infarction (MI) and angina but increased rate of stroke (101) and no increased CV mortality (100). Recently published retrospective (133) or prospective (134) studies reported no increase in CV morbidity and mortality. However, a meta-analysis showed a two fold increase in risk of arterial disease irrespective of BMI in these patients compared to the general population (11). Biomarkers associated with an increased risk of CVD such as hC-reactive protein, homocysteine, and tumour necrosis factor (TNF-α) have also shown to be increased in women with PCOS (19). In addition, women with PCOS, even at young age and after adjustment for BMI, have increased carotid artery calcification (135,136) as a predictor of atherosclerosis and CV events (16). The results were the same when comparing the carotid intima thickness in women with PCOS to the non-PCOS group after matching for all the traditional risk factors for CVD (137). However, a recent study did not find any difference between the carotid intima thickness of women with PCOS and the control group (138).

In conclusion, women with PCOS appear to be at increased risk of CV events (16,129). However, long term follow up studies are necessary to answer this question in a more robust way.

1.5.1.6 Obstructive sleep apnoea

The prevalence of obstructive sleep apnoea (OSA) is higher than expected in women with PCOS and cannot be explained by obesity alone (139-141). It is more closely associated with insulin resistance than BMI and age (139). Higher levels of androgens (140-142) or lower levels of progesterone (143,144) are

suggested to play a role in the pathogenesis of OSA, which might also explain the higher rates of OSA in women with PCOS (16). The risk of OSA in PCOS has been estimated to be at least five times higher than the matched obese population (141). However, reports of a 30 fold increase has also been published (139). OSA has an impact on the insulin resistance status of women with PCOS (145) and its treatment has shown beneficial effects on insulin sensitivity and overall cardio-metabolic function in these women (146).

1.5.1.7 Non-Alcoholic Fatty Liver Disease

Non-Alcoholic fatty liver disease (NAFLD) is a common problem in the current epidemic of obesity with 20-30 % of the general population being reported to have NAFLD and 2-3% the hepatitis status of the spectrum which is non-alcoholic steatohepatitis (NASH) (20,147). The reported prevalence of NAFLD in PCOS is as high as 55% (148) or twice as common in PCOS population as compared to the age and weight matched non-PCOS controls (149). High rates of NAFLD or abnormal liver status have been reported in the young (150,151) or even adolescents with PCOS (152). The converse is also true as in one study 71% of the reproductive age women with the established diagnosis of NAFLD would fulfil the Rotterdam criteria (27) for diagnosis of PCOS (151). However, one study reported no evidence of NAFLD in young and lean PCOS patients (153). It seems that women with PCOS, independent of their BMI, share some of the common risk factors of NAFLD such as insulin resistance, hypertension and dyslipidaemia (20,147) and are possibly at increased risk of NAFLD (20). The higher rates of obesity in women with PCOS only increases their risk of NASH and NAFLD (16).

1.5.2 Mental Health, Psychological and Emotional issue

Polycystic ovary syndrome is the most common cause of oligo-anovulatory infertility (5), and hirsutism (44) and it is commonly associated with obesity (18). These together with the other presenting symptoms such as acne, and menstrual irregularities and the associated metabolic conditions can impact on patients' emotions and quality of life (88). It is therefore not surprising that women with

PCOS have poorer health related quality of life (HRQoL) compared to some other chronic conditions such as diabetes, asthma, epilepsy and back pain (154). It seems that the low scores in HRQoL are independent of ethnicity (155) and the country of residence (156). Interviewing women with PCOS has shown that they feel "different", "freakish", "abnormal", "not proper woman", "less feminine" or "sexually undifferentiated" (157-159). In one study, these women consider their PCOS as a "theft of womanhood" (158) and want to be "normal" (157). This is also true in the teenagers with the condition who describe themselves as a "nerd" or "freak" (160). Women with PCOS have significantly higher rates of anxiety (9,161,162), depression (9,162,163) and emotional distress (9,164) even after matching for BMI (161,164). Teenagers diagnosed with PCOS also report higher rates of depression (160). A systematic review showed that women with PCOS, independent of their BMI, had a four times higher odds of an abnormal depression score as compared to the control group (90). The odds ratio for anxiety were even higher at 6.88 (95% CI 2.5-18.9) in women with PCOS (89). Other psychiatric disorders such as bipolar disorders have also been reported in association with PCOS (163). Attempts have been made to find the correlation with physical or biochemical signs of PCOS; in one study, the degree of anxiety appeared to have the same pattern as hyperandrogenaemia and insulin resistance independent of age and BMI (165). Another study showed that body dissatisfaction and age played a more important role than androgen levels (166). Hirsutism had a strong association with psychological distress in south Asian women with PCOS (156). A cross sectional analysis of 177 women with PCOS reported that "self-worth", "age", "time taken to diagnosis" and "appearance" as predictive factors for anxiety or depression (162).

In summary, women with PCOS have higher rates of depression and anxiety. It has an emotional impact on women suffering from the condition and lowers their quality of life.

1.5.3 Cancer

1.5.3.1 Endometrial Cancer

Higher rates of endometrial cancer are expected due to long term exposure to un-opposed oestrogen (167) and, therefore, this risk is potentially high for the phenotypes associated with amenorrhoea (4). However, it is difficult to differentiate the effects of associated obesity, infertility and anovulation (4). A systematic review on the related studies showed a RR of 2.7 (95% CI 1.0 – 7.29) for PCOS to develop endometrial cancer but this analysis did not match for BMI and or the phenotypes of PCOS (168).

1.5.3.2 Ovarian Cancer

It is hypothesised that infertility and anovulation may increase the risk of ovarian cancer (169). However, studies including women with PCOS are inconclusive (4). A systematic review showed 2.5 fold increase in the risk of ovarian cancer in women with PCOS (168) but the results were influenced by a large number case-control study from a cancer registry (170), which was not adequately designed to answer this question and would therefore undermine the validity of the meta-anaysis (4). For example, treatments were not included in the analysis while it is known that treatments like contraceptive pills or ovulation induction decrease the odds of ovarian cancer (4). The evidence is inconclusive and international guidelines (4) do not recommend any screening for ovarian cancer in these women.

1.5.3.3 Breast Cancer

There is sufficient evidence (4,168) to conclude that breast cancer is not increased in women with PCOS.

1.6 Summary and Conclusion

PCOS is a common condition affecting up to 18% of the women and generally starts at a very young age. The underlying pathophysiology of insulin resistance and the associated signs and symptoms like hirsutism, menstrual irregularities and obesity have major effects on their mental and physical health. Diagnosing a woman with PCOS implies a higher risk of T2DM, hypertension, dyslipidaemia, NAFLD, OSA, cardiovascular diseases, as well as anxiety, depression and a lower quality of life.

There is a need to help women with PCOS to understand their condition in depth, its long term effect and more importantly what they can do to prevent or lower the risk of these associated problems.

Chapter 2 : Phenotypic analysis and cardiovascular outcomes in a multi-ethnic cohort of women with PCOS

A large multi-ethnic cohort of women with PCOS whose data were collected over time in a clinical setting could be the source of useful information for a tailored education programme. Such a database can establish the outcomes described earlier in Chapter 1 and help study the clinical characteristics of PCOS in different ethnicities. A unique opportunity arose due to the availability of a clinical database in the Diabetes and Endocrinology department at the Leicester Royal Infirmary.

In this chapter, the database used for this analysis is described followed by a general phenotypic description of the clinical and demographic characteristics of the cohort included in the database and then the associations of ethnicity, body mass index and age with clinical characteristics. Finally, the cardiovascular outcomes are presented.

2.1 Introduction

Despite years of history behind PCOS, our knowledge of the condition, its natural behaviour and phenotypic differences is still poor (14,171). Phenotypic description of the population helps in understanding the condition; it seems geography, in terms of ethnicity, genetics and environmental factors play a role (4,51,55). The prevalence of PCOS is different among different populations even if they are compared by the same criteria (see Chapter 1, Table 1.2). Using the National Institute of Health (NIH) criteria (26) the reported prevalence varies from 2.2% in China (37) to 4%-5% in the USA (28) or Sweden (40) and up to 8.7% in Australia (29). This difference is more pronounced using the Rotterdam criteria (27). This suggests that ethnicity might play a role in the phenotypic presentation of PCOS, which indeed has some evidence in the literature (17,172-176). Indigenous south Asian (SA) women with PCOS are typically younger and at higher risk of the metabolic syndrome (60). It is suggested that SA ethnicity has an independent effect on the reduction of insulin sensitivity (177), which is cumulative with the effect of PCOS on insulin sensitivity (178). A comparison between the SA and white women with PCOS found that the SA group presented at a younger age and had higher rates of hirsutism, secondary infertility, and insulin resistance (45). The two groups had similar BMI and fasting glucose (45).

In addition, little is known about the association of age and obesity with these characteristics in women with PCOS. It is known that older age is associated with increased insulin resistance (179) and reduction in ovarian size (50). Increase in body weight accentuates anovulatory signs and increases androgenic symptoms (61,180). Nevertheless, there are few studies specifically investigating the association of age and obesity with the clinical presentation of PCOS in a large cohort of patients. Also, as described in Chapter 1, there is uncertainty about the cardiovascular (CV) risk status of women with PCOS.

A large multi-ethnic cohort of women with PCOS, which were collected over 20 years in a local database, provided an opportunity to answer some of these questions. Specific aims in this analysis were;

1- To provide a phenotypic description of the population

2- To understand the effects of ethnicity, weight and age on clinical characteristics of women with PCOS

3- To investigate whether PCOS was associated with higher rates of diabetes and CV outcomes as compared with the general female population

2.2 Data sources and Methodology

2.2.1 Sources of data

A woman with PCOS can possibly use many services in the health system and each service has its own database to register and monitor this activity. The analysis in this chapter uses the databases of two very important services which a woman with PCOS could possibly have used; a speciality clinical service for women with PCOS and the hospital admissions. [Database analysis and record linkage were approved by Leicester Research Ethics Committee Ref 09/H0406/71 and 06/Q2505/2]

2.2.1.1 Leicester Clinical Workstation Database

A departmental clinical information system (Leicester Clinical Workstation = LCW) contains detailed information on diagnosis, investigations and treatment (encoded using the Clinical Terms v3 [Read Codes]) on all patients seen since 1988 in the Diabetes and Endocrinology service at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, the main specialist endocrine provider for Leicestershire which covers a population of almost one million people. Data are collected and maintained as part of routine clinical practice and the system is used as the primary source of clinical information during every clinical contact with the patient. This database was set up by Dr Trevor Howlett in 1988. Figure 2.1 shows a snapshot from the print screen;

Figure .2.1 Snapshot of the Leicester Clinical Workstation database

"Main diagnosis" is registered for any patient who attends the clinic and is generally completed or approved by the consultant responsible for the patient. The "other problems" and "Events/Procedures/Investigations" section allows entry of any clinical concept which the clinician seeing the patient feels to be clinically relevant, but they do not insist on completion of any specific variables. Three health care assistants perform the measurements such as body weight, height and blood pressure (BP) in the clinic and document the details in the hospital notes. However, their entry into the LCW depends on the clinician. Details of the clinical examination follow the same process and while every patient has an examination and each visit is supervised by the senior endocrinologist in the clinic and documented in the hospital notes, their availability on LCW depends on the completion of data entry by the clinician seeing the patient. This database also registers the demographic data and while some are mandatory such as date of birth, some are not - for example ethnicity.

For each patient attending the clinic a letter is produced to summarise the consultation for the patient's GP or the health care professional who has referred the patient to the clinic. These letters are stored electronically in the LCW and are available for the period since the database was set up. Therefore, if a patient started to come to the clinic in 1990 their letters would be available until they were discharged. For a patient whose first appointment in the clinic was before 1988 (for example 1985), they would definitely have a diagnosis, but their clinic letters would be recorded after 1988 and anything before that may or may not be available in the database.

It is, therefore, obvious that while some variables (like diagnosis and age) are available for every single patient, other variables depend on the operator's input to the system and may be missing.

2.2.1.2 Health Informatics Services Database

The Leicestershire NHS Health Informatics Services (HIS) holds the "hospital episodes statistics" database. The HIS database covers the same stable population of approximately one million individuals served by the endocrinology

clinics and has been routinely linked to the local population register since it was established in 1985. HIS also contains demographic data such as ethnicity, index of multiple deprivations (IMD), and a record of patient's date of registration in the health system which indirectly reflects migration in and out of the region when a patient has multiple registrations over time. However, HIS does not hold data on the referrals to the general practice. The HIS database was used to extract any hospital admission or reported death in the study population. Any patient who was admitted to a hospital in Leicester would have an entry in this database and therefore it is a fairly robust database for determining the hard cardiovascular (CV) outcomes which might need in-patient admission.

I did not have direct access to the database, but our team had a collaboration with Dr Hanna Blackledge (HB) in the local strategic health authority (currently known as clinical commissioning group) which administrates the HIS database.

2.2.1.3 Data Linkage

A search criteria was set up by Dr Howlett to interrogate LCW for any recorded diagnosis of "PCOS" at any time The inclusion criteria were women who attended the clinic at LRI between October 1988 and 1st November 2009 (point of data extraction) and were assigned a clinical diagnosis of PCOS. For all the patients the same report retrieved data on presence, dates and details of: a) symptoms and signs of PCOS, b) diabetes mellitus, c) other conditions which would exclude the patient from analysis (Cushing's syndrome and congenital adrenal hyperplasia), d) any type of CV disease or CV risk factor (including hypertension and smoking), e) ethnic origin and f) death.

The extracted data at this stage was merged with Leicester hospital episodes statistics maintained by the HIS database. The anonymised linkage was done in Sept/2010 by HB in the HIS team, using two identifiers (NHS numbers and date of birth) and finalised by Dr Laura Gray, the statistician in our team.

2.2.2 Steps in processing the database

The search in LCW data linkage were finalised and the following steps were completed:

1. Reviewing the available electronic letters for all the extracted patients to ascertain the criteria for the diagnosis of PCOS in each patient and capture as much data as possible which were mentioned in the clinical letters and not directly entered into the electronic database.

   Presenting symptoms such as hirsutism, acne, infertility or menstrual irregularity were typically recorded, but in some cases further exploration of the diagnostic criteria leading to the diagnosis of PCOS such as blood test, or results of examination were not systematically recorded or dictated in the clinical letters. The defining signs and symptoms for each category of diagnosis as per the Rotterdam definition (27) were:

   Clinical or biochemical hyperandrogenism; any documentation of "hirsutism", "acne", "androgenic alopecia", or blood tests indicative of "high testosterone", or "high free androgen index". It has been a historical routine in the department to use a self-scoring modified Ferriman-Gallwey (181) scale for hirsutism as well as the clinician's examination. Unfortunately, there are hardly any electronic records of the actual score in the LCW.

   Anovulation: any documentation of "oligomenorrhoea", or "amenorrhoea", and or "infertility" (which was investigated otherwise and confirmed to be related to PCOS) was included in this category. Exclusions were reports of "menorrhagia", "polymenorrhoea", "menstrual irregularity", and spotting, which would not have a uniform description and have never been classically included in the diagnosis of PCOS.

<u>Imaging documentation of polycystic ovaries</u>; any ultrasound or Magnetic Resonance Imaging (MRI) confirmation of the cysts in the ovary (ovaries), which were reported by the radiographer as polycystic ovaries (PCO). However, it should be mentioned that during the period in which most of these patients presented it was not the clinical policy of the department to perform routine ovarian ultrasound when the diagnosis of PCOS was clear on clinical and biochemical grounds (26,27).

An example to illustrate the work is a patient whose hyperandrogenism was indicated by her blood test (high testosterone or high free androgen index) which could have been recorded in three ways in the LCW:

i)   actual level of high testosterone

ii)   a mention in the clinic letter as "Patient's blood test showed high levels of free androgen index, indicative of PCOS" or

iii)   "her examination and investigations are indicative of the diagnosis of PCOS" and the actual result or criteria was not recorded.

Diagnostic criteria for the first two examples would be updated to have "hyperandrogenism" as a criterion, but the 3rd case would be left blank as her diagnostic criteria were not clear.

Since data were all recorded in the database as part of a routine clinical practice and since a clinical diagnosis of PCOS had been applied to the patient in the endocrinology clinic and was consistently reviewed by a senior endocrinologist, it was considered that in patients where no symptoms or investigation were recorded this was most likely evidence of failure to record relevant clinical findings rather than evidence of the absence of these findings. [Subgroup analyses have been performed for those with evidence for definite PCOS [two or more Rotterdam criteria (182))].

2. Clinical letters and all the available laboratory data were reviewed for all the patients who also had a recorded diagnosis of Cushing, Congenital adrenal hyperplasia, hyperprolactinemia and hypothyroidism to make sure that the diagnosis of the PCOS stands after the related investigations or the patient is excluded if needed. The patients in this category were all reviewed together with Dr Howlett to make sure there was an input from a senior endocrinologist in establishing the final diagnosis.

3. The diagnosis of diabetes was reviewed to make sure there was evidence of follow up in the diabetes speciality clinic (an indication of correct diagnosis) or a confirmatory blood test in the laboratory database for anyone not under care of our clinic. In view of the reports of a high number of people being misclassified (183) followed by the publication of the guidelines in the Classification of Diabetes (184), all of the patients with a recorded diagnosis of Type 1 diabetes were reviewed by myself and an independent Diabetologist (Dr David Webb). Their diagnosis on the database was changed to T2DM if they met the current classification criteria.

Possible approaches to the analysis of this complex database were considered: ideally, for the CV outcome analysis, a control group matched at baseline for all the known CV risk factors would be selected and followed up in parallel to our PCOS patients. Finding a control group from the general female population in Leicester proved extremely difficult primarily due to the retrospective nature of this analysis, and changes in the structure and the data storage in the local strategic health authorities over 22 years and the complexity of a young population in the study group with their migration history, socio-economic and ethnic backgrounds. Studying patients from the same clinical database with a different endocrine diagnosis such as thyroid disease was considered, but it proved impossible to identify any group with equivalent numbers in the same age distribution who were free of endocrine-disease-associated CV risk factors. Therefore selection of the age-group matched local general female population monitored on the same database would at least eliminate some of the

confounding factors such as age, ethnicity and index of multiple deprivation (IMD).

2.2.3 Statistical methods

Descriptive characteristics of the population are presented using mean (standard deviation = SD) for continuous variables and percentages for categorical variables. The available demographics and clinical characteristics recorded at any stage during the treatment of the patients were used for this analysis, which would generally mean the data from first appointment in the speciality clinic. However, it should also be emphasised that the first presentation to a speciality clinic is not usually the first date of diagnosis of PCOS and patients would often have been diagnosed prior to that appointment by their general practitioner. Similarly, symptoms might have been present for some time before a patient sought medical advice.

For the categorical data such as signs, symptoms, smoking and history of hypertension only the presence (rather than the absence) of these parameters were recorded in the database and therefore missing fields could relate to either a negative or missing response. For the continuous data only the first available recording of the data were used for analysis.

Ethnicity was self-reported on registration in the hospital or HIS database. These reports were grouped in four broad categories; white (white British, white Irish, white), south Asians (= SA, including; Bangladeshi, Indian, Pakistani), Black (African-Caribbean, African Black), and others (Chinese, Other Asian background, other ethnic groups, mixed ethnic groups).

Ethnicity was not recorded for 19% (n=450) of the population. Two independent expert administrators assigned the ethnicity on the basis of the name and available religious orientation; for example, an Indian name with a Hindu or Sikh religion was assigned SA or an English name with a Church of England orientation was assigned White. Religious orientation was recorded for 158 of the 450 patients (35%). Any uncertainty was recorded as "other ethnic origins" and therefore excluded from this analysis for ethnic associations. Two administrators

disagreed in 23 cases (<1%) who were classified as "other". This methodology has been used in previous studies (185).

Data was not imputed for the missing variables: "diagnostic criteria for PCOS", "ethnicity", "BMI" and "BP". However, sensitivity tests were performed on the database and the groups were compared by analysis of variance (ANOVA) test.

The following sections describe the phenotypic characteristics of this population followed by their long term cardiovascular outcomes. Specific statistical methods and analysis used for each of these sections will be described separately under the related subheadings.

2.3 Phenotypic description of a multi-ethnic population of women with PCOS

2.3.1 Results

Data extraction yielded 2,422 patients. However, two had never attended the diabetes and endocrine clinic and four had double entries and therefore 2,416 women with a diagnosis of PCOS had attended the speciality clinic during the observation period. Of these a total of 63 women had to be excluded due to one or more of the following reasons; i) alternative confounding diagnoses namely Cushing's syndrome (n=14) or congenital adrenal hyperplasia (n=8), ii) having no NHS number recorded in the clinical database (n=36) or age under 16 at the time of data extraction (n=10).

Table 2.1 shows the characteristics of the 2,353 PCOS patients included in this analysis which consisted of 29% SA, 64.7% white, 1.1% black and 5.1% other ethnicities. Mean (SD) age at first clinic appointment was 26.4 (7.6) years and age range of 8.6 to 64.8 years. [Obviously the diagnosis of PCOS would not have been made at these extremes of age; some paediatric patients would have been referred to the endocrine service for other reasons such as growth problems and then stayed under follow up in the clinic and they were diagnosed with PCOS at a later age. For the post-menopausal women; they had been diagnosed with PCOS elsewhere and had been referred to the endocrine department for any other reasons such as diabetes, obesity management, etc. Their diagnosis of PCOS would have been reviewed by the endocrine consultants before being entered into the database]. Mean (SD) BMI was 30.1 (7.6) kg/m^2, ranging from 15.2 kg/m^2 to 63.9 kg/m^2.

The mean (SD) duration of follow up in the clinic was 2.9 (4.1) years, ranging from zero to 27.9 years The mean number of out-patient appointments was 5.3 (SD 5.4) visits for each patient ranging from zero to 63 visits (Median 4 and mode 2). The majority (88.8%) were under the care of two endocrine consultants; Dr Howlett and Dr Levy (82.6 and 6.2% respectively).

Table 2.1 Characteristics of the women with PCOS registered in Leicester Clinical Workstation from 1988 to 2009

Variable	Total Cohort
Total (number)	2353
Age in years; Mean (SD)	26.4 (7.6)
Ethnicity (%)	
White	64.7
South Asian	29.1
Black	1.1
Other	5.1
Smoker (%)	13.5
Acanthosis Nigricans (%)	6
BMI, Mean (SD) kg/m^2	30.1 (7.6)
IMD Mean (SD)	20.99 (15.13)
History of Hypertension (%)	9.3
Systolic BP Mean (SD), mmHg	130.6 (15.7)
Diastolic BP Mean (SD), mmHg	73.7 (11.1)
Evidence of androgen excess (%)	87.5
Hirsutism	75.5
Androgenic Alopecia	4.5
Acne	21.3
Increased Androgen Excess†	5.7
Evidence of anovulation (%)	78.5
Oligomenorrhoea	58.3
Amenorrhoea	16.1
Infertility	15.6
Polycystic ovaries (%)‡	7

SD = Standard Deviation, BMI= Body mass index, IMD = Index of multiple deprivation, BP = Blood Pressure.
† This has not been documented for every patient as explained in page 30. ‡ As explained in page 30, the imaging investigation has not been a routine practice in Leicester.

2.3.1.1 Sub-groups and sensitivity analysis

As mentioned in the methods section, there were some missing data and therefore sensitivity analyses were performed to analyse the impact of the missing data on the total population.

Definite PCOS

Some of the patients did not have a documentation of the minimum two criteria required for a definite diagnosis of PCOS as per Rotterdam consensus (27). The characteristics of the women who had at least two diagnostic criteria (72% of the total cohort) are presented in Table 2.2. Considering that ultrasound scan was not routinely done in Leicester, most of these women (94%) also would be diagnosed with PCOS based on the classic National Institute of Health criteria (26).

Those with definite PCOS were similar to the total cohort (Table 2.2) except that they were younger in age.
Those with definite PCOS, however, had slight differences with those without a definite diagnosis. Patients with definite diagnosis of PCOS were younger, had more acanthosis nigricans (AN), and higher BMI (30.3 Vs 29.3 kg/m^2 P = 0.03). They were similar in ethnicity distribution, BP, history of hypertension and smoking rates. Expectedly, there were differences in the recorded signs and symptoms. However interestingly the two groups were not different in the recorded "androgenic alopecia" and that is possibly due to the rarity of this sign and possibly its importance for the patients as something which brings them to the clinicians as a first complaint and therefore would be documented in the database in the problem list.

Table 2.2 Comparison of the cohort with and without definite diagnosis of PCOS as per Rotterdam criteria [Presented as Mean (SD) or %]

Variable		Total Cohort (A)	Definite PCOS (B)	Not Definite PCOS (C)	P-Value B Vs C
Total (number)		2353	1714	639	N/A
Age in years;		26.4 (7.6)	25.7 (7.1)	28.0 (8.6)	<0.001
Ethnicity	White	64.7%	65.2%	63.4%	0.5
	South Asian	29.1%	28.8%	29.9%	0.6
	Black	1.1%	0.9%	1.6%	0.4
	Other	5.1%	5.1%	5.2%	0.6
Smoker		13%	13.1%	14.6%	0.2
Acanthosis Nigricans		6%	6.9%	4.1%	0.006
BMI, kg/m^2		30.1 (7.6)	30.3 (7.6)	29.3 (7.5)	0.03
IMD		20.99 (15.13)	21.26 (15.4)	20.3 (14.4)	0.16
History of Hypertension		9.3%	9.1%	9.9%	0.6
Systolic BP mmHg		130.6 (15.7)	130.6 (15.1)	130.7 (18.2)	0.9
Diastolic BP mmHg		73.7 (11.1)	73.7 (10.9)	73.9 (11.8)	0.8
Evidence of androgen excess		87.5%	95.6%	66.2%	<0.001
Hirsutism		75.5%	80.3%	62.0%	<0.001
Androgenic Alopecia		4.5%	4.8%	3.4%	0.09
Acne		21.3%	23.3%	16.0%	<0.001
Increased Androgen Excess†		5.7%	7.3%	1.6%	<0.001
Evidence of anovulation		78.5%	98.0%	26.3	<0.001
Oligomenorrhoea		58.3%	74.7%	14.2%	<0.001
Amenorrhoea		16.1%	19.0%	8.5%	<0.001
Infertility		15.6%	18.1%	9.1%	<0.001
polycystic ovaries ‡		7%	9.5%	0.3%	<0.001

SD = Standard Deviation, N/A = not applicable, IMD = Index of multiple deprivation, BP = Blood Pressure
† This has not been documented for every patient as explained in page 30. ‡ As explained in page 30, imaging investigation has not been a routine practice in Leicester

Table 2.3 Comparison of cohorts of women with PCOS with Known and Unknown ethnicity [Presented as Mean (SD) or %]

Variable		Total Cohort (A)	Known ethnicity(D)	Unknown ethnicity (E)	P-Value D Vs E
Total (number)		2353	1903	450	N/A
Age in years;		26.4 (7.6)	26.7 (7.7)	24.8 (6.8)	<0.001
Ethnicity	White	64.7%	65.4%	N/A	N/A
	South Asian	29.1%	29.0%	N/A	N/A
	Black	1.1%	0.8%	N/A	N/A
	Other	5.1%	5.3%	N/A	N/A
Smoker		13%	13.6%	13.1%	0.4
Acanthosis Nigricans		6%	6.5%	4.7%	0.09
BMI, kg/m^2		30.1 (7.6)	30.5 (7.7)	27.8 (6.9)	<0.001
IMD		20.99 (15.13)	21.1 (15.4)	20.5 (13.9)	0.5
History of Hypertension		9.3%	10.8%	3.1%	<0.001
Systolic BP mmHg		130.6 (15.7)	130.9 (16.0)	128.3 (13.8)	0.09
Diastolic BP , mmHg		73.7 (11.1)	74.1 (11.2)	70.5 (10.0)	0.001
Evidence of androgen excess		87.5%	87.7%	87.1%	0.4
Hirsutism		75.5%	76.3%	72.4%	0.05
Androgenic Alopecia		4.5%	4.9%	2.7%	0.02
Acne		21.3%	20.3%	25.6%	0.01
Increased Androgen Excess†		5.7%	5.8%	5.8%	0.9
Evidence of anovulation		78.5%	78.5%	78.7%	0.9
Oligomenorrhoea		58.3%	58.6%	56.9%	0.3
Amenorrhoea		16.1%	15.4%	19.1%	0.03
Infertility		15.6%	17.4%	8.0%	<0.001
Polycystic ovaries ‡		7%	7.4%	5.6%	0.1

SD = Standard Deviation, N/A = not applicable, IMD = Index of multiple deprivation, BP = Blood Pressure
† This has not been documented for every patient as explained in page 30. ‡ As explained in page 30, imaging investigation has not been a routine practice in Leicester

Known Ethnicity

Similarly as discussed earlier, some of the patients did not have an ethnicity recorded in the database. A subgroup of the patients in whom the ethnicity was definitely recorded and self-defined by patients was identified. The characteristics of these patients are shown in the same Table 2.3.

Those with unknown ethnicity were younger, slimmer and had lower diastolic Blood pressure (BP) and less infertility (Table 2.3). However, separating their data from the total cohort did not affect any of the variables as the group with known ethnicity were similar to the total cohort in their demographic and clinical characteristics.

Missing BMI and BP

Number and percentage of patients who had their blood pressure (BP) and body mass index (BMI) recorded were 1,010 (48%) and 1,603 (68%) respectively.

Those with missing BP and BMI were healthier in some aspects (low smoking rates and lower history of hypertension) and had less hyperandrogenic and anovulatory signs. (Table A2.1 and A2.2 Appendix 2)

Those with missing data were generally associated with the earlier days of the database and their data entry had been done in the development stage of the clinical database (at the end of observation; time (SD) from first appointment for those with missing diagnostic criteria was 12.3 (6.4) years versus 9.3 (6.4) p < 0.001) and most of these missing data clustered together: for example, only 12 patients out of the 750 patients with missing BMI had their blood pressure measured.

In summary, the sensitivity analyses showed that the missing data might have an impact on the interpretation of the results especially in case of BMI and BP.

2.3.2 Summary and discussion;

This cohort of women with PCOS were young and generally overweight and obese and these characteristics were not different to the other cohorts described in the literature (92,93) . The distribution of hyperandrogenic and anovulatory signs and symptoms and other morphologic characteristics like BMI were also similar to the other described cohorts (43). Besides, the ethnic distribution of this database was also similar to the background population in Leicester with one-third SA and two-thirds white (186).

Finding these similarities support the extrapolation of the findings to the women with PCOS outside this database or non-local women with PCOS. Of course one can only expect some selection bias in dealing with a population of women with PCOS who have been referred by their primary care physician to a speciality clinic (187). However, with 70 to 90% of the women with PCOS not being diagnosed and not seeking any medical advice (29,32) there is always a degree of bias in the selected population. In the current situation a cohort which has same behaviour as the rest of the described cohorts in the literature is well placed to be studied in detail.

The general problem of the missing data in a database (especially one that is collected in a clinical setting) applies here. The sensitivity tests performed on those with missing data showed the necessary steps needed to be taken in performing further analysis on this population and also the need for a cautious approach in interpreting the results. Lower smoking rate and history of hypertension in those with missing BMI and BP records as well as lower rates of anovulatory and hyperandrogenic signs could either be a result of less documentation of all signs and symptoms together (as described before), or could be the result of an unintentional bias for not documenting the data in the "healthier" women.

2.4 Clinical characteristics of polycystic ovary syndrome in White and South Asian women; comparison of ethnicities, younger and older, obese, overweight and normal weight women with PCOS

2.4.1 Statistical methods

The general methodology and statistical methods which were described previously (section 2.2.3) do also apply to this section as well as the following additional points.

The primary aim of this analysis was to compare the phenotypic differences between ethnic groups and therefore the results of the earlier sensitivity analyses were considered. There were clinical and demographic differences between those with known and unknown ethnicity and, therefore, the cohort with known ethnicity (n=1903) has been used for this analysis (Table 2.3 page 38). Also, because of the very low number of the "Black" (n=16) and "other ethnic" (n=101) groups, in the following analyses of the effects of ethnicity, age and BMI, only the white and SA ethnic population have been considered. This has therefore reduced the total population from 2,353 to 1,786.

Three separate analyses were performed on the database to compare women based on their ethnicities, age of presentation to clinic and weight category.

Age adjusted comparison was performed between the white and SA groups, using linear regression models for continuous variables and logistic regression models for categorical variables.

In a separate analysis, women were divided into two broad age categories based on the age at their first clinic visit; younger than 30 years (<30) and older than 30 years (≥ 30). The age of 30 was used as one of the key stages in adult development and bearing in mind its psychological impact on the adult development, career and personal life (188,189). Besides, the mean age for marriage in women in UK, between 1988 to 2008, has moved up from 28 to 34 years old (190). [Consideration was given to this important developmental age

also in view of the development of the SUCCESS education programme (described in Chapters 4-6)]. Ethnicity adjusted comparison was used to compare characteristics between the two age groups, using linear regression models for continuous variables and logistic regression models for categorical variables.

Ethnic specific BMI cut points (191) [White: Normal BMI < 25 kg/m^2, $25 \leq$ overweight < 30 kg/m^2 and Obese ≥ 30 kg/m^2; Black, SA and minor ethnicities: Normal BMI < 23 kg/m^2, $23 \leq$ overweight < 27.5 kg/m^2 and Obese ≥ 27.5 kg/m^2] was also used to categorise and compare the groups. For this comparison only SA and white patients with a recorded BMI were used (n=1254)

2.4.2 Results

2.4.2.1 Comparison of the two ethnicities;

Table 2.4 shows the age adjusted characteristics of the white and SA women with PCOS. Compared to the White group, SA women presented at a younger age and therefore an age adjusted comparison was conducted for the rest of the characteristics. South Asians had a more deprived socio-economic status and had significantly higher rates of documented acanthosis nigricans (AN), T2DM and hyperandrogenic symptoms. White women had a significantly higher BMI, however, the ethnic specific cut points for BMI (191) showed that both ethnicities had the same proportions of obese and overweight women. Systolic and diastolic BP were higher in white women but the overall past medical history of hypertension was not different between the two groups. Evidence of anovulation especially, amenorrhoea, were significantly higher in white women.

Table 2.4 Age adjusted comparison of the White and South Asian women with PCOS

Variable		White(n=1246)	SA(n=540)	P-Value White Vs SA
Demographic variables: Mean (SD) or %				
Age in year:		27.6 (7.8)	25.0 (7.4)	**<0.001**
Deprivation score (IMD)		18.9 (15.1)	25.3 (15.0)	**<0.001**
Smoking		18.3	4.3	**<0.001**
Acanthosis Nigricans		2.9	13.7	**<0.001**
Type 2 Diabetes		5.9	9.6	**<0.001**
Biomedical variables : Mean (SD) or %				
Body Mass Index		31.3 (7.9)	28.8 (6.7)	**<0.001**
	Normal	24.3	21.7	0.1
Body Weight †	Overweight	22.5	23.0	0.9
	Obese	53.2	55.3	0.1
Hypertension-History		11.6	9.4	0.8
Systolic BP in clinic		133.3 (16.1)	126.3 (14.7)	**<0.001**
Diastolic BP in clinic		75.4 (11.4)	71.3 (10.2)	**<0.001**
Evidence for Androgen Excess: %				
Any Androgen criteria		85.6	92.8	**<0.001**
Hirsutism		72.4	84.8	**<0.001**
Androgenic-alopecia		4.5	5.6	0.2
Acne		21.5	17.4	**0.01**
Evidence for Anovulation: %				
Any Anovulation criteria		81.0	73.0	**<0.001**
Oligomenorrhoea		58.3	59.6	0.8
Amenorrhoea		17.7	10.7	**<0.001**
Infertility		18.1	15.4	0.6

SD= Standard Deviation, BP=Blood Pressure
† Body Weight Classification is defined based on ethnicity cut off points [White: Normal BMI < 25 kg/m^2, 25 ≤ overweight < 30 kg/m^2 and Obese ≥ 30 kg/m^2, Black, SA and minor ethnicities: Normal BMI < 23 kg/m^2, 23 ≤ overweight < 27.5 kg/m^2 and Obese ≥ 27.5 kg/m^2] (191)

2.4.2.2 Age at presentation to clinic

Considering the significant effect of ethnicity on clinical and demographic characteristics, the comparison of the two presenting age groups was adjusted for ethnicity (Table 2.5).

Patients who first presented to the speciality clinic at an older age (> 30 years) appeared to be more obese, and had higher rates of T2DM, hypertension, systolic and diastolic BP. Although the overall hyperandrogenism was not different between the two groups, there was a shift from acne to hirsutism in those who presented to clinic at an age above 30 years. Evidence of anovulation decreased except for infertility which was more common an issue with those in the older age group.

Fig 2.2 summarises the composition of the signs and symptoms in each ethnicity and age group.

Table 2.5 Ethnicity adjusted† comparison of clinical and demographic characteristics according to the age of presentation in clinic

Variable		Under 30 years (n=1212)	Above 30 years (n=574)	P-Value <30 Vs ≥30
Demographic variables: Mean (SD) or %				
Average Age (years)		22.5 (4.3)	35.9 (5.2)	**NA**
Deprivation score		21.4 (15.5)	19.6 (14.8)	0.1
Smoking-History		12.5	17.2	0.07
Acanthosis Nigricans		7.0	4.4	0.2
Type 2 Diabetes-History		4.4	12.7	**<0.001**
Biomedical variables: Mean (SD) or %				
Body Mass Index		29.6 (7.4)	32.6 (8.0)	**<0.001**
	Normal	27.4	15.4	**<0.001**
Body weight‡	Overweight	23.4	21.1	0.4
	Obese	49.2	63.5	**<0.001**
Hypertension-History		6.1	21.1	**<0.001**
Systolic BP in clinic		129.3 (15.2)	134.7 (17.0)	**<0.001**
Diastolic BP in clinic		72.4 (10.8)	77.7 (11.1)	**<0.001**
Evidence for Androgen Excess: %				
Any Androgen criteria		87.1	89.0	0.1
Hirsutism		73.3	82.2	**<0.001**
Androgenic-alopecia		4.6	5.2	0.5
Acne		22.8	15.0	**<0.001**
Evidence for Anovulation: %				
Any Anovulation criteria		81.7	72.0	**<0.001**
Oligomenorrhoea		62.1	51.4	**<0.001**
Amenorrhoea		17.0	12.5	**0.005**
Infertility		14.7	22.6	**<0.001**

SD=Standard Deviation, BP=Blood Pressure, NA=Not applicable
†Considering the significant effect of ethnicity on clinical and demographic characteristics the comparison was adjusted for ethnicity.
‡ Body Weight Classification is defined based on ethnicity cut off points [White: Normal BMI < 25 kg/m^2, 25 ≤ overweight < 30 kg/m^2 and Obese ≥ 30 kg/m^2, Black, SA and minor ethnicities: Normal BMI < 23 kg/m^2, 23 ≤ overweight < 27.5 kg/m^2 and Obese ≥ 27.5 kg/m^2] (191).

Figure 2.2 Distribution of the clinical signs and symptoms by age group and ethnicity
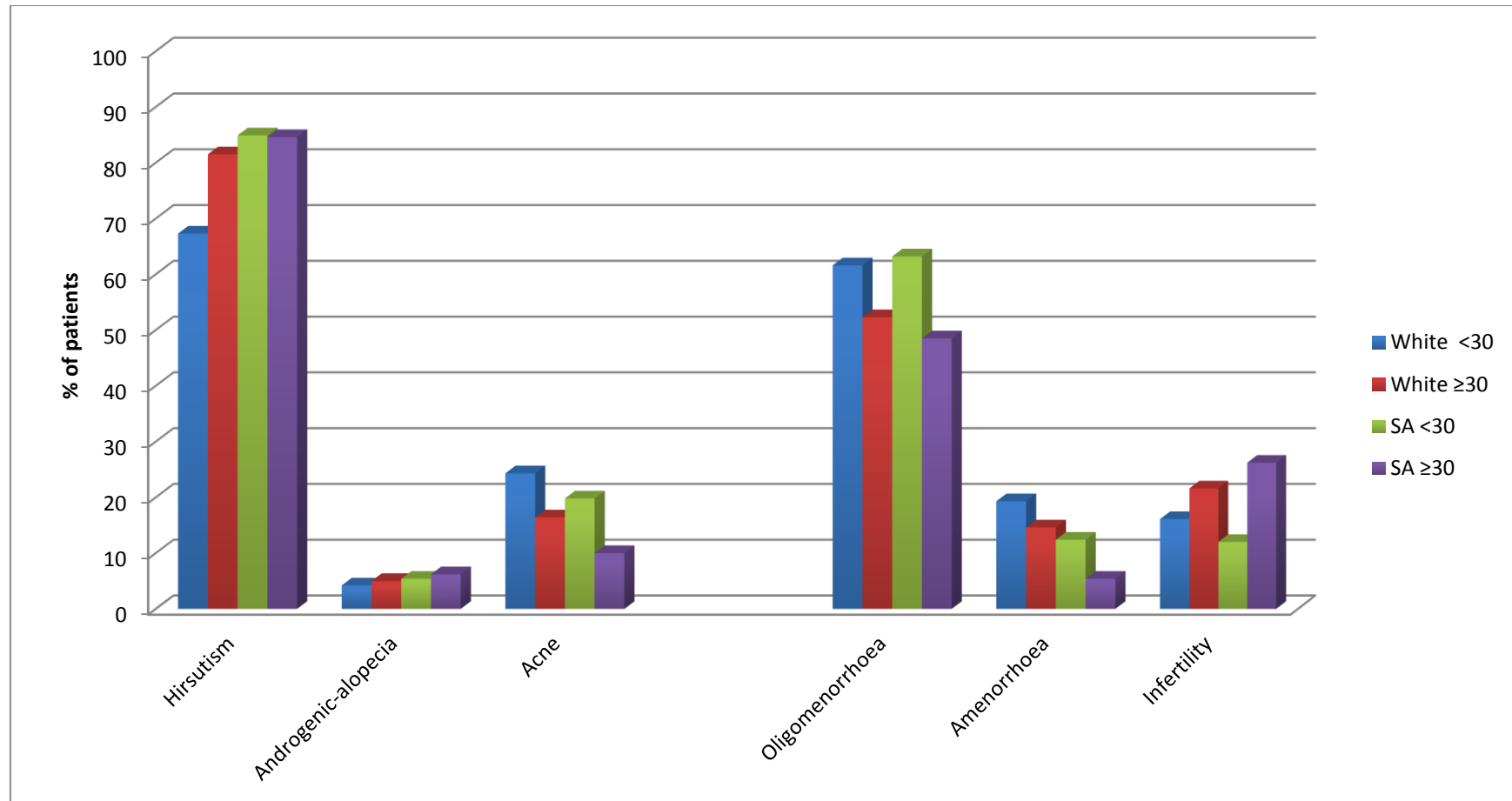
2.4.2.3 Body weight

Phenotypic characteristics of the different weight categories (191) are compared in Table 2.6. There was a significant difference in presenting age to the clinic amongst the three weight categories with the obese group being older at their first appointment [mean (SD) age at presentation was 25.2 (6.8), 26.1 (7.8), and 27.6 (8.3) years for normal, overweight and obese groups respectively]. Therefore the comparison for the rest of the variables was adjusted for age. Obese women with PCOS were more socio-economically deprived, had higher prevalence of T2DM, hypertension, and AN. There was no difference in the overall presence of androgenic criteria between the three groups, however prevalence of hirsutism was higher and that of acne was lower in the obese group as compared to the normal weight group. Infertility was much higher in the overweight and obese groups.

Table 2.6 Age adjusted† comparison of the morphologic symptoms as per body weight category‡

Variables	Normal Weight (n=295)	Overweight (n=284)	Obese (n=675)	P ValueℲ
Demographic variables: Mean (SD) or %				
Age (at first clinic)	25.2 (6.8)	26.1 (7.8)	27.6 (8.3)	**0.006**
Deprivation Score	19.1 (14.3)	20.6 (14.9)	22.2 (15.9)	**0.001**
Smoking	15.9	18.0	15.9	0.8
Acanthosis Nigricans	1.4	4.2	13.0	**<0.001**
Type 2 Diabetes-History	2.4	4.2	12.9	**<0.001**
Biomedical variables: Mean (SD) or %				
Hypertension-History	3.7	9.5	17.5	**<0.001**
Systolic BP mmHg	123.0 (13.7)	127.3 (14.0)	135.7 (15.8)	**<0.001**
Diastolic BP mmHg	70.2 (9.1)	71.5 (11.7)	76.7 (10.9)	**<0.001**
Evidence for Androgen Excess: %				
Any androgen Criteria	89.5	90.8	90.1	0.9
Hirsutism	72.9	78.5	80.6	**0.007**
Androgenic alopecia	5.4	5.3	6.4	0.8
Acne	32.2	24.6	16.0	**<0.001**
Evidence for Anovulation: %				
Any anovulation criteria	75.9	79.2	85.0	**<0.001**
Oligomenorrhoea	41.7	39.8	34.8	**0.01**
Amenorrhoea	20.7	16.2	16.4	0.2
Infertility	9.8	21.1	18.4	**0.04**

SD= Standard Deviation, BP=Blood Pressure,
†Considering the significant effect of the age, the comparison was adjusted for age. Body ‡Weight Classification is defined based on ethnicity cut off points [White: Normal BMI < 25 kg/m^2, 25 ≤ overweight < 30 kg/m^2 and Obese ≥ 30 kg/m^2, Black, SA and minor ethnicities: Normal BMI < 23 kg/m^2, 23 ≤ overweight < 27.5 kg/m^2 and Obese ≥ 27.5 kg/m^2] (191).
ℲComparison of obese to normal weight category

2.4.3 Summary of results and discussion

This analysis showed the differences in clinical and demographic characteristics of SA and white women with PCOS and also showed that body weight and age has some effect on their presenting complaint to a speciality clinic. Compared to the white women, SA were generally referred to the clinic at a younger age, had more hyperandrogenic and less anovulatory symptoms. Overall, white women had a higher mean BMI but the proportion of women with "obesity" and "overweight" as defined by ethnic specific cut points (191) were not different. A significant proportion of both white and SA women over 30 years were obese. White women had a higher prevalence of smoking which is important in terms of cardiovascular (CV) risk. Most of the patients who complained of acne in our clinics were younger with normal body weight, as opposed to women presenting with infertility who were generally older and more obese.

The association of ethnicity with metabolic and phenotypic presentations of PCOS have been described previously (173,174,192), however, previous multi-ethnic studies are of small scale and dominated by one single ethnicity and might not have been a true representative of the background population (45,172,193). Comparison between white and SA has also been conducted previously and less insulin sensitivity and higher BMI in SA women has been reported (45) as well as higher rates of hirsutism, acne and AN (45) and this study confirms some of these findings and adds that SA women were younger than white women at their first referral. More importantly this analysis showed that although the BMI was significantly higher in the white women, after adjusting for ethnic specific cut points of BMI, the prevalence of obesity was the same in both ethnicities.

In view of other CV risks there was a mixed status for white and SA women with PCOS. South Asian women had higher rates of T2DM, while white women had higher systolic and diastolic BP and much higher rates of smoking.

The observation that presenting features of PCOS are associated with age, BMI and ethnicity may be a reflection of differences in health seeking behaviour as well as pathogenetic associations. For example, young slim women with PCOS may be more likely to have a consultation for their acne, whilst older women may

be more likely to seek fertility assistance. Understanding these specific characteristics will have to be considered in the development of the structured education programme to address patients' psychological (194,195) and metabolic needs (4,129).

Our cohort were similar to the literature in view of their signs and symptoms; almost 75% of our patients were either overweight or obese and the prevalence of clinical signs and symptoms of PCOS was similar to the previously described rates in large and small populations of PCOS patients (4,5,43) as detailed in Chapter 1.

2.5 Diabetes and cardiovascular outcomes in a multi-ethnic population of women with PCOS

2.5.1 Statistical methods

The general methodology and statistical methods described previously (section 2.2.3) do also apply to this section as well as some additional points.

The PCOS database from Leicester clinical workstation (LCW) was linked to the hospital episode statistics in health informatics services (HIS) database to observe the admission behaviour of women with PCOS. The outcomes of interest were T2DM, myocardial infarction (MI), angina, heart failure (HF), stroke, and cardiovascular (CV) death. Additionally, in some analyses a composite CV outcome, defined as any of MI, angina, HF, stroke and CV mortality.

The incidence rate of each of these outcomes was calculated as the number of new cases divided by the total number of person-years at risk for that condition. Individuals started contributing person-years from their first clinic visit or earliest registration on local HIS, whichever was last, if they were free of the disease of interest at that time. Registration on HIS was required because CV incident events were extracted from that data source. Individuals were then followed up until they had the event of interest, died, migrated out of the Leicestershire area or reached the end of observation (1st November 2009), whichever occurred first. If someone who had previously migrated was re-registered then each period in the database was treated separately to the above end points.

Prevalence at the end of the observation period was estimated for each of the outcomes among all of the study participants and separately in four age groups (15-44, 45-54, 55-64 and ≥65 years) based on their age at 1st November 2009. Prevalence was defined as having a history of the event of interest by the end of the observation period. For example, prevalent MI means that the patient had had a MI at any point up to 1st November 2009.

Risk factors for T2DM and the composite CV outcomes were determined using multiple logistic regression. The explanatory variables used in the model were

age, body weight, index of multiple deprivation (IMD) as a marker of socio-economic status, hyperandrogenism, anovulation, ethnicity, smoking and history of hypertension (and additionally, diabetes status when analysing the composite CV outcome). Regression analysis was not performed on individual CV outcomes as the number of events was not large enough to make a meaningful comparison.

Odds ratios were used to compare the proportion of women with an event of interest at the end of observation with comparable data in the local and national female population. Local data were available from the HIS database calculated based on the number of the hospital admissions for that event of interest over the population denominators for that age group. National data were available from the Health Survey for England (196-198).

Sensitivity analyses were performed by repeating all analyses with those women who were classified as definitely having PCOS according to Rotterdam (182) criteria (Table 2.2 page 37).

2.5.2 Results

2.5.2.1 Description of subjects

Of the 2,353 women with PCOS, 52 patients had to be excluded because they had migrated out of the local HIS database before their first clinic visit (e.g. patients referred to the clinic from outside Leicestershire and/or after moving out of Leicestershire) leaving us a total of 2,301 women with PCOS. The deletion of the 52 patients did not affect the general description of the population as described in the Table 2.1 (page 35).

Mean (SD) age at the start of the observation was 29.6 (9.1) years and at the end of observation was 36.3 (10.0) years, ranging between 16 and 79 years.

2.5.2.2 Incidence rates

Table 2.7 shows the details of follow-up periods and the number of incident cases for each outcome of interest. Incidence of T2DM, MI, angina, HF, stroke, and CV

death rates were 3.6, 0.8, 1.0, 0.3, 0.0, and 0.4 per 1000 person-years, respectively.

2.5.2.3 *Disease prevalence at the end of the observation period*

Table 2.8 shows the prevalence of T2DM, MI, angina, and HF at the end of the observation period by age groups. As expected, given the cumulative nature of the data, there is an increasing pattern of age group-specific prevalence of these conditions.

By the end of the observation period, a diagnosis of T2DM had been recorded in 138 (6%) patients with a mean age of diagnosis of 34.5 years (SD 11.1). In total, 31 patients (1.3% of total PCOS population) experienced at least one of the events included in the composite CV outcome (16 MIs, one stroke, five HFs, 22 anginas and five CV deaths). Eighteen patients had had angiography; all 16 patients with MI and two with angina. Five had angioplasty; one had coronary artery bypass graft and four had percutaneous angioplasty.

Table 2.7 Incidence rate for Diabetes and Cardiovascular events per 1000 person-years in women with PCOS

Outcome	Baseline population at risk	Total observation period person-years	Observation period per person-years Mean (SD)	Number of new events	Incidence rate per 1000 person-years (95% Confidence Interval)
Type 2 Diabetes	2,164	11,349	5.2 (5.1)	41	3.61 (2.59 to 4.90)
Myocardial Infarction	2,295	12,087	5.2 (5.1)	10	0.83 (0.40 to 1.52)
Angina	2,291	12,059	5.2 (5.1)	12	1.00 (0.51 to 1.74)
Heart Failure	2,299	12,124	5.2 (5.1)	3	0.25 (0.05 to 0.72)
Cerebrovascular Accident	2,300	12,129	5.2 (5.1)	0	0.00
Cardiovascular Death	2,301	12,129	5.2 (5.1)	5	0.41 (0.13 to 0.96)

SD, Standard Deviation

Table 2.8 Age-Specific prevalence of the reported conditions shown as % (95 % confidence interval)†

	Age Group, years				
Disease	16-44 (N=1855)	45-54 (N=352)	55-64 (N=83)	≥65 (N=11)	Total (N=2301)
Type 2 Diabetes	4.4 (3.4 to 5.3)	11.1 (7.8 to 14.4)	15.7 (7.8 to 23.5)	45.5 (16 to 74.9)	6.0 (5.9 to 6.9)
Myocardial Infarction	0.1 (0.0 to 1.2)	1.9 (0.5 to 3.4)	6.0 (0.9 to 11.1)	27.3 (1.0 to 53.6)	0.7 (0.4 to 1.0)
Angina	0.3 (0.0 to 0.5)	2.6 (0.9 to 4.2)	6.0 (0.9 to 11.1)	27.3 (1.0 to 53.6)	1 (0.6 to 1.4)
Heart Failure	0.1(0.0 to 0.3)	0.3 (0.0 to 0.8)	1.2 (0.0 to 3.6)	9.1 (0.0 to 26.1)	0.2 (0.0 to 0.4)

Data shown are percentage (95% confidence interval). †Stroke is not shown here as there was only one case at age of 21 years old.

2.5.2.4 Factors associated with T2DM and CV events

Logistic regression was used to assess the impact of a number of factors on the development of T2DM or CV events (Table 2.9). In unadjusted analyses, an increased risk of T2DM was significantly associated with a history of hypertension, older age, being overweight or obese, SA ethnicity, and smoking, while androgen excess was associated with a lower risk of T2DM. The same factors remained significant after adjustment except for smoking. In unadjusted analyses, factors associated with an increased risk of CV events were a history of hypertension, older age, being obese, smoking, and having diabetes, while evidence of anovulation was associated with a lower risk of CV events. After adjustment for other factors, obesity and diabetes no longer had a significant effect.

Table 2.9 Logistic Regression Analysis for factors associated with T2DM and composite Cardiovascular Outcome†; Odds Ratio (95% CI)

	T2DM		Composite CV outcome†	
Variable	Unadjusted Odds Ratio	Adjusted‡ Odds Ratio	Unadjusted Odds Ratio	Adjusted‡ Odds Ratio
History of hypertension (Yes Vs No)	11.60 (7.99 to 16.86)	6.47 (4.17 to 10.02)	22.59 (10.49 to 48.68)	9.94 (3.77 to 26.19)
Age, years	1.06 (1.04 to 1.08)	1.04 (1.02 to 1.06)	1.13 (1.09 to 1.17)	1.08 (1.03 to 1.12)
BW (Overweight Vs Normal)	3.25 (1.44 to 7.31)	2.77 (1.20 to 6.39)	5.25 (0.61 to 45.19)	3.33 (0.36 to 30.92)
BW (Obese Vs Normal)	6.46 (3.11 to 13.40)	4.28 (1.99, 9.17)	10.80 (1.45 to 80.42)	4.00 (0.49 to 32.39)
Evidence of Androgen Excess (Yes Vs No)	0.50 (0.32 to 0.77)	0.33 (0.19 to 0.56)	0.58 (0.23 to 1.43)	0.36 (0.12 to 1.14)
Evidence of anovulation (Yes Vs No)	0.86 (0.58 to 1.30)	0.96 (0.59 to 1.56)	0.32 (0.16 to 0.67)	0.37 (0.15 to 0.88)
Ethnicity (Asian Vs White)	1.60 (1.11 to 2.29)	3.08 (1.95 to 4.86)	0.66 (0.28 to 1.54)	1.54 (0.53 to 4.50)
Smoking (Yes Vs No)	1.60 (1.03 to 2.49)	1.66 (0.99 to 2.78)	3.11 (1.45 to 6.67)	3.33 (1.23 to 8.59)
Diabetes (Yes Vs No)	N/A	N/A	6.62 (3.12 to 14.05)	1.18 (0.44, 3.17)
IMD Score	1.01 (1.00 to 1.02)	1.00 (0.99 to 1.02)	1.00 (0.97 to 1.02)	1.00 (0.98 to 1.03)

CI = Confidence Interval, CV = Cardiovascular, T2DM = Type 2 Diabetes Mellitus, BW= Body Weight, hypertension = Hypertension, IMD= Index of Multiple Deprivation.
†The composite CV outcome includes any of Myocardial Infarction, Angina, Heart Failure, Cerebrovascular accident, or CV Death. ‡ Adjusted for all the other variables in the table.

2.5.2.5 Comparison of PCOS patients with the local and national population

Age specific prevalence of MI, angina and the composite CV outcome was significantly higher in PCOS patients aged over 45 years compared with the local female population with odds ratio as high as 12.88 in women with PCOS over 65 years of age (Figure 2.3).

The age-specific prevalence rates for T2DM and CV events in the PCOS group were also compared with estimated national rates. The odd ratios for prevalence of MI and diabetes in our PCOS population are higher ranging from 1.2-11.00 fold as compared to national data (Figure 2.3).

Despite the high rates of the age-specific ratios, when it comes to the relative ratio for the total cohort of women with PCOS the ratio drops significantly when it is compared to the local and national female population.

Figure 2.3 Odds Ratio (OR) of Cardiovascular events and T2DM; PCOS Vs Local† or National† Female Population 2009‡
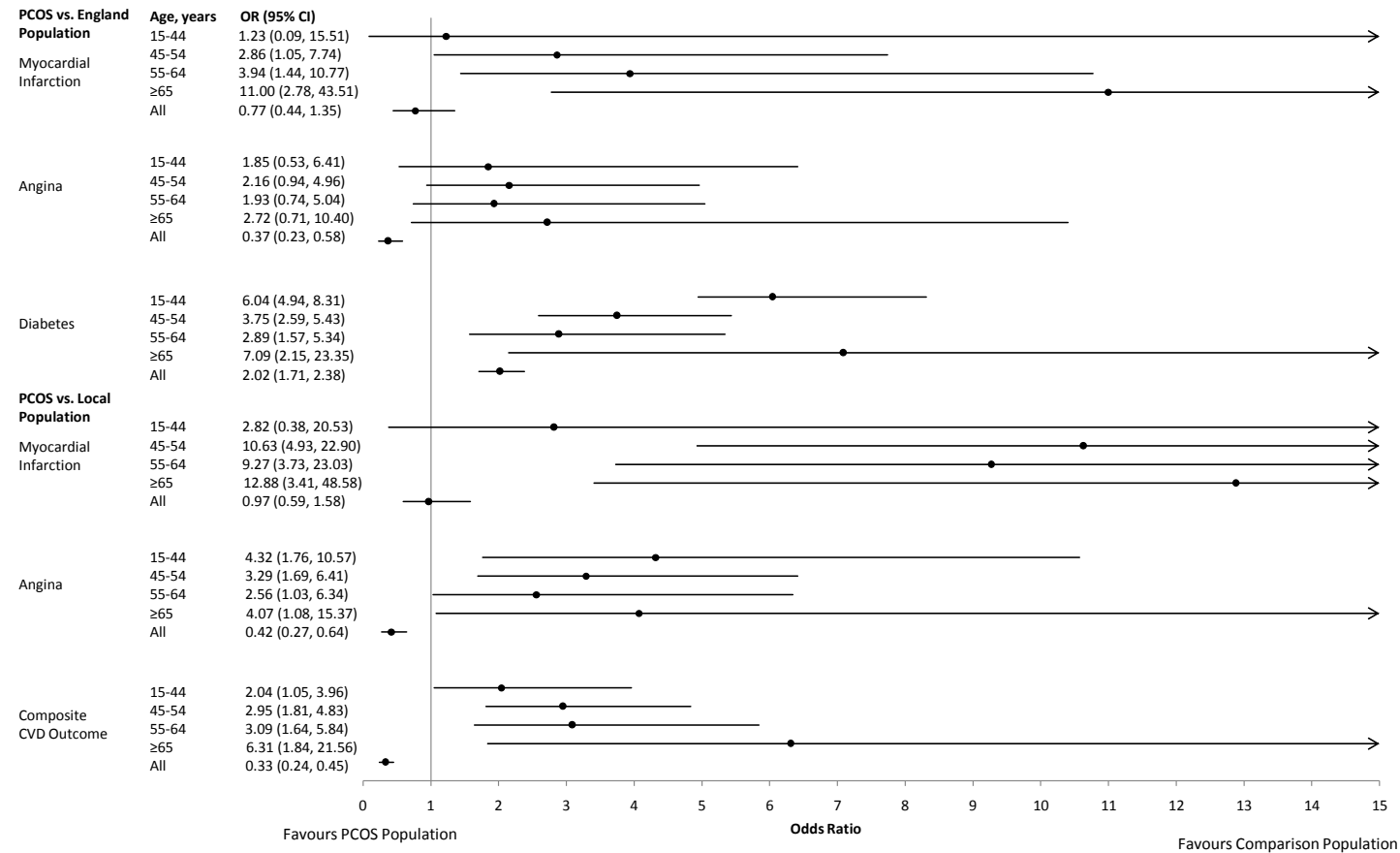
†Local age specific data for Diabetes and England composite CV data were not available, ‡Odds ratio for comparison of sub category "All" in each outcome event could have been affected by the Simpson's paradox(199)

2.5.2.6 Sensitivity analysis;

This analysis was performed on the subgroup with definite diagnosis of PCOS (Table 2.2 page 37) who were shown to be similar to the total PCOS cohort in view of their metabolic and clinical characteristics (page 36).

Total follow up for this group was 8,660 person years [mean (SD) 5.1 (5.1) person years] with incidence rates as follows (per 1,000 person-years): T2DM = 4.0, MI = 0.3, angina = 0.8, HF = 0.1, stroke = 0, and CV death rates = 0.2.

At the end of observation there were 88 (5.3%) patients with T2DM and 16 (1.0%) composite CV events in this group; four (0.2%) MI, one (0.1%) HF, nine (0.5%) anginas, and two (0.1%) CV death.

Due to the low number of the events, detailed analysis would possibly be subject to statistical errors (200) and therefore were not performed in this group.

2.5.3   Summary of results and discussion

There was increased age-specific prevalence of diabetes, and CV morbidity compared to the local and national female population in a cohort of women identified with a clinical diagnosis of PCOS.

Unsurprisingly, patients with CV events also demonstrated an excess of other well-established CV risk factors compared to those without events including hypertension and smoking - but interestingly not ethnicity. This is despite the un-even distribution of the CV risk factors in the two ethnicities as described earlier in this chapter: such as higher smoking rate in white and higher T2DM in SA women. Additionally, the effect of T2DM on CV risk was explained by adjustment for other factors, including age and hypertension. Patients who developed T2DM showed the expected excess of risk factors (overweight, obesity and SA ethnic origin).

This study confirmed the previous findings of increased prevalence of T2DM in women with PCOS (100,201) and also showed an increased incidence of diabetes in this population. In view of the CV events, the analysis confirms some

of the previous studies either in a group of PCOS patients, (121) or larger health surveys associated with signs and symptoms of PCOS (130) but contrasts with some others. Iftikhar and colleagues (133) did not find any difference between their patient and controls, despite the fact that their study population was much older than this current cohort (average age at the end of observation 48.8 years) and we know that age has a significant effect on the prevalence of CV events (196) . Pierpoint (101) and Wild (100) also examined the CV events and only found an increased stroke rate in PCOS as compared to control group. They also studied an older population (mean age=56.7 years) which together with a longer follow up (30 years), would possibly explain the higher number of stroke reported as compared to the much younger population in the current cohort.

It should be emphasised that both these studies report overall rates of the events, where in our analysis it is only the age-specific prevalence which are significantly higher and not the overall rates. This could be due to the fact that over 80% of our population were under 45 years old, which have very low rates for CV events in any case and the small number of the events in the older groups was diluted in the total population. However, a more statistically sound explanation is the "Simpson Paradox" (199). Simpson, in his mathematical modelling for the Contingency Tables, explained that: "*An association between a pair of variables can consistently be inverted in each subpopulation of a population when the population is partitioned*" (202). This conversion of the ratios is also possible when comparing the subpopulation with total population. This paradox possibly explains the inverted ratio when comparing the events in the total populations. In this analysis the population was partitioned into different age categories and compared to the partitions in the general population. Therefore when the total population of PCOS and general female population were compared, the relation was inverted.

Presenting symptoms in our cohort were examined in view of the previously reported associations (203-205). Unexpectedly, women who presented with evidence of androgen excess or anovulation had a reduced risk of T2DM and CV events. It seems clinically unlikely that lack of these symptoms is causally related to the increase in CV events observed, and possibly this represents a

combination of incomplete data capture in the routine clinic situation, particularly in the earlier years of use of the clinical information system. As discussed in the section on sensitivity analysis (page 36 - 40); patients seen during the earlier years of the database had a higher chance of having missing data and they are the people who would be older and at the end of observation and at higher risk of cardiovascular events. The number of events in the group with a confirmed diagnosis was not high enough to repeat all the comparisons but still the incidence and prevalence of diabetes was high given the background of their average young age, 1% having a cardiovascular event is significant.

Other obvious confounders in this analysis could be the high proportion of SA ethnicity as a known risk factor for T2DM and CV disease (177), but the distribution of the ethnicities reflected the local population and therefore would not explain the findings. Indeed, the SA ethnicity did not come up as a significant in factor analysis. Other possibility is the bias in the referral to a speciality clinic, especially in the context that our department is "diabetes and endocrinology" and so more patients with abnormal metabolic profile might have been referred to us. However, the rate of diabetes reported in this analysis is not higher than previously published reports in women with PCOS (13,97), and although the average BMI is over the threshold of obesity (BMI 30.1 kg/m^2) but the association of PCOS and obesity is well established (18) and described in Chapter 1 of this thesis. This cohort like others (92,93) had almost a 75% rate of overweight or obesity.

Therefore the presence of these factors should not detract from the basic finding that a simple diagnosis of PCOS in younger women, as a possible marker of CV disease, should be regarded as an opportunity to review and hopefully reduce other established CV risk factors in this population.

2.6 Summary of Chapter 2

Background: Phenotypic analysis of a large multi-ethnic cohort of women with PCOS can examine the associations of ethnicity, age and BMI with the clinical characteristics and also evaluate the long term cardiovascular outcomes of these patients. These findings can inform the content of an education programme tailored for women with PCOS.

Methods: A large local clinical database of women with PCOS was linked to the database of hospital episodes in the health informatics services. Descriptive analysis of the database, as well as comparison of the CV outcomes with the age matched local female population was conducted.

Results: In summary, this database analysis showed that there are differences in clinical and demographic characteristics of women with PCOS according to their ethnicity, body weight and age at their first clinic presentation and more importantly a long term follow up of these patients showed there was high age-specific prevalence of T2DM, myocardial infarction (MI), and angina in the women with PCOS with over a quarter having had a MI or angina in those over the age of 65 years.

Conclusion: This information confirmed high rates of age-specific cardiovascular outcomes in women with PCOS and ethnic differences in clinical and demographic characteristics of the condition. These findings helped in designing a tailored education programme for women with PCOS in order to change their lifestyle and improve their cardiovascular risk status.

Chapter 3 : A systematic review and meta-analysis comparing the effect of pharmacotherapy (insulin sensitizers or incretin based therapies) to lifestyle management on body mass index in women with polycystic ovary syndrome

The previous two chapters described the complexity of PCOS, the role of insulin resistance in this condition and the accentuating effects of associated obesity on the underlying insulin resistance, the signs and symptoms of PCOS and its long term cardiovascular outcomes.

This chapter describes the process and results of a systematic review and meta-analysis comparing the effects of lifestyle interventions and pharmacotherapy to lower body mass index (BMI) in women with PCOS.

The protocol for this systematic review is available in the PROSPERO website; (http://www.crd.york.ac.uk/prospero/ , ID = CRD42013004169). The planned review and analysis, as described in the published protocol, is a complex network analysis to compare the effects of these interventions on body mass index, weight, waist circumference, indices of insulin resistance and other cardiovascular indices. This project forms the subject of an ongoing collaboration with Department of Health Sciences in University of Leicester. Framing the research question, developing the protocol, running the search, performing the data extraction has been my contribution to the pre-analysis stages of this project.

The analysis started by focusing on one outcome, BMI, to test the methodology of the network and pair wise analysis. The pair wise analysis is the subject of the current chapter in my thesis.

This chapter is my work except for the input which the statisticians (LG, DB, and GC) had in the analysis.

3.1 Introduction

The beneficial effects of weight loss on the signs and symptoms of PCOS and indices of insulin resistance have previously been described (17,206,207). Improving insulin sensitivity in women with PCOS is suggested to improve cardiovascular risk indices as well as signs and symptoms of PCOS (4). A minimum of 5% weight loss in women with PCOS is recommended to improve reproductive outcomes (4,207). The choice of the treatment in PCOS needs to weigh up the risk and benefits on the combination of the effects on insulin function, weight reduction, improvement in signs and symptoms and the side effects profile of that treatment. Available treatment options to address both insulin sensitivity and weight, are lifestyle interventions (diet or exercise) and medical management specially insulin sensitizers (207-209).

A systematic review of randomised trials of lifestyle interventions in PCOS (8) including calorie deficit dietary change (210) or supervised exercise in the gym (211) showed some benefits in reducing weight, waist circumference and fasting insulin levels (8). A recent systematic review of the dietary interventions in PCOS emphasized the beneficial effects of the weight loss on signs and symptoms of PCOS (212), however it did not recommend a specific diet.

The beneficial effects of increased physical activity in women with PCOS on weight, waist circumference and insulin sensitivity are independent of the type, frequency and length of the exercise session (213). Another study showed that increased walking activity improved insulin sensitivity without any change in BMI (214,215).

The effects of insulin sensitizers on weight and insulin function in women with PCOS depend on the mechanism of action of the drug. Major insulin sensitizers used in treatment of PCOS are Metformin, Thiazolidindiones (TZDs) and Inositol (216); with Metformin being the most used drug among this group (217).

Metformin, a biguanide, inhibits the hepatic glucose production and increases peripheral sensitivity of insulin (218). The latter, is the mechanism that is of interest in women with PCOS (217,219). Meta-analyses of Metformin studies in

women with PCOS showed improvement in fasting glucose, fasting insulin and weight as well as reducing the incidence of diabetes (220,221).

Thiazolidinediones (TZDs) improve insulin sensitivity through their effect on the peroxisome proliferator-activated receptor (PPARɏ) (222,223) and have been effective in ameliorating hyperinsulinemia and lowering fasting glucose in women with PCOS (224). Pioglitazone has been superior to Metformin in these effects (225), however TZDs have less beneficial effects on body weight and BMI in comparison to placebo (224) or Metformin (225,226).

Inositol is another insulin sensitizer used in women with PCOS which is less studied (227). Inositol is part of the Inositol triphosphatase and phospho-Inositol phosphates which act as secondary messengers and modulate some of the sub-receptor effect of insulin and therefore their deficiency might induce insulin resistance and their supplement might improve the insulin function in women with PCOS (54,228,229). Initial studies showed lowering effects on lipids, insulin and glucose levels (228,230). However, they were never pursued (231) and there is a lack of data in this group. The interest in their beneficial effects on metabolic conditions is re-emerging (229).

Incretin based therapies in the forms of tablet (Dipeptidyl Peptidase-4 Inhibitors = DDP-4i) or injection (Glucagon Like Peptide – 1 agonist = GLP-1A) are a new class of medication with promising outcomes in patients with T2DM in view of weight profile and improvement in glycaemic control (232). Although this group does not directly affect insulin sensitivity, they potentiate the glucose dependent insulin secretion and glucagon suppression and consequently improve β cell function (233). Studies of incretin based therapies in women with PCOS are limited (234,235), however considering their emerging effect on weight loss in people without diabetes (236) and beneficial effect on β cell function they were also included in this systematic review.

The objective of this systematic review was to assess and compare the effects of lifestyle intervention, insulin sensitizers and incretin based therapies on BMI, in women with PCOS to inform the development of an education programme for this patient group.

3.2 Methods

3.2.1 Identifying research evidence

A systematic search was conducted to identify the published articles on lifestyle, insulin sensitizers or incretin based therapies in PCOS. Cochrane Trials register, MEDLINE, EMBASE, CINAHL and PsychINFO were searched. Rich Site Summary (RSS) filter as well as "content alert" were set up on search engines and important endocrine and reproductive medicine journals to catch the most up-to date publications after the final search and up to the point of data extraction [October 2012]. Published systematic reviews on the related subjects and references of the related reviews and clinical trials were also hand searched. Search terminologies were based on previous Cochrane reviews (8,216). Gray literature (conference abstracts) were not included in the systematic review.

Searches broadly included any variety of terms for "PCOS", "lifestyle", diet", "physical activity" and named medication (search terminology are shown in Appendix 3). They were reviewed by the specialist information librarian in our department (Mrs Sarah Sutton). Only English language papers were included.

3.2.2 Defining the inclusion criteria

Inclusion criteria in terms of PICOS (population, intervention, comparison, outcomes, and study type) were:

Population: Women with PCOS diagnosed by any of the internationally recognised criteria (5,26,27). There were no restriction for age, weight or medication used to treat signs and symptoms of PCOS except for anti-obesity medications (e.g. Orlistat, Sibutramine, Rimonabant) due to their effect on BMI.

Intervention: "Lifestyle intervention" was defined as any structured dietary, exercise or education intervention aiming to change behaviour. Pamphlets and education materials without direct and specific intervention of the researchers or health care professionals, and routine dietary and lifestyle advice in a clinic visit were counted as "standard care".

Included "insulin sensitizers" were: Metformin, Thiazolidindiones (TZD), Inositol. Although not an insulin sensitizer by nature, incretin based therapies (GLP-1 agonists and DPP-4 inhibitors) were also included in the search and analysis.

Comparison: Clinical trials comparing lifestyle interventions or pharmacotherapy (as listed above) with each other, placebo, or standard care were included;

1) Lifestyle   Vs   Pharmacotherapy

2) Lifestyle Vs Standard care

3) Pharmacotherapy Vs. Placebo

4) Pharmacotherapy Vs Standard care

5) Pharmacotherapy Vs Another Pharmacotherapy

Placebo and standard care were considered as two different interventions and vitamins were not considered to be placebo. Therefore studies which prescribed the placebo to all intervention arms were excluded (for example "Metformin + Placebo Versus Placebo" was excluded).

Outcomes: The primary outcome was change in BMI at six months. Weight and BMI was considered to be two different outcomes and BMI was chosen for this current analysis. Different time points (3, 6 and 12 months) were also thought to be grouped separately and six month was chosen for this analysis.

Study type: Only randomised studies were included;

1- Randomised Clinical Trials

2- Randomised cross over studies (the first period was used)

3.2.3 Study Selection

The preferred reporting items of systematic reviews and meta-analyses (PRISMA) guidelines (237,238) were followed. The initial search was performed by myself. Mr Joseph Henson (JH) conducted the independent review of the extracted abstracts. Full text review and data extraction from the selected articles were reviewed by myself and the statisticians. Included articles were assessed for the

risk of bias (239-241) on four domains: randomisation; allocation concealment; double blinding; and description of participants' flow.

3.2.4 Statistical analysis

Pair-wise meta-analysis was performed to compare interventions. Random effect models were used due to the expected heterogeneity in the type of the interventions as well as the phenotypic characteristics of women with PCOS. Heterogeneity was assessed using I^2 statistics (low, moderate, and high heterogeneity for I^2 values of 25%, 50%, and 75%) (242). Forest plots were presented for all the possible meta-analyses. Analysis was carried out [by statisticians] in STATA version 12 [StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845 USA]. Results are presented as weighted mean (95% confidence interval (CI)).

3.3 Results

3.3.1 Selected studies

Figure 3.1 shows the flow of study selection; out of the 8313 initial abstracts 254 full texts were reviewed and 15 studies were included in the systematic review.

Table 3.1 is the summary of the included studies and their data; 12 studies included Metformin, eight included TZDs and three lifestyle interventions. Only one study (235) included GLP-1 agonist (Exenatide) and none of the Inositol studies met the inclusion criteria.

Details of lifestyle interventions in the three included studies were;

- A package of 500 Calorie/day deficit diet plus monthly supervised exercise consisting of 30 minutes walk, and 30 minutes of weight resistance exercise (243).

- Standard nutrition lectures, hands on kitchen training, electronic communication, weekly structured unsupervised group exercise. Aim was 500 Calorie/day deficit

diet and 30 minutes/day of moderate to vigorous physical activity. Overall 16 group sessions in 24 weeks plus interspersed individual contacts happened (210).

- 16 weeks of regular physical exercise including brisk walking, cycling or any aerobic exercise which lasted for at least 30 minutes and increased the heart rate to > 120 beats/minute. One face to face individual session was followed by weekly telephone advice and monitoring (244).

Figure 3.1 PRISMA flow of information through different phases of the systematic review

Identificatio

8305 abstracts identified through search engines

8 abstracts identified through other sources

Screenin

8313 abstracts were screened

8049 Excluded

254 Full text articles were assessed

239 Excluded:

6 Non PCOS Patients **(P)**

42 Did not meet intervention criteria **(I)**

60 comparison was not suitable **(C)**

80 BMI at 6 month not reported **(O)**

26 not randomised **(S)**

8 Not in English

14 Conference abstracts/Letters/Reviews

31 Duplicate papers reported on same study/data

3 Could not find the full text

Eligibility

15 studies Included in Systematic review

Included

13 included in 4 different Quantitative Meta-Analyses

Table 3.1 Characteristics of the included studies and summary of data (Foot notes on page 72)

Study	Country	Pheno type	Diabetes Excluded	Randomi sation (0-2)	Allocation concealment (0/1)	Blinding (0-2)	Participant flow (0-2)	Interventions (N†)	Age (yrs)	Baseline BMI (SD)	BMI change (SD)
Ahmad (245)	India	HA / AN	Yes	2	0	0	1	Metformin (31)	22.8	27.6(5.44)	-0.3(5.4)
								Rosiglitazone (30)	23.2	26.94(5.24)	-0.4(5.2)
Aroda (246)	USA	HA / AN	Yes	1	0	1	2	Placebo (10)	27.0	35.63(6.64)	-0.4(6.7)
								Pioglitazone (13)	28.0	36.8(6.49)	0.0(6.5)
Bailargeon (247)	Venezuela	HA / AN	Yes	2	1	2	2	Metformin (28)	27.2	24.6(1.06)	-0.3(0.9)
								Rosiglitazone (22)	27.9	24.3(1.41)	0.7(1.2)
								Placebo (30)	27.2	24.6(1.10)	-0.3(0.9)
Curi (243)	Brazil	HA + AN / PCO	Yes	1	0	0	2	Metformin (15)	24.6	31.4(5.42)	-1.2(4.7)
								Lifestyle (12)	26.3	31.8(5.54)	-1.7(5.4)
Elkind_Hirsch (235)	USA	HA / AN / PCO	Yes	2	0	0	2	Metformin (22)	28.2	40.3(2.0)	-1.0(2.0)
								Exenatide (14)	27.7	43.3(2.0)	-1.0(2.0)
Hoeger (210) ‡	USA	HA / AN	NS	2	1	1	2	Metformin (6)	16.0	35.0(8.2)	0.7(8.4)
								Placebo (10)	15.4	34.9(6.7)	0.6(6.8)
								Lifestyle (8)	15.4	36.0(6.2)	-1.1(6.6)
Jedel (244) ‡	Sweden	HA / AN / PCO	Yes	2	0	0	2	Lifestyle (30)	30.2	27.7(6.44)	0.1(1.2)
								Standard care (15)	30.1	26.8(5.56)	0.2(0.7)
Jensterle (248)	Slovenia	HA / AN	Yes	2	0	0	2	Metformin (18)	22.9	29.34(6.49)	-0.7(0.6)
								Rosiglitazone (17)	25.2	27.03(3.87)	0.1(0.9)

Study	Country	Pheno type	Diabetes Excluded	Randomi sation (0-2)	Allocation concealment (0/1)	Blinding (0-2)	Participant flow (0-2)	Interventions (N†)	Age (yrs)	Baseline BMI (SD)	BMI change (SD)
Lam (249)	China	PCO + HA/AN	Yes	2	1	2	2	Rosiglitazone (35)	26.0	24.1(6.2)	0.5(5.9)
								Placebo (35)	26.0	26.0(5.6)	0.0(6.1)
Naka (250)	Greece	HA / AN / PCO	Yes	2	0	0	2	standard care(15)	24.3	28.3(4.9)	-0.2(5.2)
								Metformin (15)	22.2	29.4(6.5)	-0.1(6.5)
								Pioglitazone (15)	23.6	28.5(5.4)	1.3(5.6)
Onalan (251)	Turkey	HA / AN	NS	2	1	2	2	Metformin (55)	26.9	NS	1.2(3.6)
								Placebo (61)	25.5	NS	-0.4(2.7)
Ortega-Gonzalez (252)	Mexico	HA / AN / PCO	Yes	2	0	0	2	Pioglitazone (17)	28.8	32.2(4.1)	1.8(4.6)
								Metformin (18)	29.0	34.1(6.8)	-1.2(7.0)
Palomba (253)	Italy	HA / AN	NS	2	1	2	2	Metformin (15)	24.3	22.4(2.7)	-0.2(2.5)
								Placebo (15)	24.8	22.7(1.9)	-0.1(1.9)
Romualdi (254)	Italy	HA / AN / PCO	Yes	2	1	2	1	Metformin (30)	24.7	22.1(2.52)	-0.1(2.4)
								Placebo (30)	27.2	23.3(4.1)	1.0(4.0)
Yilmaz (255)	Turkey	HA / AN / PCO	Yes	1	1	2	1	Metformin (43)	24.7	27.1(6.2)	-1.0(6.2)
								Rosiglitazone (45)	25.1	26.6(6.5)	1.4(6.6)

HA = Hyperandrogenism, AN = Anovulatory, PCO = Polycystic ovaries, SD = Standard deviation, NS = Not specified
†N = number of participants in that arm.
‡ These studies had more than 2 arms and one or more arms were not included in the analysis as they had used a treatment modality which was not of interest in this review.

3.3.2 Pair wise analysis

It was possible to compare nine pairs of treatment as shown in Table 3.2, however five pairs only consisted of one study and therefore only four meta-analyses were performed.

Table 3.2 List of the interventions compaired in pair wise analysis with Weighted Mean reduction in body mass index

No	Intervention 1	Intervention 2	No of Studies	BMI difference† / 95% CI
1	Lifestyle	Standard care	**1** (244)	-0.13 (-0.57, 0.31)
2	Lifestyle	Placebo	**1** (210) ‡	-1.7 (-4.52, 7.92)
3	Lifestyle	Metformin	**2** (210,243) ‡	-0.74 (-2.76, 4.24) $I^2 = 0.0\%$
4	Metformin	Placebo	**5** (210,247,251,253,254)	0.19 (-0.70, 1.08) $I^2 = 53.7\%$
5	Metformin	Standard care	**1** (250)	0.10 (-4.18, 4.38)
6	Metformin	Exenatide	**1** (235)	0.00 (-1.48, 1.48)
7	Metformin	TZD	**6** (245,247,250,252,255,256)	**-0.92 (-1.30, -0.54)** $I^2 = 0.0\%$
8	TZD	Standard care	**1** (250)	1.50 (-2.50, 5.50)
9	TZD	Placebo	**3** (246,247,249)	**0.97 (0.37, 1.58)** $I^2 = 0.0\%$

N = Number in study, BMI = body mass index, I^2 = Index of heterogeneity, CI = Confidence interval, TZD = Thiazolidindiones
† This is the difference in BMI change after 6 month (Intervention 1 - intervention 2).
‡These are 2 arms of a 4 arms intervention (Placebo, Metformin, lifestyle, contraceptive pills)

Lifestyle had a tendency to reduce BMI in comparison to placebo and standard care (Table 3.2) and Metformin (Figure 3.2), but did not reach statistical significance.

Figure 3.2 Effect of Lifestyle versus Metformin on body mass index
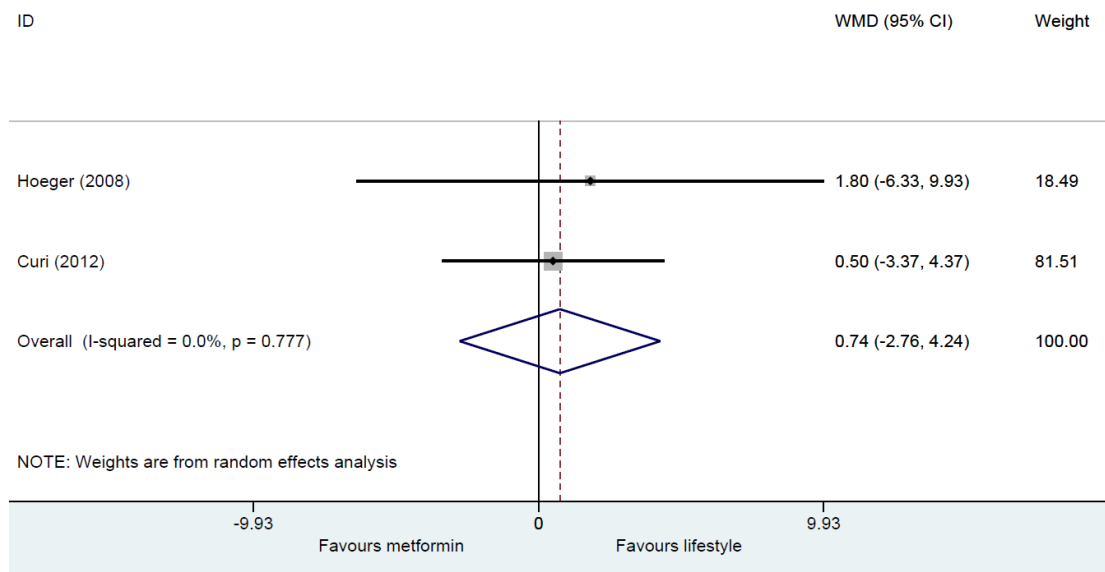
The effect of Metformin on BMI had no difference compared to Exenatide and was not superior to standard care (Table 3.2) or placebo (Figure 3.3).

Figure 3.3 Effect of Metformin versus Placebo on body mass index
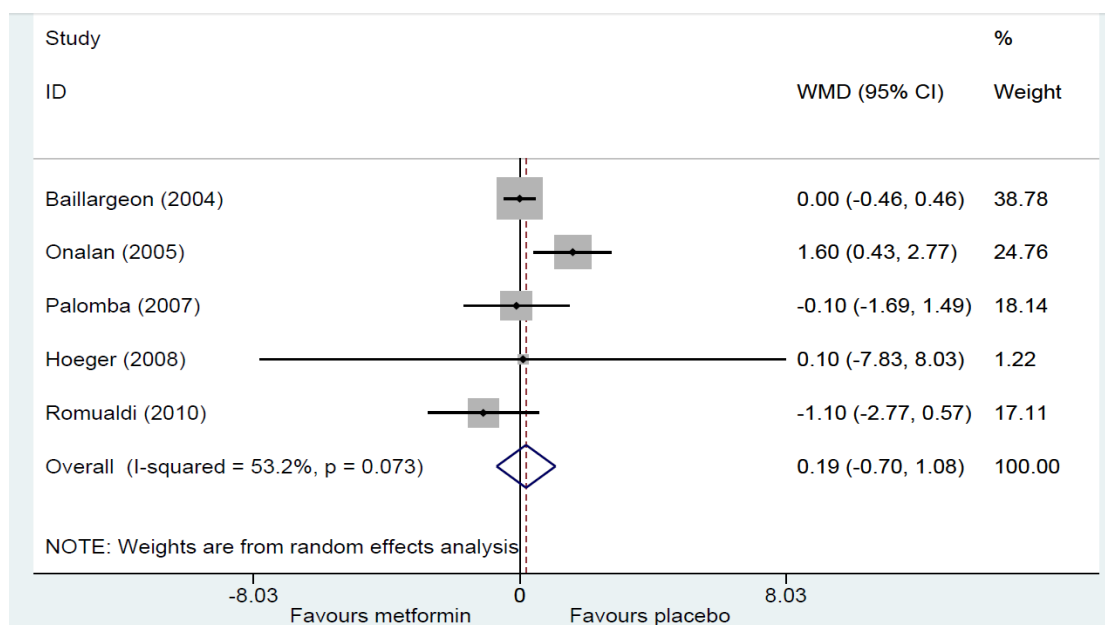
Metformin, however, significantly reduced BMI in comparison to TZDs; weighted mean BMI difference after 6 month treatment was -0.92 kg/m^2 (95% CI -1.30, -0.54) (Figure 3.4).

Figure 3.4 Effect of Metformin versus Thiazolidindiones on body mass index
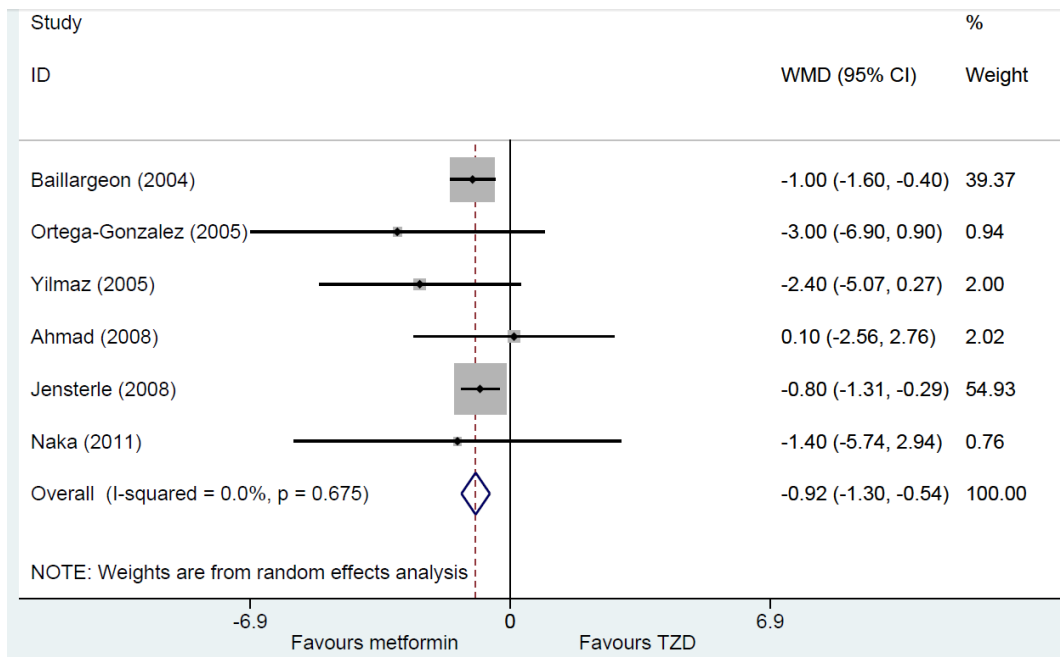
TZDs also resulted in higher BMI when compared to placebo (Figure 3.5) or standard care (Table 3.2).

Figure 3.5 Effect of Thiazolidindiones versus Placebo on body mass index
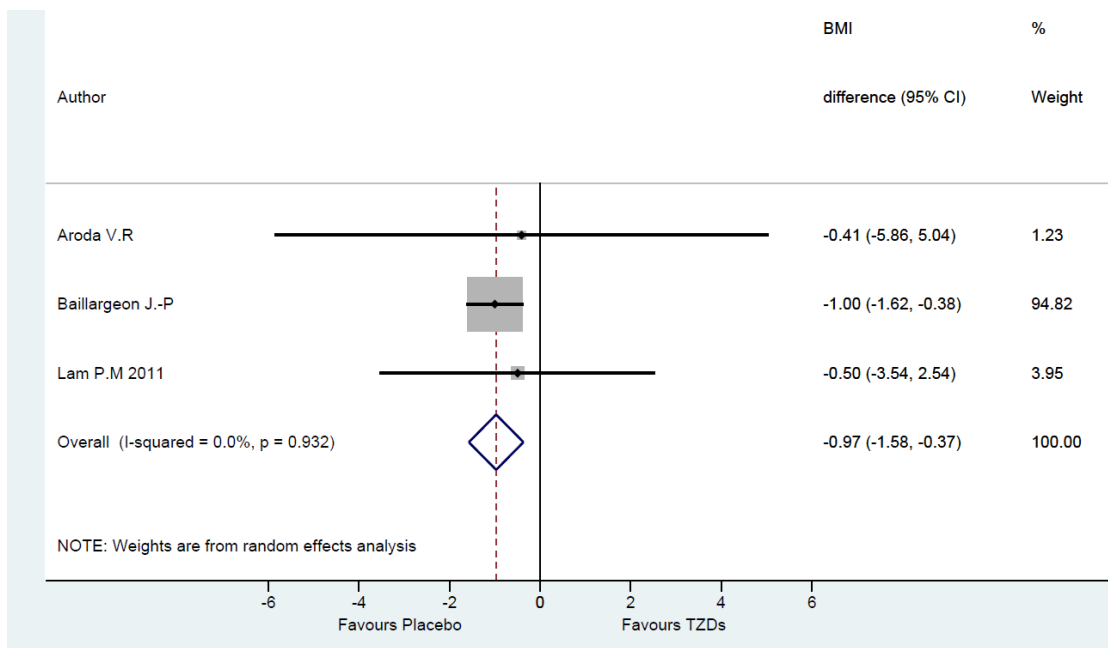
There were some variation in clinical characteristics of the studies for example the starting BMI in the studies grouped for comparing Metformin and placebo (210,247,251,253,254) ranged from 22 to 35 kg/m^2 (Table 3.1) or two studies (210,243) comparing lifestyle and Metformin included women with different phenotypic presentations of PCOS (Table 3.1).

3.4 Discussion

This study indicates that lifestyle has a tendency to perform better than Metformin in reducing BMI in women with PCOS. TZDs are inferior to Metformin and placebo.

The superiority of the lifestyle to Metformin does not reach statistical significance and it is only a weighted average of two studies (210,243) with only 45 participants in total. This, however, is in line with the expert recommendations that lifestyle is the preferred first treatment of choice for women with PCOS (4,129,207,257).

Unfortunately there was only one study using incretin based therapies (Exenatide) which showed similar effects to Metformin (235). Combination of GLP-1 agonists and Metformin have had superior effects compared to either treatment alone ((234,235), but this was outside the scope of this review.

In this systematic review, Metformin did not show any superiority to placebo in reducing BMI and this is in contrast to a previously reported meta-analysis comparing Metformin and placebo and reporting a weighted mean difference of BMI -0.68 (95% CI -1.13 to -0.24) in favour of Metformin (221).The aforementioned meta-analysis however included studies with any length of follow up (four weeks to six months) and the majority were under four months follow up as compared to our analysis which only included the outcome at six month follow up. This difference could be due to difference in the number of studies and participants included in two the analyses (n=280 in our analysis versus n=480 in the other analysis). It however, raises the possibility that Metformin may reduce BMI at short-time with loss of effect when continued longer.

76

Our study confirms the previous reviews which had shown the inferior effects of TZD on BMI in comparison to placebo (224) or Metformin (225,226) in women with PCOS. However, this current study for the first time compares all the insulin sensitizers and lifestyle interventions together.

Reduction in BMI is one of the many important factors in choosing a treatment for women with PCOS; side effects of treatment, improvement in signs and symptoms and the effects on insulin resistance are some of the other factors included in decision making. Although the current analysis does not answer these specific questions and there is evidence from literature:

TZDs increase weight and BMI as shown above, but they have better effects on indices of insulin resistance in comparison to Metformin (225). Unfortunately associated complications such as liver failure with Troglitazone, or cardiovascular problems with Rosiglitazone resulted in their withdrawal from market (258). Pioglitazone has not been an exception and recent reports about the increased risk of bladder cancer following its long term use have resulted in concerns (259). There is also a caution for their use in pregnancy and its prescription in reproductive age female needs to be accompanied with contraceptive care [British National Formulary].

Metformin has beneficial effects on the indices of glycaemic control as well as some of the signs and symptoms of PCOS (216,260) but there is no consensus on its overall benefits for this condition (219,261,262). The use of Metformin for prevention of diabetes in women with PCOS has been recommended in multiple expert statements (4,129,257) with an added caution that there is a need for further studies. As shown in current analysis, it is not superior to lifestyle and even placebo in regard to BMI reduction when the results are analysed at six months follow up.

The decreasing effect of exercise on cardiovascular death has already been reported (263). Studies in people at risk of diabetes as well as healthy individuals show a weight independent correlation between the increase in physical activity and improvement in insulin/glucose haemostasis (264,265).

Increased physical activity such as aerobic exercises in the gym in women with PCOS has been shown to have beneficial effects on all aspects of the syndrome (213,266,267), independent of the type and frequency of the exercise (213) and baseline weight of women with PCOS (268). A combination of diet and exercise has also shown similar effects on the indices of insulin resistance, ovulation, fertility and general well being of women with PCOS (269-271).

Comparison in our study showed neither superiority nor inferiority of the lifestyle intervention to placebo, standard care or Metformin in their effect on BMI. However, a recently published meta-analysis (272) showed significant reduction in fasting insulin levels following lifestyle interventions as compared to the minimal interventions as concluded in a previous Cochrane meta-analysis (8). In balance lifestyle interventions with beneficial effects on cardiovascular risk and insulin sensitivity, and low or minimal side effects profile seems to be the best choice to start treatment for women PCOS.

The Combination of the lifestyle interventions and Metformin has had more impact on the weight and insulin indices (273-276) or ovulation induction (277) as compared to lifestyle alone or placebo. Therefore, Metformin can be added if lifestyle fails to achieve the desired effect, as also recommended for prevention of diabetes in high risk population (2).

3.4.1 Strengths and Limitations

This is the first review in treatment options of PCOS which is inclusive of lifestyle interventions and all available insulin sensitizers as well as incretin based therapies. Inclusion criteria were set to be broad to include as many studies as possible. Medications were not grouped together due to reflect the clinical application, and this reduced the heterogeneity in analysis. Three of the studies had no heterogeneity.

Lifestyle interventions had to be grouped due to scarcity of the studies which fit the inclusion criteria. For this reason as well as the lack of subgroup data on

different phenotypes and age groups, small number of patients in each study, and a wide range of baseline BMI, it was not possible to perform subgroup analysis. This high variation in the study populations indicate high chance of clinical heterogeneity (278) despite a very low statistical heterogeneity. Therefore, generalization of the outcomes to all clinical situations has to be done cautiously.

It is also important to note that neither of the included lifestyle interventions was pragmatic to implement in the community. They involved either supervised physical activity (210,243), or intense weekly face to face or telephone follow up (210,244).

This analysis only reported the six month outcome data for BMI, but similar methodology for screening the published studies raises the opportunity to compare all treatments and other secondary outcomes by using a network analysis (mixed treatment comparison) (279,280). [This analysis is being performed in collaboration with the statisticians in our group]

3.4.2 Conclusion

Outcomes of this systematic review and meta-analysis is in favour of lifestyle as the first treatment option in women with PCOS, however none of the reviewed lifestyle interventions were pragmatic to be implemented in the community. This might be an indication for the need to develop a pragmatic lifestyle intervention for women with PCOS.

Further studies are needed for all the groups of medications specially a comparison with lifestyle intervention to allow better judgment of their effects.

3.5   Summary of Chapter

Background; Lifestyle interventions have traditionally been suggested as the first treatment option in women with PCOS but there is a lack of high level evidence, systematic review and meta-analysis to compare their effects with medical therapy on BMI reduction in women with PCOS.

Methods: RCTs on women with PCOS, were included if they compared lifestyle, and medications (insulin sensitizers and incretin based therapies) with placebo, standard care or each other. The primary outcome was the change in BMI at six months follow up.

Pair wise meta-analysis was performed and random effect model was used for analysis.

Results: 15 studies out of the 8313 abstracts were included with a total of 775 patients. There was a non-significant reduction in BMI when lifestyle was compared to Metformin: 0.74 (-2.76, 4.24) and a significant reduction when Metformin was compared to TZDs -0.92 (-1.30, -0.54). Placebo was superior in reducing BMI when compared to TZDs 0.97 (0.37, 1.58) but not Metformin 0.19 (-0.70, 1.08).

Conclusion: Outcomes of this systematic review and meta-analysis is in favour of lifestyle as the first treatment choice in women with PCOS and support the development of the SUCCESS education programme.

Chapter 4 : Rationale and structure of SUCCESS
SUCCESS: Struct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome

The first three chapters of this thesis have shown that PCOS is a chronic and complex condition with long term health consequences. This has been described through the literature review, and the example of a multi-ethnic cohort of women with PCOS which showed higher rates of cardiovascular events compared to the background population. A review of the lifestyle interventions in PCOS showed some beneficial effects on the metabolic risk status of these women. However, as mentioned earlier, most of these interventions are based in secondary care and require intensive supervision by health care professionals. Therefore, there is a need for a pragmatic structured education programme which can be implemented in the health system at a primary care level.

In this chapter, after explaining the rationale behind the development of the SUCCESS education programme, the process will be described through which the structured education was designed. The underpinning learning and behavioural theories are reviewed and finally the design of the SUCCESS study is explained.

4.1　Why SUCCESS?

Women with PCOS feel that they are "not being taken seriously" (160), there is lack of communication with health care systems (157,160) and their emotional and psychosocial needs are not met (157). Some of the major themes encompassing women's lived experience of managing PCOS are "frustration", "confusion", "searching", and "gaining control"(157,281,282). One study showed that providing information improved their quality of life (92).This is also true for the teenagers who are keen to know more about the nature of the condition and emotional and physical aspects of PCOS (160).
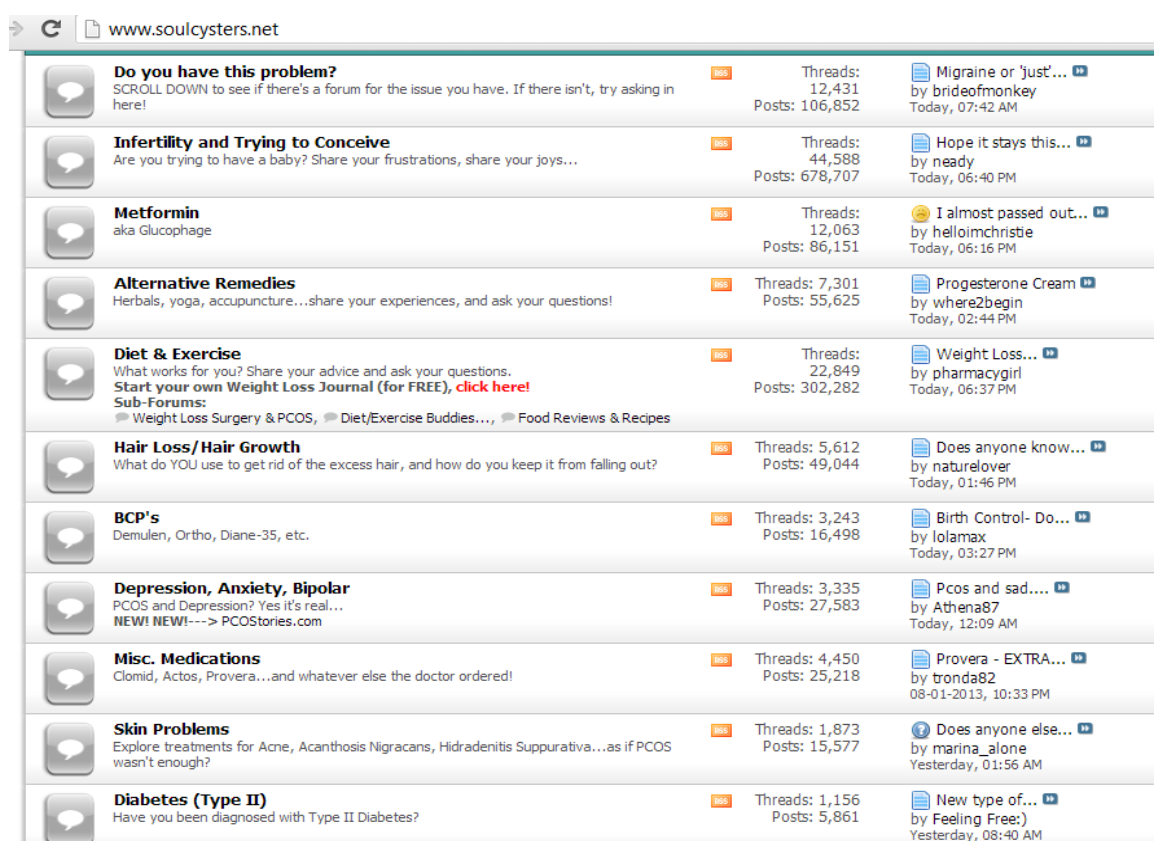
Patients seek to have the support and look positively at peer support groups (283). They would like to get information about the condition from their doctor (194,282) although this is not the case for some patients (157,160,194), who refer to the internet as their main source of information (194). However, the information on the internet is not necessarily clear and concise, and users may need to refer to multiple sites to find their answers (284). Another problem with the internet is that this cannot give them the level of peer support women need. Although this is sought in forums and chat rooms specific for PCOS; "NHS choice", "SoulCysters", or "Verity website/ (facebook page)".

Fig 4.1 shows a print screen of a popular website for women with PCOS and the interest in topic varies as shown by the number of threads; 1156 (T2DM) to 44588 (Infertility).

In summary, it can be asserted:

i)　　　PCOS is a complex condition with long term health consequences (Chapters 1 and 2)

ii)　　　Lifestyle interventions seem to be a successful first step in treatment (Chapter 3)

iii)　　　Women with PCOS want to know about their condition, available treatment options and complications

Figure 4.1 Print screen of the SoulCysters website (accessed 1/August/ 2013†)

Do you have this problem? SCROLL DOWN to see if there's a forum for the issue you have. If there isn't, try asking in here!		Threads: 12,431 Posts: 106,852	Migraine or 'just'... by brideofmonkey Today, 07:42 AM
Infertility and Trying to Conceive Are you trying to have a baby? Share your frustrations, share your joys...		Threads: 44,588 Posts: 678,707	Hope it stays this... by neady Today, 06:40 PM
Metformin aka Glucophage		Threads: 12,063 Posts: 86,151	I almost passed out... by helloimchristie Today, 06:16 PM
Alternative Remedies Herbals, yoga, accupuncture...share your experiences, and ask your questions!		Threads: 7,301 Posts: 55,625	Progesterone Cream by where2begin Today, 02:44 PM
Diet & Exercise What works for you? Share your advice and ask your questions. **Start your own Weight Loss Journal (for FREE), click here!** Sub-Forums: Weight Loss Surgery & PCOS, Diet/Exercise Buddies..., Food Reviews & Recipes		Threads: 22,849 Posts: 302,282	Weight Loss... by pharmacygirl Today, 06:37 PM
Hair Loss/Hair Growth What do YOU use to get rid of the excess hair, and how do you keep it from falling out?		Threads: 5,612 Posts: 49,044	Does anyone know... by naturelover Today, 01:46 PM
BCP's Demulen, Ortho, Diane-35, etc.		Threads: 3,243 Posts: 16,498	Birth Control- Do... by lolamax Today, 03:27 PM
Depression, Anxiety, Bipolar PCOS and Depression? Yes it's real... NEW! NEW!---> PCOStories.com		Threads: 3,335 Posts: 27,583	Pcos and sad.... by Athena87 Today, 12:09 AM
Misc. Medications Clomid, Actos, Provera...and whatever else the doctor ordered!		Threads: 4,450 Posts: 25,218	Provera - EXTRA... by tronda82 08-01-2013, 10:33 PM
Skin Problems Explore treatments for Acne, Acanthosis Nigracans, Hidradenitis Suppurativa...as if PCOS wasn't enough?		Threads: 1,873 Posts: 15,577	Does anyone else... by marina_alone Yesterday, 01:56 AM
Diabetes (Type II) Have you been diagnosed with Type II Diabetes?		Threads: 1,156 Posts: 5,861	New type of... by Feeling Free:) Yesterday, 08:40 AM

† Unfortunately I did not take a snap shot at the beginning of SUCCESS study.

It appeared that there exists a gap in the health system to address these women's needs. There was no previous or ongoing study of a patient centred, group oriented, structured educational programme for women with PCOS [http://clinicaltrials.gov/ct2/home was last searched on 02/12/10]. SUCCESS is the programme developed to address this gap; an education programme for lifestyle change in women with PCOS aimed at increasing their knowledge of their condition. Although diabetes prevention programmes were available or in the process of development in our department (7,285-287), their target population were those at risk of diabetes in both sexes and did not take into account the specific issues facing women with PCOS. Women with PCOS are young and also have hyper-androgenic and anovulatory symptoms resulting in a unique psychological need. A specific intervention was therefore needed and SUCCESS was the response to this demand.

The initial concept of SUCCESS was based on the general question: "Can a structured education programme developed for women with PCOS improve their understanding of their condition, lead to healthy behaviours and improve their health condition?"

As an education programme, SUCCESS would have to show some degree of behavioural change as an index of efficacy and as a measurable primary outcome. Increased step counts had previously shown beneficial effects on glycaemic indices of the people at high risk of diabetes (288), and therefore was chosen as the index behaviour and primary outcome in SUCCESS programme. This will be discussed in more detail in Chapter 6.

Therefore, the primary research question (hypothesis) in SUCCESS was:

"*Does a structured lifestyle intervention to promote weight loss and increasing walking activity in a self-directed programme result in a behaviour change of increased step count and consequently affect weight, glucose tolerance, insulin resistance and other metabolic, physical, and mental health aspects in women with PCOS*?"

4.2 Development pathway for self-management interventions; from idea to research

To develop SUCCESS the "Development pathway for self-management interventions" (Fig 4.2) was followed, as designed and developed by Leicester Diabetes Centre. This is based on:

a) NICE recommendations on education programmes and behaviour change (3,289-291)

b) MRC guideline for the development of the complex interventions (292-294)

c) Bartholomew's intervention mapping protocol (295)

d) Previous experiences in developing structured education programmes (7,285-288,296,297)

Figure 4.2 Development Pathway for Self-Management Interventions (Developed by Heather Daly and team at Leicester Diabetes Centre)

Development Pathway for Self Management Interventions: From Idea to Research

Explore The Idea
- Literature Review
- Peers
- Target Groups
- Interest Group
- Explore Local & National Agenda
- Service Development Or Research?

Draft Intervention
- Curriculum
- Patient Resources
- Educator

Feedback/Reflect/Refine
- Participant Feedback
- Educator Feedback
- Observer Feedback
- Resources
- Initial Impact Indicators
- Make Changes

2nd Feedback/Reflect/Refine
- Make Final Changes
- Repeat Process From 1st Pilot
- Draft Assessment Tool

Retraining
- Review Training and Refine
- Observe Delivery
- Re -Train in Relation To Intervention Changes

Ready For Research
- Curriculum /Target Group
- Training Programme
- Trained Experienced Educators
- Resources
- Training Programme
- Research Q's
- Desired Outcome
- Pathway Plan Intervention Fidelity
- Cost Of Intervention

Idea! → Developed Idea to meet a need → Intervention Framework → Refined Intervention → Ready For Evaluation → Ready To Go

Establish A Working Group
- Theories & Philosophies
- Potential Outcomes
- Describes Intervention
- Confirm The Target Group
- Education Delivery Indicators (QD) Observation Tool

1st Pilot
- Structure/Design
- Uptake/Recruitment
- Pilot Curriculum
- Intervention Receipt
- Piloting Resources
- Observe Delivery & Describe

2nd Pilot
- 2nd Pilot Of Refined Intervention
- Acquired Feedback (See 1st Pilot)

Training
- Skills & Knowledge Required
- Don't Re invent Wheel
- Scope Existing Training
- What do you want Educators to do/achieve
- Target intervention Behaviours
- Write /Deliver Training
- Trial Resources

For This To Work You Will Need
- Curriculum /Target Group
- Training Programme
- Trained Experienced Educators
- Resources
- Training Programme
- Research Questions
- Desired Outcome
- Pathway Plan Intervention Fidelity
- Cost Of Intervention

4.2.1 NICE principles

Based on the principles set out by the "patient education working group" in 2005, NICE sets out a standard for diabetes education programmes (289,291), which could potentially be applied to a structured education programme in any long term condition. The education programme should:

➢ *have a person-centred, structured curriculum that is theory-driven and evidence-based, resource-effective, has supporting materials, and is written down*

➢ *be delivered by trained educators who have an understanding of education theory appropriate to the age and needs of the programme learners, and are trained and competent in the delivery of the principles and content of the programme they are offering, including the use of different teaching media*

➢ *provide the necessary resources to support the educators, and that the educators are properly trained and given time to develop and maintain their skills*

➢ *have specific aims and learning objectives and should support development of self-management attitudes, beliefs, knowledge and skills for the learner, their family and carers*

➢ *be reliable, valid, relevant and comprehensive*

➢ *be flexible enough to suit the needs of the individual (for example including the assessment of individual learning needs) and to cope with diversity, for example meeting the cultural, linguistic, cognitive and literacy needs in the locality*

➢ *offer group education as the preferred option, but with an alternative of equal standard for a person unable or unwilling to participate in group education*

➢ *be familiar to all members of the healthcare team and integrated with the rest of the care pathway, and that people with [the condition] and their carers have the opportunity to contribute to the design and provision of local programmes*

➢ *be quality assured and be reviewed by trained, competent, independent assessors who assess it against key criteria to ensure sustained consistency*

86

> *Have its outcomes regularly audited.*

NICE also suggests incorporating specific mechanisms within interventions designed to change people's behaviour (3,290):

> *Outcome expectancies (helping people to develop accurate knowledge about the short, medium and longer-term consequences of health-related behaviour*

> *Personal relevance (emphasising the personal salience of health behaviours)*

> *Positive attitude (promoting positive feelings towards the outcomes of behaviour change)*

> *Self-efficacy (enhancing people's belief in their ability to change)*

> *Recognising how people's social contexts and relationships may affect their behaviour*

> *Intention formation and concrete plans (helping people to form plans and goals for changing behaviours, in terms of easy sustainable steps over time)*

> *Behavioural contracts (asking people to share their plans and goals with others)*

> *Relapse prevention (helping people develop skills to cope with difficult situations and conflicting goals)*

4.2.2 Medical Research Council (MRC) framework for development of complex intervention

Medical Research Council (MRC) defines an intervention as "complex" when it involves multiple variables and different levels in the design, test and implementation of the outcomes of that intervention (292-294). Development of a structured education programme based on the recommendations from NICE with an ultimate aim of implementation into health system fulfils the MRC criteria for a complex intervention (294).

The process from development to implementation of a complex intervention has four key stages: development of the idea to pilot, evaluation, feasibility and implementation (Fig 4.3), which need to be followed.

Figure 4.3 Key elements of the development and evaluation process (294)

Feasibility/piloting
1 Testing procedures
2 Estimating recruitment /retention
3 Determining sample size

Development
1 Identifying the evidence base
2 Identifying/developing theory
3 Modelling process and outcomes

Evaluation
1 Assessing effectiveness
2 Understanding change process
3. Assessing cost-effectiveness

Implementation
1 Dissemination
2 Surveillance and monitoring
3 Long term follow-up

4.2.3 Intervention Mapping

Intervention mapping is a systematic approach to developing health education programmes that provides a useful and coherent method for identifying which theoretical determinants are likely to be important in the development of an intervention (295). This approach ensures that empirical evidence is used to confirm or reject a broad range of potentially useful theoretical domains that are not necessarily confined to a particular theory or theories, thus ensuring identification of a comprehensive set of domains that are likely to be important in the promotion of a given health behaviour. This was especially important in the context of the significant difference in the target group for SUCCESS as compared to previously developed education programmes.

Core steps of the Intervention Mapping process are:

1. Conduct a needs assessment

2. Create matrices of change objectives based on the determinants of behaviour and environmental conditions

3. Select theory-based intervention methods and practical strategies

4. Translate methods and strategies into an organised programme

5. Plan for adoption, implementation and sustainability of the programme

6. Generate an evaluation plan

4.2.4 The experience in our group: DESMOND Programmes

The Leicester Diabetes Centre has a decade of experience in developing structured education programmes based on the above principles.

DESMOND - Diabetes Education and Self Management for Ongoing and Newly Diagnosed - is a diabetes group structured education programme designed for adults with recently diagnosed T2DM. DESMOND successfully improved lifestyle, depression, illness beliefs, weight and modelled CV risk in a 12 month randomised controlled trial (296). It has proved to be cost-effective when compared to clinical care (298) and has maintained some of its positive behavioural changes and improved illness perceptions three years after the initial education intervention (299). DESMOND has been implemented nationally since 2003 and is currently delivered in adults with T2DM in over 100 primary care organisations throughout the UK. It has been adopted in Europe and Australia. Success of the DESMOND approach has led to further development of structured education programmes such as DESMOND BME (Black and minor ethnicities) which is developed specifically for the south Asian community (300) and some diabetes prevention programmes as described here.

PREPARE - Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement-(288,301), is a group structured education course based on DESMOND principles and tested by our group in Leicester. The aim was to increase walking activity in adults with prediabetes. The PREPARE programme comprised a group-based, person-centred, education programme which targeted perceptions, knowledge, self-efficacy, barriers, and self-regulation in adults at risk of diabetes. It was tested in an RCT with three arms; education programme and a pedometer for self monitoring the walking steps, education only, and control. The PREPARE programme successfully increased physical activity levels and reduced two hour glucose values at three and 12 months in the arm which received both education and pedometer (288). It is important to note that it maintained glycaemic improvement two years after education (301). PREPARE was then developed into the "Walking Away from Diabetes" programme and is

being tested for efficacy in a national definitive trial (7) and is now implemented in the health system as a national prevention programme sharing its underpinning theories structure with DESMOND (6).

Other interventions developed based on the DESMOND approach are; "Let's prevent diabetes" (a diet-oriented approach for prevention of diabetes) (285); TRIMS (The Reversal Intervention for Metabolic Syndrome) (287), which focuses on reduction of waist circumference and weight; and STAND (Sedentary Time AND diabetes) (286) which targets young adults at risk of diabetes to reduce their sitting time. Fig 4.4 is an example of an intervention developed in our centre: DESMOND.

Figure 4.4 DESMOND an intervention model developed in Leicester Diabetes Centre

This wealth of experience together with the principles of NICE, MRC and Bartholomew's intervention mapping protocol, have lead to the "Development pathway for self management interventions; from idea to research" (Fig 4.2) which is the pathway followed to develop SUCCESS. This pathway recommends the identification of the appropriate learning theories to underpin the intervention, which is summarised here.

4.3 Health Psychology: Learning theories underpinning a structured education programme

Psychology has direct and indirect effects on health status (Fig 4.5) and health psychology (302):

❖ evaluates the role of the behaviour in the aetiology of illness and interactions between psychology and physiology

❖ Predicts unhealthy behaviours

❖ Understands the role of psychology in the experience and treatment of illness

Figure 4.5 Psychology and Health: direct and indirect pathways (302)
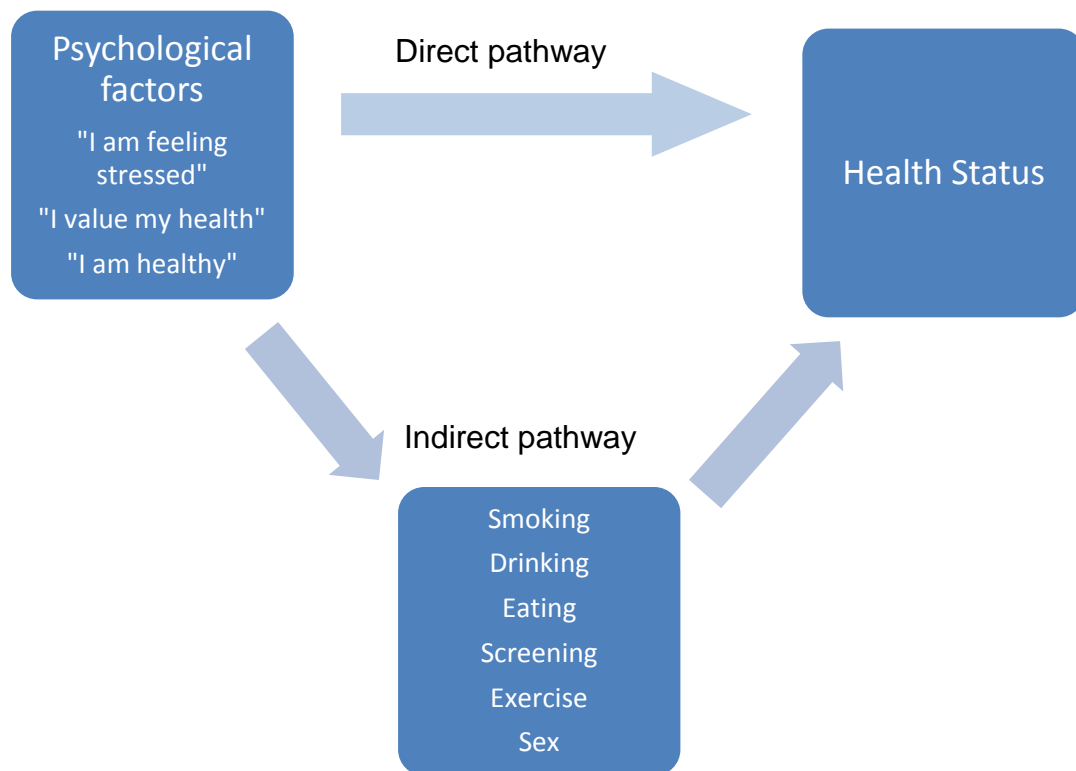
Therefore, understanding the link between the health psychology and health related behaviours is the cornerstone for the development and implementation of the education programmes.

Our group, in the development of the DESMOND programmes, have identified appropriate health behaviour theories on which to base structured education programmes using the core processes proposed by Bartholomew's intervention

mapping protocol (295). These theories were utilised in the development of SUCCESS intervention:

- "Common Sense Model" (303-306)

- "Social Cognitive Theory" and "Self-efficacy Model" (307-312)

- "Implementation Intentions" (313-317)

- "Dual Process Theory" (318-321)

4.3.1 Common sense model

Leventhal and colleagues found five common dimensions to illness cognition among a variety of illnesses (303-306) as shown in Fig 4.6 (302);

1- Identity; the label for the illness "*I have polycystic ovary syndrome.*"

2- Perceived cause; this is what the patient believes has caused the illness "*My PCOS is happened because of the pills which I used to take since I was 18.*"

3- Time line; how long does the illness last. "*When does my PCOS go away?*"

4- Consequences: what are the long term complications of the illness "*My PCOS will put me at risk of diabetes. It also causes mood swings.*"

5- Curability and controllability; patient's concept of whether the condition is curable or has any specific treatment. "*There is no treatment, I am going to live with it and try to forget it.*"

Many diseases have been tested and the five dimensions applied to a diversity of conditions (322). There also appears to be aspects which are similar across different cultures (302).

Figure 4.6 the five core dimensions in illness cognition (302)
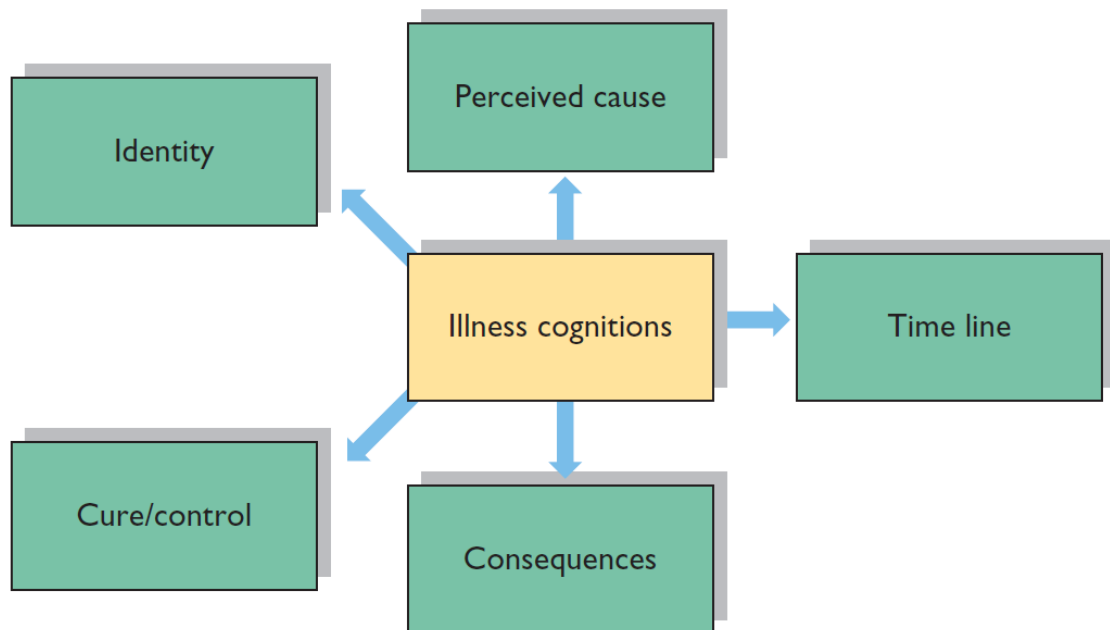
Leventhal incorporated his illness cognition elements into a self-regulatory model to explain how patients cope with illness (302,306) (Fig 4.7). This is based on the traditional models of problem solving which believe that a change (illness) is a disruption of the state of normality and the person interprets the abnormality (= illness cognition) and uses strategies to cope with and assess and reassess the process until he is satisfied that the status quo is established (= health or no deterioration in illness) (302). Obviously, the status quo may have to be redefined for chronic conditions such as PCOS and diabetes.

It is worth mentioning that Leventhal's common sense model is in the background of the education model in SUCCESS. The education starts by establishing the five aspects of the Leventhal's model and expands on this through the day (see session B, curriculum for SUCCESS, Appendix 4.1).

Figure 4.7 Leventhal's self regulatory model (302)
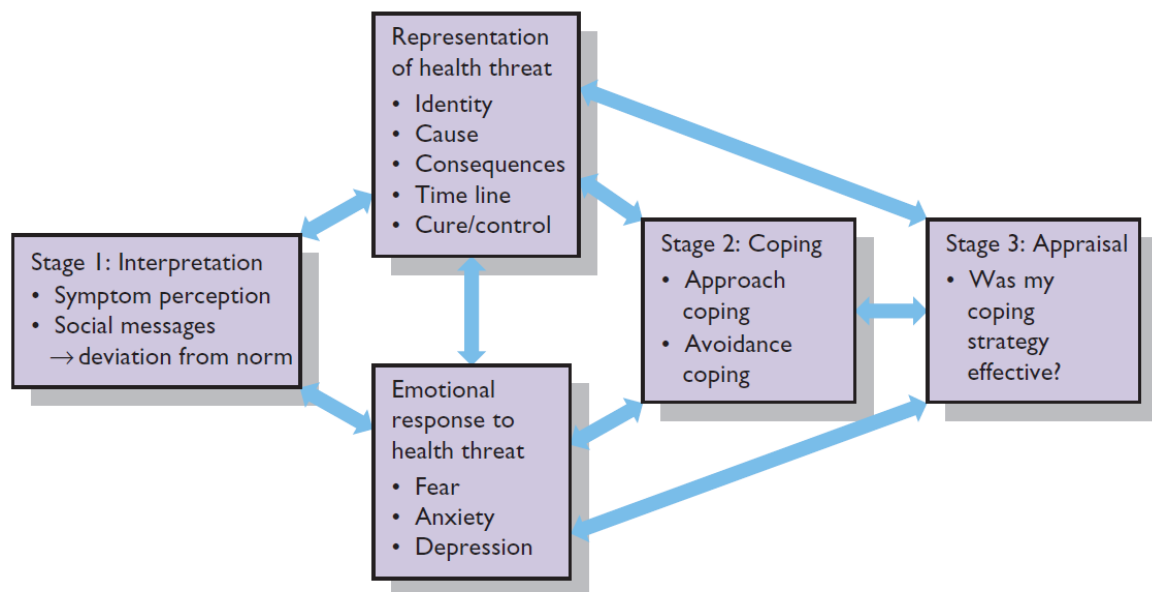
4.3.2 Social cognitive theories

Social cognitions reflect the individual's perception of their social world (302). Social cognitive theory puts the individual in the context of others with a similar condition, and the wider social world, to address health behaviours. Cognitive processes help in the acquisition and retention of new behaviours and understanding the consequences of behaviour to inform individuals of what they must do to gain benefit or avoid punishment (307). Bandura's self-efficacy model is based on "the belief in one's capabilities to organise and execute the sources of action required to manage prospective situations" (308). This self-efficacy is dependent on patients' belief in their capabilities (efficacy expectations): "*I am confident I can stop smoking*" and their belief on the beneficial outcomes of the action (outcome expectations): "*If I stop smoking, I will have a healthier life and less cardiovascular and cancer risk*" (Fig 4.8).

Figure 4.8 Differences between efficacy and outcome expectations (311)

94
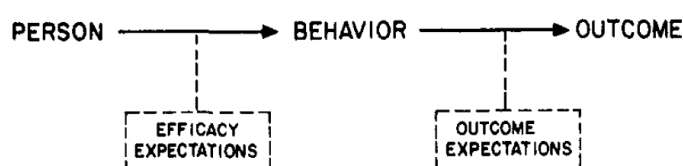
Efficacy expectations are informed by (307,308,311):

❖ Performance accomplishments (Mastery performance): "*People fear and tend to avoid threatening situations they believe exceed their coping skills, whereas they get involved in activities and behave assuredly when they judge themselves capable of handling situations that would otherwise be intimidating*" (311) Success raises mastery performance and repeated failure lowers them. It is therefore of high importance to set manageable and realistic goals.

❖ Vicarious experience (learning from other's experience and behaviour): "*This woman who has the same problem as me and is in the same situation has been able to stop smoking and has seen so much benefit*". Matching expectations comes from the peer group and the people who have achieved the behaviour or outcome while in the same circumstances. See Box 4.1 for other sources of learning.

❖ Verbal persuasion: Encouraging individuals in their attempts to achieve their expectations

❖ Physiological and emotional states: Controlling and diminishing emotional arousal as well as avoiding over-stress in pursuing an expectation will increase the chances of success and achievement.

Box 4.1: Other sources of learning

Other sources of learning and information for an individual, other than the vicarious experience, are:

"Direct experience": "*I stopped smoking in the past and slept better*"

"Symbolic sources" like facts: "*Within 2 to 12 weeks of stopping smoking, your circulation improves. This makes all physical activity, including walking and running, much easier*" (NHS-Choices website, accessed Aug/2013)

Outcome expectations (Fig 4.8) can be positive (incentive) or negative (disincentive) (308).

Successful implementation of the social cognitive theory approach also depends on other factors such as understanding the barriers and self-regulation.

❖ Barriers can be personal (situational) or socio-cultural (308,310). In SUCCESS, issues with body image and family commitments can be examples of the personal barriers, and work related issues can be an example of the socio-cultural barriers. Recognising barriers and their impact on efficacy expectancies increases the chances of achieving the index behaviour (310).

❖ Self-regulation is a key element in health interventions. Having the intention to make a change, "*I want to go for a walk*", does not guarantee that the behaviour happens. This is a well recognised phenomenon in behavioural psychology known as "intention-behaviour gap" (323). This is the subject of considerable research to find strategies which minimises the gap (314). Development of self-regulatory skills such as action planning is one of the effective methods (314,324,325). Documented action plans with short and long term goals provides the individuals with feedback on their realistic achievements and may improve self-efficacy (309). [Example of how this is used in SUCCESS is shown in Fig 4.10 after discussing the implementation intention]

Elements of the social cognitive theory have been put together in different models for behaviour change. One of the most recognised ones is the "stage of change" model described by Prochaska and DiCelemente for smoking cessation (326-331). Adaptation of this model in SUCCESS is shown in (Fig 4.9).

4.3.3 Implementation Intentions

Implementation intentions increase the chances of goal achievement including health performances (332,333). The concept of the implementation interventions is to bridge the "intention – behaviour gap" in addition to the self-regulation in this process, by focusing on "where, when and how" in a planned behaviour, the individual will try to minimise the gap (313,314,316). The "if-then" process will increase possibilities of performance by creating specific cues relevant to the situation which is highly anticipated (313,315). Therefore, when the person is "perceptually ready" (334), there is a high chance that the "cue" is identified (317).

This together with the social cognitive theory increases the chances of attainment by using specific anticipated situational cues (316). Fig 4.10 shows how this approach has been used in SUCCESS.

Figure 4.9 SUCCESS study Self management plan; behaviour change
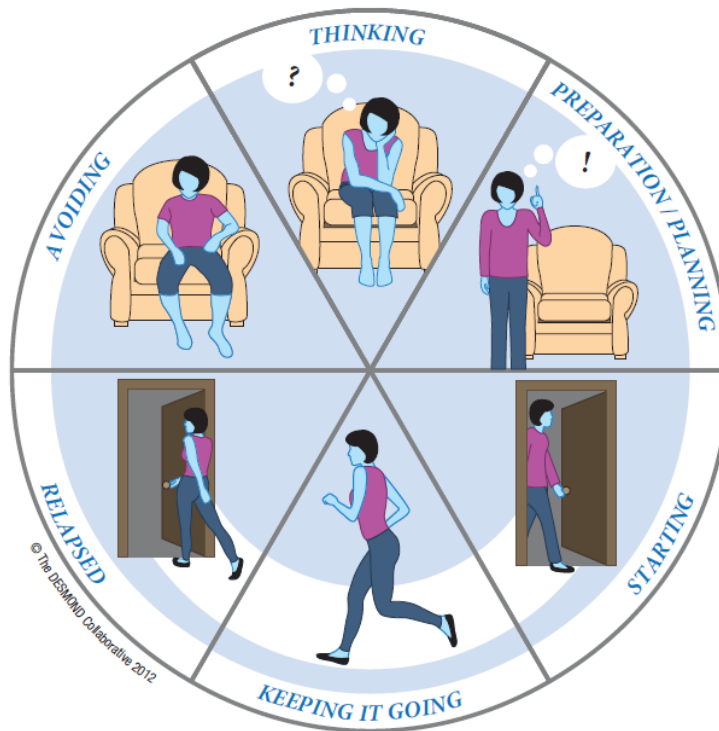
Polly (the character used in SUCCESS education] goes through the cycle: her target behaviour is increasing her physical activity. She relapses and goes through the avoiding phase before she thinks about the process again and uses the "action planning" [Fig 4.10] to make a more manageable plan and start again.

Figure 4.10 SUCCESS study self-management plan; "Action Plan"

What Am I Going To Do Now?

What activities could I do?

What will I do to overcome the barriers?
Think about and include support you may need

Which of these activites am I more likely to do?
Choose some of the above to work on

How confident do I feel that I can do this?
Choose a number between 1 and 10 (where 1 is not at all confident and 10 is very confident)

The number I choose is: . . . .

How exactly am I going to do this?

What can I do to increase my confidence?
If my confidence is less than 7

What is going to stop me?

When will I review my plan?

Date: . . . .

SUCCESS Study

Participants in SUCCESS were provided with this chart at the education session and one example would be discussed in detail. Spare charts were supplied for future use at home.

It is thought that if people make their own plan, there will be a sense of ownership and more motivation to carry out the plan (302). *They would be able to set "personal cues" relevant to their situation: "I will go out for a walk when my son has gone to bed".*

4.3.4 Dual Processing model

Chaiken argues that social cognition is a thoughtful event and there are two modes of processing in order to make social judgments; Heuristic versus Systematic modes of processing (318-321).

Heuristics [heur (Greek): "to find out, discover" (dictionary.com)] are knowledge structures which are stored in the memory, and judgment is based on easily processing cues such as "source expertise". For example,

"The doctor in BBC 4 'Horizon' programme said that the benefits of 90 seconds high intensity training which is repeated 3 times per week, is equal to 30 minutes walking or may be even more. I will therefore join the gym for the course and plan my activities based on that'

Therefore, there is minimal cognitive effort when using heuristic processing (= cognitive economy).

Systematic processing, however, needs detailed examination of the information before the judgment is processed. For example,

"The doctor in BBC 4 'Horizon' programme said that the benefits of 90 seconds high intensity training which is repeated 3 times per week, is equal to 30 minutes walking or may be even more: Why? Am I not better to do my 30 minutes walking on top of that? Which one is actually better? Does that apply to all people? Does that apply to me? Do I need to consider that? I will discuss with my doctor'

Therefore, systematic processing requires cognitive ability and capacity to analyse and is more effortful (= not economic), but the judgments based on the systematic processing are more in-depth and consequently more reliable (321).

Heuristic and systematic processing can occur alone or in combination and it is argued that individuals generally tend to make a balance between the cognition economy and the reliability, which is called "sufficiency principle" (318,320). Motivational persuasions aim to create a bridge between the two modes of processing. In SUCCESS this principle is one of the core elements of the educators' behaviour when they ask questions and create discussions in the

groups and allow the information to be judged and processed before the message is finalised.

The aforementioned learning and behavioural theories are used in combination in SUCCESS to make sure participants are actively involved in discussions, process the message, make a plan and leave the education with an in-depth understanding of the condition they live with and how they can make some changes according to their circumstances.

Fig 4.11 is the first page of the "Physical activity" session in the SUCCESS education curriculum; looking at the enlisted items on the "Participant Learning Opportunities" and "Educator activities" shows how a combination of learning theories are used in one session.

Figure 4.11 An example from SUCCESS curriculum showing the combination of learning theories used in practice

Session D: Physical Activity 1

Duration 45 minutes (approx)

Key Messages

- Increasing physical activity will have an impact on some of the symptoms and long-term health consequences of PCOS

Participant Learning Opportunities

Participants will have the opportunity to explore/learn:

- How physical activity improves the management of Polycystic Ovary Syndrome and reduces their risk of complications associated with PCOS.
- The current recommendations for activity and what it means for them
- The possible options and barriers for implementing activity within their personal lives
- Useful strategies for becoming more active around the house and local environment
- Potential solutions to their personal exercise barriers
- The benefits of wearing a pedometer, forming an action plan and keeping a physical activity logbook
- The importance of building up to their goals slowly

Educator Activity

Uses core behaviours (open questions, reflection, visual resources) to:

- Generate a list of the benefits of physical activity, current recommendations and options for increasing activity
- Encourage the group to consider strategies to overcome barriers to physical activity
- Encourage the use of pedometers for self monitoring of physical activity
- Enable participants to appreciate the benefits of forming action plans and monitoring their progress
- Enable participants to explore personal options for change and barriers to success
- Provide information, where necessary, to address gaps in participants' knowledge

4.4   Design of the SUCCESS Study

In the development and testing of the SUCCESS programme, the "MRC framework for development of the complex interventions" (Fig 4.12) was considered and the steps recommended in the Leicester Diabetes Centre's "Development pathway for self-management interventions" (Fig 4.2) were followed.

Figure 4.12 MRC continuum for the development of a complex intervention (292).
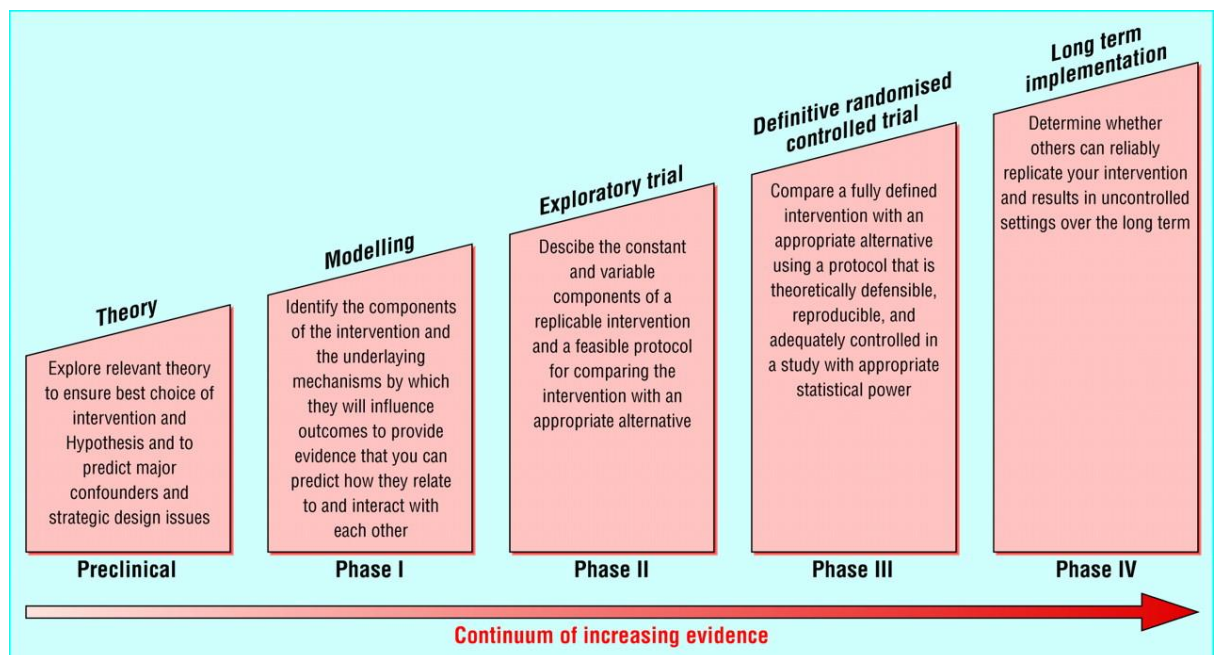
4.4.1   Research Question

The primary research question in the SUCCESS randomised controlled trial was:

"Does a structured life style intervention to promote weight loss and increasing walking activity in a self-directed programme result in a behaviour change of increasing step count and consequently affect weight, glucose tolerance, insulin resistance and other metabolic, physical, and mental health aspects in women with PCOS?"

4.4.2 Phases in SUCCESS

PHASE 1: Assessment of the components of the intervention (needs and available management options) in the target group via: reviewing of the literature, understanding a local multi-ethnic cohort of the patients with PCOS, and interviews with women with PCOS.

PHASE 2: Development and pilot of an evidence-based structured self-management education programme incorporating findings from Phase 1.

PHASE 3: Randomised controlled trial of an education and lifestyle intervention.

The first three chapters of this thesis reviewed the literature and examined a multi-ethnic population of women with PCOS. Interviews with women with PCOS will be described in Chapter 5, followed by design and pilot testing of the education programme. Chapter 6 to 9 describe the design of RCT, and some of the results.

4.5   Summary of the chapter

A review of literature shows that women with PCOS look for information regarding their condition and the available treatment options. They seek peer support and demand more communication with health system. A need for a structured education programme in the health system was identified and therefore SUCCESS was planned.

Patient education needs to be evidence based, tailored to the target population and underpinned by learning theories. Appropriate learning theories were identified for the SUCCESS programme namely; "common sense theory", "social cognitive theory", "implementation intentions" and "dual processing theories". Combinations of these theories are used in SUCCESS to ensure the messages are clearly communicated and meet the needs of the variety of participants attending the education.

A structured education programme is a complex intervention; needs to be focused on a specific aim, be evaluated in a pilot and tested before implementation in the health system. Therefore a research question was identified as a focus for SUCCESS study, which was subsequently designed in phases of development, pilot, and feasibility testing.

Chapter 5 : Development of the education programme

Phases 1 and 2 of the SUCCESS study were designed to gather information, then design and test the curriculum for the education programme for feasibility, to ensure that it is ready for testing in a randomised controlled trial (Phase 3).

In this chapter, the last part of data collection is described, which was the qualitative interviews conducted with women with PCOS. This is followed by description of the process of developing the education programme, including the pilot studies performed to inform the content and resources of this programme.

I should note that, to improve my understanding of qualitative research, I observed the "Qualitative research module" as part of the MRes course in the department of Health Sciences, University of Leicester (UoL). I also attended a workshop for conducting interviews and co-ordinating focus groups (UoL). Additionally, qualitative researchers from the Department of Health Sciences at UoL, provided support.

This has been a collaborative work and the process of the curriculum development, especially, was not something that I could do single-handed. A list of people who have had an input into the study is presented in Appendix 1. A few colleagues in the research team disclosed to a very limited number of us that they had been diagnosed with PCOS. This information stayed known to only a closed circle of the SUCCESS team and their invaluable opinions were sought during the process without having to disclose their condition.

5.1   Phase 1: Qualitative interviews

Information gathered in this part was intended to complement the results of the database analysis and the literature review, to help tailor the education programme to the needs of women with PCOS. Women who were interviewed were the potential target of this programme and therefore their experiences of living with PCOS were important.

The dynamic process for the development of the education programme started in parallel with the interviews. Based on previous experience in the group (as described in chapter 4), it had provisionally been predicted that the education programme would be 3.5 hours in duration and could be delivered in one half-day or two 2-hour parts in the evenings. The content of the programme were thought to be broadly about what happens in the body with PCOS, and beneficial lifestyle changes in terms of weight management and physical activity.

5.1.1   AIMS

Using qualitative research methods, the aims were to:

- Identify and explore understanding of PCOS, and educational requirements, amongst patients with the condition.

- Understand their interaction with PCOS.

- Understand the barriers to self-management and attitudes to education programmes in women with PCOS.

5.1.2   METHODS

Ethics approval was granted by the National Research Ethics committee, East Midlands, Leicester (Appendix 5.1)

5.1.2.1 Sample size and recruitment for interviews

Interviews were planned to be carried out until the point of data saturation (that is where no new themes were emerging). Although it was difficult to estimate the point at which data saturation would occur, it was anticipated that a maximum of 30 participants would be needed, as per the experience from the previous qualitative studies in this group (157,158). The intention was to include a purposive sample, comprising a variety of patients in terms of age, ethnicity and duration of diagnosis with PCOS.

5.1.2.1.1 INCLUSION CRITERIA

Adult women (aged 18 to 70) with a clear diagnosis of PCOS based on Rotterdam or NIH Criteria (26,27). A wide age range was considered to ensure diversity of opinion and lived experience with PCOS during the interviews.

Recruitment had been planned to be conducted at the out patient clinic in Leicester Royal Infirmary (LRI). However, following the registration of the SUCCESS study on the clinical trials website in October 2011 (NCT01462864), patients showed interest in getting involved with the study; some were even happy to pay for their travel to commute from London or Manchester. Unfortunately the recruitment was limited to Leicester, Leicestershire and Rutland and therefore only three patients could be recruited from this group. Their diagnosis of PCOS was confirmed using the above criteria.

5.1.2.2 Data collection

The choice between contributing qualitative data through an interview, focus group or both was subject to the preference of the participants; they generally preferred the interview format.

A topic guide was used for the semi-structured interviews to facilitate and direct the process of qualitative data collection (Appendix 5.2). This topic guide was developed after extensive discussion within the research team and was reviewed during the process of data collection, in order to make sure that the emerging

themes were explored. Items included in the topic guide are summarised in BOX 5.1.

<div style="border: 2px solid blue; padding: 10px;">

BOX 5.1

The items broadly included in the topic guide included:

- The experience of being given a diagnosis of PCOS
- Understanding of, and attitudes and beliefs about, PCOS
- Educational needs of people with PCOS
- Thoughts on what would have better prepared them for managing their PCOS

</div>

Interviews were mostly conducted between November/2011 to March/2012. One interview was conducted at the person's home, two at their work place and the rest in the Diabetes and Endocrinology Department at the LRI. The first two interviews were conducted by an experienced qualitative researcher, Mrs Naina Patel (NP) and I listened repeatedly to the interview tapes to learn techniques (for example; how to follow a lead in the interview). My first two interviews were reviewed by Dr Margaret Stone (MS) to make sure that I had gained the required skills and that data collection would not be seriously affected by my lack of experience. Interviews were audio recorded and were transcribed by an audio typist experienced in transcribing qualitative interviews.

My technique improved through practice; the first interview lasted 18 minutes and the last interview was 2 hours. I gradually learned to take the lead from what might have seemed a trivial comment made by the individuals. More importantly, I learned that by being patient, maintaining silence at the right time and allowing the person to breathe and think, they would often continue to speak and open up about their "untold" stories. This is a skill which I have rarely had a chance to practice in the 7-10 minutes consultation time in the clinical setting.

5.1.2.3 Data analysis

Data analysis was planned to be broadly iterative and based on the 'Framework' methodology (335,336). This included familiarisation through reading and re-reading transcripts and the development of a coding frame based on key themes that have been identified. The initial coding frame was agreed after a review of the first three interviews. A constant comparative approach (335) was adopted whereby the coding frame was open to revision as further interviews were coded.

Data collection was planned to end at the point of data saturation when new themes were no longer emerging from the interviews and those identified had been fully explored. The themes identified as being relevant for informing the education programme reached the point of saturation after the eleventh interview. One additional interview was conducted to confirm that no new theme would appear. For the purpose of this thesis, exploration of the interview data was limited to preliminary analysis focusing on information that would be useful for the design of the education programme. It was noted, however, that the interviews had the potential for further in-depth analysis about experiences of living with PCOS; this additional analysis is outside the scope of the thesis, but has been planned to be carried as part of a collaboration with qualitative researchers in the UoL (explained more in Chapter 10).

The preliminary data analysis was conducted by hand without the use of any software.

5.1.3 Results

5.1.3.1 General characteristics of the sample

Twelve women were interviewed (Table 5.1) with an age range from 17 to 51 years (median 36 years). There were seven white and four south Asians (SA) women and one Black African woman, reflecting the multi-ethnic nature of the local population. Their experience with the diagnosis of PCOS also ranged from less than a year to over 20 years. This was their official diagnosis with PCOS,

however some reported that they knew about their condition before their diagnosis (self-diagnosed through reading and information gathering) or that their symptoms were present prior to the diagnosis by their doctors. These women are identified in Table 5.1. The interviewees also represented a variety of occupations including student, nurse, computer expert, manager, independent businesswoman or housewife.

Considering that weight related issues appeared to be a significant point of discussion for many of these women, a column in Table 5.1 shows whether they considered that they had a problem with their weight. Their BMI was not calculated at the interview session and they were not asked to mention their weight. Some of the participants' experience with high weight was from some years ago and therefore their actual weight would be subject to a bias of remembering their weight from memory and not related to their current weight.

Table 5.1 Characteristics of women who attended the interview

No	Age	Ethnicity	Diagnosed as PCOS (yrs)†	Occupation	Weight issues	Symptoms
1	28	African	6 (possibly 12)	Nursery teacher	Yes	Hirsutism, Amenorrhoea, Infertility
2	44	White	3 (possibly 20)	Hospital Employee	Yes	Hirsutism, Oligomenorrhoea, infertility
3	51	Pakistani	6	Own business	Yes	Hirsutism, Menorrhagia, PCO,
4‡	17	White	0.5	Student	No	Hirsutism, Amenorrhoea, PCO
5	29	Pakistani	17	Pharmacist	Yes	Hirsutism, Oligomenorrhoea, Infertility
6	43	Indian	23	House wife	Yes	Hirsutism, Oligomenorrhoea
7	51	Indian	10	NHS Nurse	Yes	Hirsutism, Menorrhagia, PCO,
8	26	White	0.5	Desk Job	No	Acne, blood test, PCO
9	40	White	8 (possibly 20)	Computer analysis	Yes	Hirsutism, Oligomenorrhoea, PCO
10	45	White	20	Management	Yes	Hirsutism, Oligomenorrhoea
11	26	White	1 (possibly 3)	Waitress	Yes	Hirsutism, Oligomenorrhoea, PCO
12	29	White	14	Event organiser	Yes (initially)	Amenorrhoea, and PCO

PCO = Polycystic ovaries on Ultrasound Scan
†Some women mentioned during the interview that they thought they had had PCOS for longer; this is presented in parenthesis.
‡ I conducted this interview at the person's home with her mother present. The mother also had PCOS with the same signs and symptoms, but she had never been officially diagnosed; she consented separately to take part in the interview and although my intention was to explore her experience as well, most of the interview was around the daughter's experience and the mother, apart from some trivial mentions, would not make any comments on her experience. I did not insist on exploring her PCOS, as I felt she did not want to and I was not able to re-arrange to meet the mother.

5.1.3.2 Themes identified in the study

Themes relevant to the design of the education programme that were identified within the interview data could be categorised to two main topics: how did the patients deal with their diagnosis of PCOS and what was their attitude towards a possible education programme. One theme which emerged strongly through the interviews was their emotional relationship with the diagnosis of PCOS and their symptoms and "how did they live with their PCOS".

[Please note that an interview (=Int) is referred to as per order in the Table 5.1; an example from the first woman in Table 5.1 is shown as (Int 1).]

5.1.3.2.1 Diagnosis of PCOS

This category can be subdivided into the following sub-themes:

News of the diagnosis:

In response to the news of the diagnosis, patients' feelings varied from puzzlement to relief, getting upset or even anger. This possibly related to the events which led to the diagnosis.

When the diagnosis was given as part of a series of investigation into menstrual problems there was a general lack of understanding of what the diagnosis meant.

"Oh well! What does that mean?" (Int. 7), or *"it did not mean anything"* (Int 12)

In some cases the diagnosis led to feelings of relief because fears about cancer had been allayed or because it was helpful just having a label for the combination of symptoms.

 "… initially relief that it wasn't cancer" (Int. 9).

"I think kind of like a little bit of a relief because I could put a name to it, you know but it was more of a case of this is what I have got to live with for the rest of my life" (Int 11)

One woman who had undergone extensive investigations for infertility felt angry when she was told about PCOS almost 15 years after her treatment:

"*I was really annoyed, really angry, quite let down by it. Just felt 'Did I ask enough questions or?' … I was never told what it was. Although I have since went on and had a child, but only until I came to this clinic was I told what it was*" (Int 2)

Although 11 patients had hyperandrogenic symptoms of PCOS (hirsutism or acne) only one patient (No 8) had originally consulted their GP because of acne, and the rest had started their journey due to their menstrual problem. They had not considered their excess hair to be a problem needing doctors' attention:

"*I didn't care then, I wasn't bothered* "(Int 2)   "*hair can be resolved with beauticians*" (Int 7)

Understanding PCOS:

While a couple of patients knew about the "*hormonal imbalance and cysts on the ovary*" (Int 12, Int 9), the majority reported that they did not know the exact cause of their PCOS. Patients had generally started to look up the condition in the internet; some had also joined groups like "Verity-PCOS-UK" (www.verity-pcos.org.uk) to gain information and some had bought books.

Some had increased their knowledge over time, for example moving from:

 "*I had no clue*"

to:

 "*It's just that I know from reading and speaking to doctors it's got to do with having is it too much testosterone? Or something like that*" (Int 1)

Even years after the diagnosis, however, others had not progressed in terms of understanding the condition:

"*I have absolutely no idea. No idea whatsoever. I don't know*" (Int 2)

In the case of one patient, lack of understanding of the condition had led to feelings of self-blame. This patient was so upset about the cause of her PCOS

that it had to be explained to her after the interview that she was not at fault for causing her PCOS:

"*I did have a termination and I don't know whether or not something like that [pause]. Because I don't know [pause] whether or not that's [pause], I don't know whether that triggered it [crying]*" (Int 11)

The experience of a patient who was "happy" (Int 8) with her doctor, was unique and most of them even months or years after their diagnosis still had unanswered questions about their condition:

"*I think I'd been to see* [Dr X in the speciality clinic] *I think it's about my third visit, I was seeing him every six months, so about 18 months later. I was struggling to get my head round PCOS*" (Int 9)

Or

"*I still don't* [know] *whether, you know, whether there is a cure or whether at some point in life things may balance out and it might go away or whether it is with you for the rest of your life*". (Int 3)

When asked about long term health risk associated with PCOS, most of them replied that they did not know anything about it or they had only found out about diabetes when they read the information sheet from the SUCCESS study. The few, who were aware of the increased risk of diabetes (Int 5 and Int 6), had an extensive family history of diabetes and were aware anyway.

In summary, the interviews identified generally low levels of understanding of the condition in women with PCOS. This suggests that either health care professionals involved in the treatment or diagnosis of the PCOS had not spent enough time in explaining the condition and its associated risks to these women, or the patients had not been given access to a good information source to answer their questions.

What advice did they receive?

Those interviewed appeared to have received a limited level of advice:

"*The only thing he [GP] did say is: it shouldn't give you any cause for concern now, but at a later date when you might consider having children you may have difficulty*" (Int 5)

114

Despite the fact that lifestyle change has been the first line of treatment in PCOS, when they were asked about the advice they had received on lifestyle change, it was either "nothing" or a general comment that they needed to lose weight:

"They told me to do it but I never was offered like help to go and do something or anything" (Int 6).

One patient (Int 9) was referred to a dietician 10 years after diagnosis.

None of the patients had received any offers for a routine check, or screening for health risks related to PCOS.

What would they want to have been offered to them by the health system?

When questioned about the type of help they would like to have been offered by the health system one response was:

 "*Just that option that you can go and talk to somebody*" (Int 6)

It was easily noticeable that these patients wanted more input from health care professionals and they missed an informative communication with their doctor. All those interviewed would have liked to have been offered some information about their condition and to have a person to refer to in case there was a question:

"*Probably years ago would have been* [nice] *if somebody had actually sat me down and explained to me exactly what having PCOS meant. What the symptoms might be, what I can do to help myself to deal with, to cope with, deal with the symptoms, the things that might happen ………The diagnosis I received was on a phone call to say 'You've got PCOS' just get on and deal with it and that was it. I didn't even have a one-to-one meeting with my GP*" (Int 10).

All the women interviewed would like to know about lifestyle changes they could make, including diet, and physical activity choices. The majority would like to have a point of contact in the health system who would understand PCOS, for example, a "specialist nurse" was suggested. This was also true for those under the care of a specialist:

"*You are left to go with tablets that you think to yourself 'Oh this will be it, this will be it. This will work.' It's the fact there's no more follow-up from that. It's just*

'Come back again. Tell us how you are.' I don't think there's enough information at all on it."…(Int 2)

In summary, the need for education and support emerged clearly from the interviews.

5.1.3.2.2 Education

Mode of delivery:

Everyone interviewed wanted some educational input about their condition; however, when asked to compare group education with the option of having a DVD to take home and watch, one suggested that she did not like either of the modes, as she was "*a big fan of the good old-fashioned poster*"(Int 2).

The other women interviewed, all expressed a preference for group sessions. Three (Int 3, 5, 6; all SA) would prefer group education because of the dynamic of the group and learning from other patients, but they suggested that they would come to a group session only if they could be certain that they did not know any of the other people in that group:

"*Because obviously the people that have been diagnosed with PCOS are probably going through the same things that I am. Everybody handles stuff differently. But it would be on a basis that I don't know anybody in that room and they don't know me and once we leave the hospital, or wherever the meeting is, you go your own way.*" (Int 3)

Every one else stated preference for group education.

Barriers:

When they were asked about the potential barriers to attending a group education programme the issue of embarrassment came up regardless of ethnicity;

116

"I think it's something that you could potentially be quite like embarrassed about I suppose because it's quite an intimate kind of illness to have. I think, for me, the encouragement would be to meet somebody else that has it so it's common ground then isn't it? Something that you can discuss with somebody else who knows how you kind of feel" (Int 8)

When they were asked about other barriers which would stop patients from participating in the group education: time and life commitments were mentioned. The majority preferred two days of two hours education as compared to a full day of 3.5 hours education.

Content:

As to the content of the education programme, those interviewed all wanted to know more about PCOS, its causes, treatment options including advice on diet and physical activity, and also coping with the condition and emotional support:

"I think just knowing that it's okay if you feel angry, frustrated, perhaps even just acknowledging that, that might be how people feel" (Int 9)

"Because you can't be self-centred around your illness all the time. It would be good to see how other people deal with it" (Int 7)

Partners:

Most of the women who preferred the group education would bring their partner;

"I'd bring my husband. Yes definitely. I think it would be better actually because it's nice to see how other people feel. Because I sometimes ask my husband and he says 'I'm sick of you being tired all the time. I wish you'd get better. I wish you'd sort it' ". (Int 7)

This was not always due to lack of sympathy from partners or family, but also to help them understand the condition better.

The issue of the emotional need and coping with PCOS was identified as a specific and important theme.

5.1.3.2.3 Living with PCOS

It appeared through the interviews that in some of the patients their PCOS had created a very deep sense of hate or shame in regard to their body.

Their relationship with their symptoms:

"I feel, I feel a freak and nobody at the house, nobody is allowed to discuss it." (Int 3)

"You can't get away from it; it's there when you wake up in the morning, you go in the bathroom, wash your face it's there in the mirror" (Int 6)

This was a common feeling mixed with shame and embarrassment:

"Except for my partner, nobody's seen my face out of the street since I was about 18." (Int 1)

For some patients the body shape was a bigger problem than excess hair:

"Whilst yes I was dealing with excess hair and stuff, but a good pair of tweezers, paying for a bit of laser treatment, waxing from time to time, I'd deal with that .... my weight; maybe, it might be difficult to believe, but I would be very shy and retiring and not actually want to go to a party because I didn't have anything nice to wear because I was too fat to get anything nice to wear" (Int 10)

Sometimes cultural background would add some extra distress; the possibility of infertility was a big problem for the African patient:

"I can say like you might be like cast out if you can't have any children and people call you names and they say things like 'Oh that barren woman' . But with the facial hair in Africa it's okay because a lot of women have it. It's just here in England it's something that a lot of people you have to shave your legs and you have to shave this and that, when back home it's not like that. It's okay you're accepted." (Int 1)

Infertility was an issue for any of the patients who had experienced this, regardless of their ethnicity; however, it seemed that women from ethnic minority backgrounds (African and SA) had a higher level of concerns regarding this issue. Specifically, at the time of an arranged marriage it was a big issue to mention to the other family.

118

"[Asked whether her husband knew?]   And my parents, because it was an arranged marriage, so I always said 'I don't want to deceive anybody so you have to mention it', you know. This is the case. [Long pause from patient]" (Int 6)

Day to day life:

Feelings about the condition had obviously affected the day to day life and social interactions of the women interviewed. Not only would they like to hide their image issues from friends and family but even the menstrual irregularity could be a source of stress:

"*I never know when I am going to have a period and that I think that plays on my mind a huge amount because it's like oh am I going to have a good week this week or is it going to be a bad week.*" (Int 11)

When it came to the job and work interactions, the majority said that they could put their PCOS issues aside and function well. They had separated their personal/social life from their professional interactions to the extent which was possible.

Eventually the majority thought that they had to live with the condition and accept it in the background of their life; while it was distressing they had to get along:

"*I feel sorry for the people, the women that get up in the morning and do what I used to do and then just like you spend half your life wasted before you get out of the front door in the morning because you feel such a freak*" (Int 2)

5.1.4 Discussion

Interviews had been planned to contribute to the design and modification of the education programme. Analysis of the collected qualitative data was conducted in parallel with the process of the development of the training curriculum for the education programme. Some important issues were directly fed into that process of developing the intervention and necessary actions were taken to address them. These are listed in Box 5.2, and explained below:

Box 5.2

Summary of important findings from interviews to inform SUCCESS education programme;

> ➤ Women with PCOS identified education and information as a need priority
> ➤ Emotional Management and coping strategies need to be considered
> ➤ Patient look for education and educators must be ready to answer their questions
> ➤ They preferred group sessions and would like their partners/family to be involved
> ➤ Potential barriers to attend education programme are; time, and embarrassment in sharing their condition
> ➤ They generally preferred two evening sessions

i)   Clearly there was a need for education to know more about the causes of PCOS, its long term health risks and the options on lifestyle changes. This confirmed the rationale for developing an educational intervention.

ii)   There was also a need for strategies to manage and cope with this condition. The emotional impact of PCOS had already been reported in the literature (157,158) and is reviewed in Chapter 1 of this thesis. However, these interviews highlighted their impact on the patients' day to day life. This could potentially have a negative impact on their lifestyle change by affecting their self-regulating behaviour and outcome expectancies (as discussed in Chapter 4) and therefore needed to be addressed in the education programme. Based on the findings from the interviews, a specific time was allocated to address "balancing life with PCOS" in the education programme.

iii) An important barrier to involving people in the education programme was thought to be the embarrassment and the sense of privacy attached to the symptoms of PCOS. Patients clearly wanted the education; it was the question of getting them to attend the group sessions. Therefore, two booklets were designed: one to introduce the study (Flyer for SUCCESS, Appendix 4.2) and a booklet to introduce the education programme and the dynamics of the group interaction to the women who would be randomised to the education arm of the study. (Preparing for SUCCESS, Appendix 4.3)

Other findings were addressed in the process of SUCCESS: educators were trained according to standards of group education, patients were offered to bring a friend/partner/family member, and time was mutually agreed with a group.

As indicated previously in this chapter, the analysis of the qualitative data presented in this thesis is focused on the ways in which the data was useful for the development of the intervention. Further in-depth exploration of the data will be conducted as an additional project. Potential areas for further exploration include cultural differences, the impact of stigmatisation and psychological distress associated with body image issues.

5.2 Development of the training curriculum for the SUCCESS structured education programme

5.2.1 Introduction

The aim of the education programme was to improve the modifiable risk factors by introducing a lifestyle programme in terms of physical activity, diet and weight management and encourage a behavioural change, including increasing walking steps. A written curriculum was needed as the source of information and plan for the educators, so the delivery of the education would be consistent for different groups and by different educators. This written curriculum is therefore a reflection of the education programme and what happens in the group education.

The curricula from previously developed structured education programmes such as DESMOND (296), WALKING AWAY (7), and LET'S PREVENT (285) were used to structure the curriculum. Learning theories described in Chapter 4 of this thesis were implemented in the curriculum and it was tailored towards the target group (women with PCOS) using the information gathered in the phase 1 of the SUCCESS study: literature review (Chapter 1), database analysis (Chapter2), systematic review (Chapter3) and the interviews which were presented earlier in this chapter.

At the beginning of my PhD study I attended a two day training course to become a DESMOND educator and started to deliver DESMOND education in patient groups in the community. This was an invaluable experience which gave me an insight in to what really goes on in the education sessions, a real life experience of patient-educator interaction and the type of the questions which would be asked by participants. In addition, it was a good experience to adjust the level of discussion to lay language, understandable by everyone. The experience of delivering DESMOND helped significantly in the development of the SUCCESS education programme.

5.2.2 Aim

The aim of this phase was to produce a piloted, evidence based curriculum for the SUCCESS structured education programme.

5.2.3 Methodology

As described in Chapter 4, the pathway developed in Leicester Diabetes Centre (LDC) for development of self-management interventions was followed to develop the SUCCESS structured education programme (Fig 4.2 in page 85).

5.2.4 Process; step by step

The process of writing the curriculum started in parallel with the interviews from November/2011 and finished in July/2012. In view of the available expertise within the LDC, in collaboration with CLAHRC[3] Curriculum and Development Training Team (CCAT), a group was formed consisting of myself, Janette Barnett (JB) and Heather Daly (HD) to discuss the content of the curriculum under the general guidance of my supervisors (MJD and KK).

The initial sections predicted for the curriculum are shown in Table 5.2, and the duration of the education was thought to be 3.5 hours which could be delivered in one "half-day" or two "2-hour parts" in the evenings

---

[3] Collaboration for Leadership in Applied Health Research and Care (CLAHRC)

Table 5.2 Predicted Outline for the SUCCESS structured education programme at the start of the process

Module name	Main aims and educator activities	Theoretical underpinning	Time weighting
Patient story	Give participants a chance to share their knowledge and perception of PCOS, associated metabolic risk factors and conditions and highlight any concerns they may want addressed in the programme	Common sense model	10% (20 min)
Professional story	Use simple non-technical language, analogies, visual aids and open questions non-didactic method to provide participants with an overview of PCOS and its aetiology, Insulin Resistance, Cardiovascular Risk Factors	Common sense model / Dual process theory	35% (60 min)
Diet	Give participants an accurate understanding of the link between diet and metabolic dysfunction	Social cognitive theory / Dual process theory	20%(40 min)
Physical Activity	Use simple language, analogies, visual aids and open questions to help participants identify how increasing physical activity may improve insulin sensitivity, body weight and PCOS. Understand the current recommendations; explore options for increasing physical activity in everyday life; identify barriers to increasing physical activity; form action plans and set personal goals. Participants were to be provided with a pedometer based on the experience form the PREPARE study(288)	Social cognitive theory Behavioural Choice Theory	35% (60 min)

5.2.4.1 Professional story

In the first draft of the curriculum, the patient's story, diet and physical activity were modifications from previous programmes. The professional story was a new section which was written as an evidence-based lay language story, with inputs from the previous steps of this PhD project. Other available on-line resources for women with PCOS such as Verity (verity-pcos.org.uk), Patient information (patient.co.uk), NHS-Choice (nhs.uk/conditions) and the information sheet provided for the patients in the reproductive medicine clinic at LRI (as shown in Appendix 4.4) were also reviewed for this purpose.

One important factor in the curriculum [and more generally in patient education] is the flow of the story; therefore, as well as the content, the narrative style had to be checked. This was a particular challenge in the professional story of PCOS due to its complex underlying pathophysiology, the number of hormones involved, the range of criteria included in the diagnosis, and also the many unanswered questions about the pathophysiology of PCOS (4,14).

A document was prepared listing all the facts and points that should be included in the story; together with JB, we reviewed and practised the delivery of the professional story. Each time the delivery was voice recorded and then we would listen to the re-play to make sure that the sequencing worked. If there was any problem, the necessary changes were made to ensure that the narrative "flowed" well. Once we were happy with the story, we asked a group of trained DESMOND educators to listen to our narration of the professional story and their comments were taken on-board.

We then invited a group of the staff working in the administration and or clinical trials sections of our group to listen to the professional story and give us their feedback. This audience, unlike the previous group of DESMOND educators, were not familiar with diabetes-related education programmes such as DESMOND, and therefore the structure and flow of this type of education session was not a familiar theme for them.

Their comments, especially on the complexity of the pathophysiology and the way it was described, suggested that this needed further simplification. Appropriate changes were therefore made to the curriculum, for example, a graph was put into the curriculum and patient's handbook to show some of the hormonal changes ("My SUCCESS handbook", page 5; Appendix 4.5).

5.2.4.2 Balancing life with PCOS

As described earlier, the analysis of the interviews showed the extent of the psychological problem that some of these women encounter in their day to day and social life. There was therefore a need for allocating some time to deal with this aspect. Considering the extent of the effect described by some of the patients, these emotional issues could affect their "efficacy expectations", "self-regulation" behaviour and ultimately "intention – behaviour gap". However, it was considered that we had only interviewed 12 patients and some of the participants had found their own coping mechanisms, or some patients might find it too personal to want to attend the emotional management sessions. These problems were discussed by the curriculum team and, considering the complexity of the psychological issues, Dr Yvonne Doherty (YD) the expert clinical psychologist working in our department was invited to join the group for this part. A group was formed consisting of myself, JB, HD, YD and Michelle Hadjiconstantinou (MH) [who has a background in the health psychology] to consider the way in which this section of the programme might be delivered. Coping strategies had been used in other education programmes such as DESMOND Newly Diagnosed and DESMOND On-going (300), which was a good starting point. A similar model was adopted for the pilot sessions.

The planned "balancing life with PCOS" included four sessions (Curriculum for SUCCESS Appendix 4.1)

Your thoughts about PCOS:

In this session the participants would be asked to express their feelings about PCOS, when they were diagnosed and also how they feel now about their condition. This would allow them to open up. Educators would take the lead from

the expressed words to expand and try to bring all the participants into the discussion.

Other stresses in Life:

It should be acknowledged that PCOS is one of the stressors in life for those with the condition. There are many other stressors which also influence the behaviour and the potential choice of lifestyle change. Participants would be invited to share and discuss other things which they see as contributing to the overall burden of stress in their lives. Educators would facilitate the discussions to help participants talk to each other and make suggestion about how to deal with that situation.

Your relation with PCOS:

This session explores how people see themselves with their PCOS and how they think others see them. In the final model, a pair of binoculars was used and patients were asked to think about how people might use those binoculars to watch them.

Developing strategies for living with PCOS:

This is a summary of all sessions and how the discussions in the previous three sessions could be put together to avoid strong feelings which could affect a person and adversely affect behaviour.

5.2.4.3 Final Structure

Initially, the length of the education programme had been estimated as 3.5 hours. Adding the "balancing life with PCOS" part would mean an extension of at least one hour so that the overall length would not fit with the plan for "half-day" education. Additionally, the women interviewed had indicated that they would prefer to have two 2-hours session (data presented earlier in this chapter); therefore it was decided that we would add a third part to the education and offer patients the choice of whether to attend a 1.5 to 2 hour education specifically on "balancing life with PCOS". In our group discussion we also had in mind that some

women might not feel comfortable to openly express their emotional concerns during an education programme, so they might not wish to attend this part.

5.2.4.4 Resources

The aim was to make the session as interactive as possible, therefore the resources were designed to be laid down on a table and participants could stand around the table. This was easy for the "Diet" and "Physical activity" sections as we could choose from the available resources used in other programmes such as Walking Away and Let's Prevent Diabetes. New resources had to be designed for the professional story. It was also important to avoid any stigmatisation associated with body image and skin colour; therefore a figure in light blue (called "Polly") was designed [Fig 5.1]. (A full range of the images created after the pilot stage based on Polly's day-to-day activities are presented in the curriculum and educational resources in Appendix 4).

For the pilot sessions, Polly and the body parts were cut from felt textured fabric; they were then printed on special cloth (Reich Digital Felt) and were laminated. For other resources such as treatment options, some images were copied from Google images and laminated. After the pilot sessions they were modified to fit with the SUCCESS style; Fig 5.2 shows an example of the infertility card before and after piloting.

Figure 5.1 Resources used in SUCCEESS; "Polly"
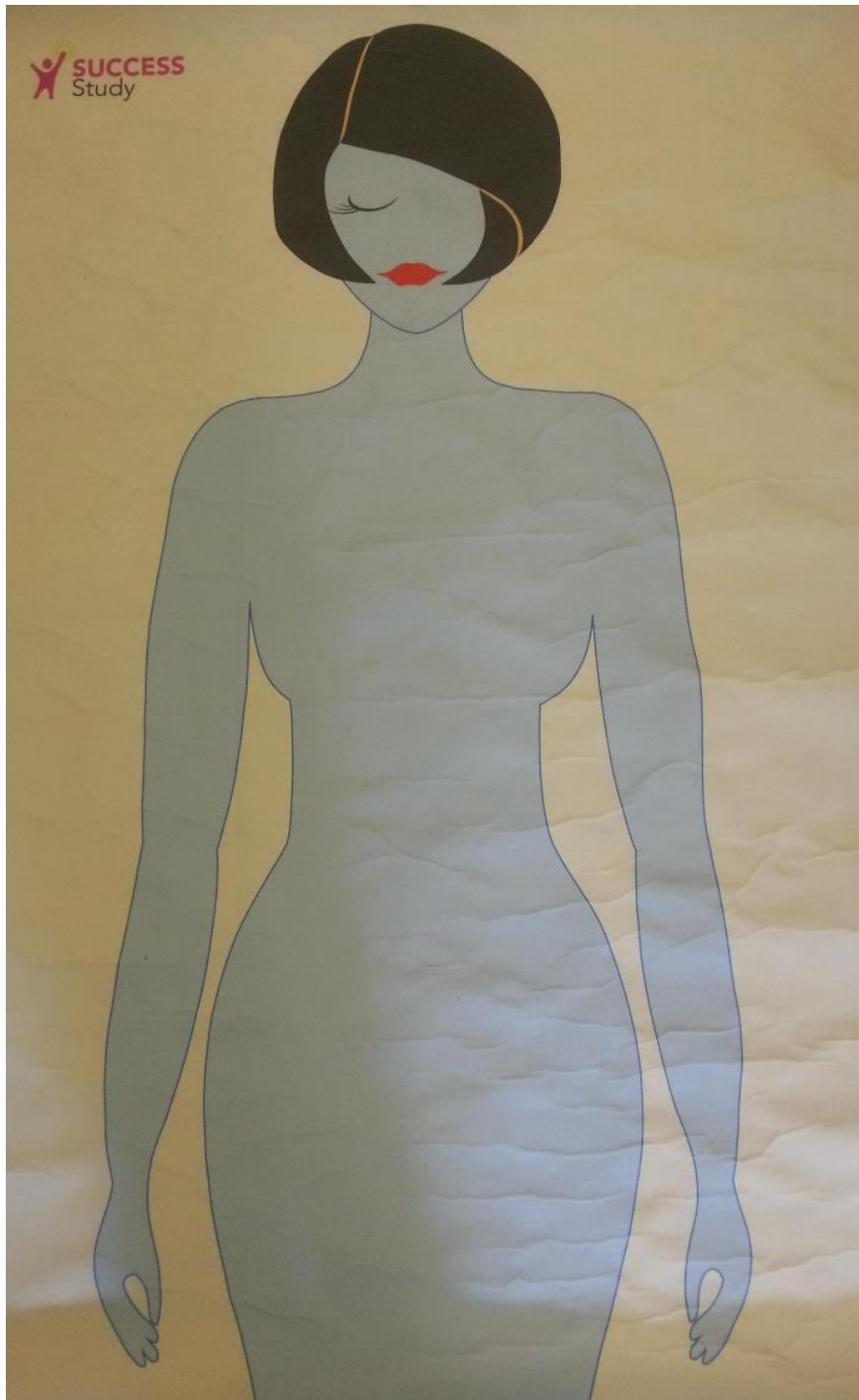
Figure 5.2 Resources for SUCCESS; infertility treatment card before and after pilot
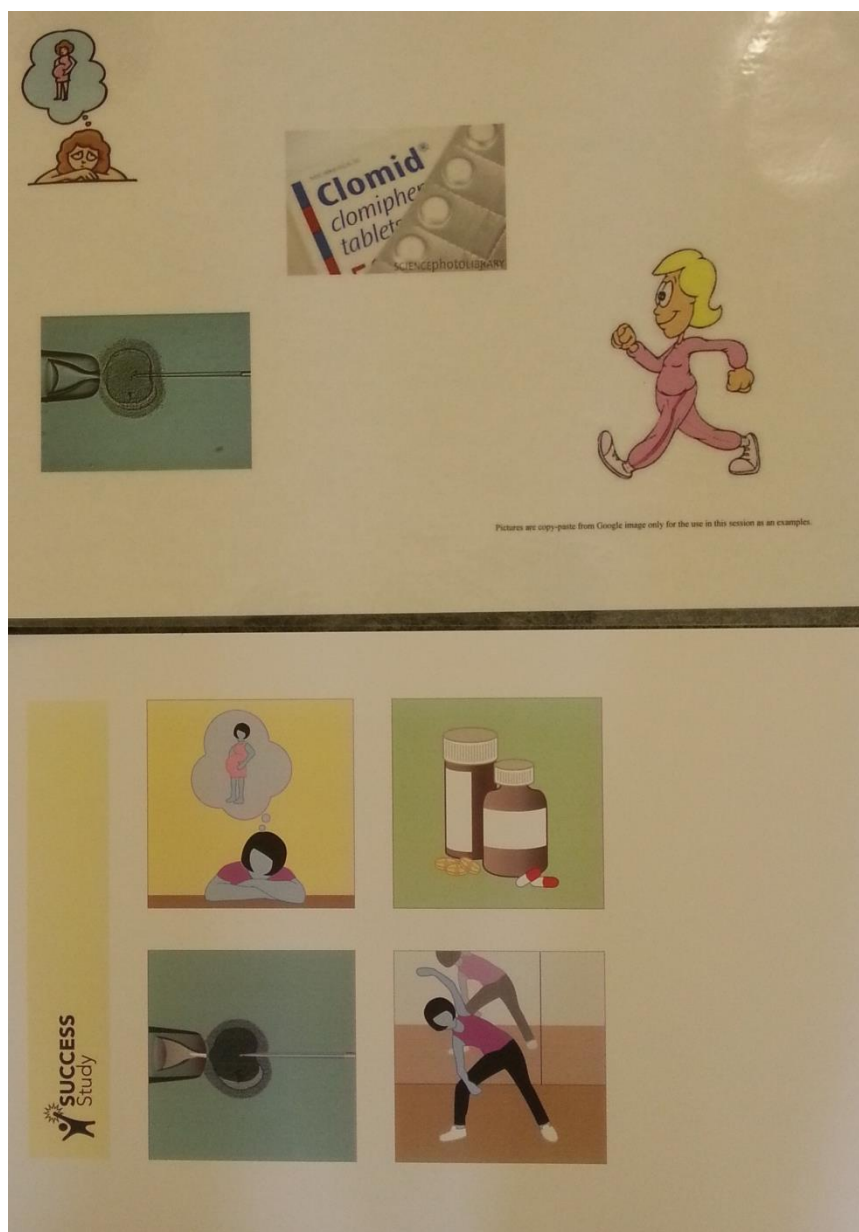
5.2.5 Piloting and subsequent modifications

5.2.5.1 Aim of the pilot sessions

The aim was:

"To test whether the education programme (content of the curriculum, resources and the flow of the sessions) was acceptable, relevant and of interest to the target population".

5.2.5.2 Recruitment for the pilot sessions

To reflect the target population in the next step (the RCT), overweight women with PCOS between 18 to 50 years old who were able to communicate in English were recruited.

Recruitment was carried out through the outpatient clinic at LRI as well as inviting the patients whom I had interviewed in Phase 1. Some participants self-referred as they had seen the study on the internet or had heard about it from friends and family.

Two groups of patients went through the pilot education; in total seven women had the pilot education, two SA and five white, age range 20 to 45, three self-referred.

5.2.5.3 Delivery of the pilot education:

Pilots were run at the Leicester Diabetes Research Centre in the evenings, starting from 17:30 to 20:00 on a specific day of the week for three consecutive weeks for each group. All the participants were happy with the location and time as it would give them parking access as well as time to finish their jobs and attend the education. The day of the week was chosen with all parties' (participants and educators) mutual agreement.

Parts one and two of the education programme (Patient and professional story, physical activity, diet and self-management plans) were delivered by myself and JB. We made sure that we alternated the sections of the curriculum that we delivered in the two pilots, so both of us could deliver the whole curriculum for

these parts. Delivery of these sessions was observed by an expert in patient education (HD). The "balancing life with PCOS" (third part of the education) was delivered by HD for the piloting stage, and she was observed by JB and MH.

The observers timed the session and commented on the delivery. All the participants attended a semi-structured focus group interview after the last part, to provide feedback on the programme (topic guide in Appendix 5.3). They also gave feedback at the end of each day using the workshop feedback form shown in Appendix 5.4)

The education sessions were also voice recorded so we could listen back and reflect on the delivery.

5.2.5.4 Feedback

Feedback was generally very good; patients felt that the education increased their understanding of PCOS and gave good examples of the changes they could potentially make in terms of their lifestyle. All of them indicated that they would like to have a recap session once a year, and they exchanged telephone numbers so that they could meet up with each other after the education.

Feedback from the first pilot was implemented into the curriculum and the refined version was tested in the second group. Table 5.3 shows the summary of the key feedback and the changes made. As well as feedback on the content and resources, there were some practical points to learn from pilot stage regarding recruitment and practical arrangements for the SUCCESS study. The target population in SUCCESS was a young and socially active group with jobs or family to look after. Points for consideration were therefore as follows:

- Most of the communications were conducted via e-mail and mobile to arrange the time and date of the education as compared to the traditional form of sending letters through post. The patient information and invitation letter would be attached to an e-mail.

- Arranging three evenings for education would be a challenge for the RCT which would involve a larger number of participants.

Table 5.3 Feedback after the Pilot education and actions made to modify the Curriculum

Key Item	Feedback	Action
Content		
Key message passed	Yes (some had already stated that they had made changes when they returned for the second day)	No change
Professional story	OK	No change
Physical Activity	Include more activity in the session and how to change	Some of the activities in the session were redesigned to be done while standing and also a part was allocated to write a plan to increase walking steps.
Diet	OK	No change
Balancing life with PCOS	"Excellent"; really useful	No change, and make sure it is offered to all the patients
Resources		
Polly	Perfect*	No change
Others	OK	No change
Experience of the education day		
Time	Evening is good, weekends could also be offered	Weekends were included in the planning of the RCT
Length of the day	OK	No change
Breaks	OK; Better to provide healthy snacks and fruit instead of biscuits!	Point taken on-board and fruit was also provided for the education sessions in RCT

*They were specifically asked about the body shape and the hair and they were all happy with the figure. They liked the fact that Polly was not overweight or obese and had a "perfect shape". They justified their opinion by saying that they would not want to see any of their body image issues in front of them or on any of the images to remind them of the problem. Besides everyone with PCOS does not have the full range of the signs and symptoms.

5.2.6 Final Curriculum

The changes suggested throughout the pilot stage were applied to the resources and the curriculum to prepare the final draft of the curriculum. This draft was circulated to the expert educators in our department for their final comments. Table 5.4 shows the overall areas covered in the SUCCESS education programme and the proportion of time allocated to each.

The SUCCESS education programme was ultimately planned to be delivered in two possible formats:

1) Formula (F) 1 Whole day 7 hours education (to be offered on weekdays or Saturday)

2) Formula (F) 2 Three evening sessions each lasting 2.5 hours.

Fig 5.3 shows the content list of the F1 format

Table 5.4 Outline and proportion of time for the areas covered in the SUCCESS education programme

Module name	Main aims and educator activities	Underpinning Theory†	% Time
Patient story	Give participants a chance to share their knowledge and perception of PCOS, associated metabolic risk factors and conditions and highlight any concerns they may want addressed in the programme	Common sense model	10%
Professional story	Use simple non-technical language, analogies, visual aids and open questions non-didactic method to provide participants with an overview of PCOS and its aetiology, Insulin Resistance, Cardiovascular Risk Factors	Common sense model Dual Process Theory	25%
Lifestyle: Diet and Physical Activity	Use simple language, analogies, visual aids and open questions to help participants understand the link between diet and physical activity and metabolic dysfunction. Also, to help them identify how increasing physical activity may improve insulin sensitivity, body weight and PCOS. Understand the current recommendations; explore options for increasing physical activity in everyday life. Participants were provided with a pedometer.	Common sense model Dual Process Theory Implementation intention	22%
Balancing life with PCOS	Provide an environment for the participants to share and discuss their thoughts, feelings and their relationship with PCOS and other possible contributing stresses in their life.	Common sense model Social cognitive theory Implementation intention	18%
Reflections and self-management plan	Facilitate a discussion about "making change", using the "Cycle of Change" (327) or "Vicious Flower" (337) model as appropriate. Demonstrate an example of making an action plan and providing the group with the opportunity to complete an action plan using personalised goals that are specific, measurable, achievable, realistic, and timed.	Social cognitive theory Dual Process Theory Implementation intention	25%

Figure 5.3 SUCCESS study; plan of the education day

SUCCESS Session Plan

F1 Format: To be delivered over one day

Part 1:	Duration	Total
A: Introduction and Housekeeping	10 mins	10 mins
B: Your PCOS Story	20mins	30 mins
C: PCOS Story 1: Understanding PCOS	45 mins	1hr 15 mins
Break	15 mins	1hr 30 mins
D: Physical Activity	45 mins	2 hr 15 mins
E: Reflections so Far	05 mins	2 hr 20 mins
Lunch	30 mins	2 hr 50 mins
Part 2:		
F: Reflections 2 (Optional in F1)	5 mins	2 hr 55 mins
G: PCOS Story 2: Long Term Health Risks of PCOS and Treatment Options	45 mins	3 hr 40 mins
H: Weight Management	40 mins	4 hr 20 mins
Break	10 mins	4 hr 30 mins
J: PCOS Self management Plan	30 mins	5 hr
K: Burning Questions	5 mins	5 hr 05 mins
Break	10 mins	5 hr 15 mins
Part 3: Balancing Life and PCOS?		
L: Introduction to Part 3: Balancing Life and PCOS	5 mins	5 hr 20 mins
M: Your thoughts and Feelings about PCOS	20 mins	5 hr 40 mins
N: Other stresses and Pressures in our Lives	20 mins	6 hr
Break	10 mins	6 hr 10 mins
O: Your relationship with PCOS	25 mins	6 hr 35 mins
P: Developing Strategies for Living with PCOS	20 mins	6 hr 55 mins
Q: Next steps for self managing your PCOS	10 mins	7 hr 05 mins

5.2.7 Training the educators

Some additional trained educators were needed to deliver SUCCESS; this was necessary for logistical reasons, but also in view of possible future implementation into the health system after the study. It was also felt that it would be useful for a range of educators to test the delivery of the education programme. Their feedback on the delivery would be incorporated into the further development of the education programme.

There is extensive experience of educator training and quality assurance within the Leicester Diabetes Centre (LDC), in collaboration with the CLAHRC Curriculum and Development Training Team (CCAT). Their proven processes were used for training the additional educators.

5.2.7.1 Part 1 and part 2 of SUCCESS

Together with JB, we set up the training for five colleagues in LDC with different experiences in terms of patient education; two had experience of training educators for DESMOND, two were experienced educator for another programme, and one was new to patient education and had just seen the "Lay Educators course" in DESMOND. All the trainees were supplied with a copy of the printed SUCCESS curriculum and the related resources before the training day.

The day lasted for 3.5 hours and included the following:

- ➢ A brief review on PCOS was presented for the trainees and their questions were answered.

- ➢ The content of the curriculum was reviewed.

- ➢ Some questions based on each session in the curriculum were designed and trainees were asked to answer these questions; this tested their understanding of the content and the learning theories behind each session. (Learning theories are discussed in Chapter 4).

> ➢ Trainees selected two sessions from the Curriculum and performed a mock delivery to the other participants (one session had to be one of the professional stories).

At the end of the day, feedback was sought from participants on the process, curriculum and resources.

5.2.7.2 Balancing life with PCOS

Considering the special skills required to deliver this session, the educator training for delivering this session was conducted separately by Dr Yvonne Doherty who had been extensively involved in the development of this part of the curriculum. Together with the other educators, I attended this session as a trainee. The format of the session was similar to the previous one, as described above.

5.2.8 Conclusion

In line with MRC framework for the development of complex interventions and NICE recommendations for the development of an education programme, and underpinned by learning theories, an evidence based education programme was developed tailored to the needs of women with PCOS.

The final product was ready to be tested in a randomised controlled trial to test the effect of a structured education programme, including a primary outcome measure of increasing walking steps in women with PCOS. To our knowledge, this is the first structured education programme tailored for women with PCOS in the UK.

5.3   Summary of the chapter:

In this chapter, the process and preliminary findings of the interviews conducted with women with PCOS was reviewed, focusing specifically on the ways in which the qualitative work informed the development of the education programme. These women expressed the need for an education programme. During these interviews the issue of coping with PCOS and body image was revealed and it appeared that some women had very strong feelings towards their PCOS. This problem could potentially have an impact on willingness to engage in empowerment and lifestyle change in these patients; therefore the "balancing life with PCOS" was incorporated into the education programme which was tailored for this group. This draft programme was subjected to multiple pilot tests and feedback was sought from patients and experts. Resources were prepared, educators were trained and the education programme was finally made ready for testing in an RCT.

Chapter 6 : A randomised controlled trial to assess the effect of SUCCESS education on increasing walking steps in women with PCOS; Design and methods.

SUCCESS: Struct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome

In Chapter 4, the rationale for development of a structured education programme for women with PCOS was explained. An evidence based programme was developed for these women (Chapter 5) and it was time to test its feasibility in the target group and see whether it results in a behaviour change leading to a beneficial outcome such as an increase in step counts in this group.

Here in this chapter, the design and methodology of the randomised controlled trial (RCT) is described and the rational for the primary and secondary outcomes is explained.

6.1 Hypothesis in the SUCCESS-RCT

The primary hypothesis in this RCT is that "A structured life style intervention to promote healthy lifestyle, weight loss and increasing walking activity in a self-directed programme (SUCCESS education) results in a behaviour change of increasing walking steps in the women with PCOS".

6.2 Methods

This is single centre, two arm, and parallel randomised controlled trial with 12 months follow-up. The defined intervention is a seven hour structured education programme which will be delivered in either a single day education programme or three parts of 2.5 hours each in the evenings.

6.2.1 Primary outcome and Sample Size

The effectiveness of a lifestyle intervention could either be assessed via its immediate and direct behavioural change or its effect on biomedical measures. Therefore in the SUCCESS RCT the measure of effectiveness or the primary outcome could either be a behavioural change (such as increase in physical activity) or biomedical (such as; weight loss, change in BMI or change in glycaemic indices).

It has been shown that a 1 mmol/L drop in two hour glucose during OGTT following a lifestyle intervention is significantly effective in diabetes prevention equal to a 50% reduction in progression to T2DM (338,339). PREPARE - Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement-(288,301) , was another group structured education course aimed at people at risk of diabetes (with impaired glucose regulation) and designed and tested by our group in Leicester. PREPARE aimed to improve glycaemic control by inducing and increasing walking behaviour in a three arm RCT; three hours education program and a pedometer for self-monitoring steps, education only and control. The PREPARE programme successfully achieved a significant drop of 1.31 mmol/L (standard deviation = SD 2 mmol/L) in two hours glucose tolerance through an increase of 2000 steps per day in walking activity

(SD 4000 steps/day) in the arm which received the education and pedometer (288).

Due to the complexity of the underlying pathophysiology of insulin resistance in women with PCOS and considering the emphasis of the education programme on promotion of the healthy behaviour it was proposed to measure the effectiveness of the education by a change in a behaviour. The behaviour of choice was walking and the primary outcome was therefore set to be a 2,000 steps increase in daily walking activity after one year in the intervention group. The closest cohort to the population in SUCCESS-RCT would be the cohort in PREPARE study considering their similarity in the background population and therefore 4,000 steps was considered as the standard deviation of change (288). Aiming for 80% power, α=0.05 and allocating a 25% drop out rate SUCCESS needed 80 participants per group and a total number of 160 women with PCOS for the RCT.

6.2.2 Inclusion Criteria

Women aged between 18-50 years with the diagnosis of PCOS according to the Rotterdam Criteria (27) who were Overweight by ethnic specific cut points (191):

Body Mass Index ≥ 23 kg/m^2 for Black and Minor Ethnicities

Body Mass Index ≥ 25 kg/m^2 for White Europeans

And

If already on medical treatment for their PCOS, they should be on a stable regime for at least six months prior to the recruitment.

6.2.3 Exclusion Criteria

Due to the nature of the intervention, the exclusion criteria in SUCCESS RCT were: disabling physical or mental condition, inability to communicate in English; steroid use; diabetes, pregnancy, involvement in other research studies with a similar nature.

6.2.4 Recruitment:

Three sources of the recruitment were identified in the study;

Speciality Clinic in Secondary Care

Poster and flyers were put up in the endocrinology and gynaecology clinics at University Hospitals of Leicester (UHL) NHS trust. A pop up reminder was also put up on the "clinical workstation" (the database which was described in Chapter 2), this would remind the physician in clinic to introduce the study to the patients.

Primary care network

A second source of recruitment was through the Primary Care Research Network (PCRN). An invitation was sent to all the general practices in the area and the database of those who were interested in being involved was searched for patients who matched the inclusion/exclusion criteria in SUCCESS RCT. An invitation letter was sent from GP to the selected people and their reply slip would come to the SUCCESS team.

Posters and flyers of the study were also distributed to the involved practices as well as to the pharmacies via the PCRN.

Opportunistic recruitment

Experience from phase 1 and 2 (qualitative interviews and pilot of the curriculum) had shown us an unprecedented expression of interest from women with PCOS who wanted to get involved in the study. While the flow of e-mails from all over the country and some other countries was coming to the SUCCESS team, it was considered that we could also actively approach the patients via the internet. Study was already registered on the Clinical Trials website (NCT01462864) and NHS choices (by proxy through the link from the clinicaltrials.gov website), and it was subsequently registered on the Leicester Diabetes Website (www.leicestershirediabetes.org.uk/624.html) with a link to the patient information sheet (Appendix 5.5). The SUCCESS study was mentioned in the University of Leicester weekly news feed (e-mail distribution) with the notice of the study, it

was distributed via e-mail in some of the departments in the DeMontfort University (as well as the poster) and was put up in the internal website of UHL-NHS trust (Insite). After approval from the ethics committee a Facebook page was registered and the poster for study was put on the Facebook page (http://www.facebook.com/SuccessPcos).

Any patient approaching the study team via any of these routes would be sent an information sheet and then contacted via telephone by myself to confirm their diagnosis of PCOS and eligibility for the SUCCESS study. [In Leicester the majority of the investigations requested by the primary care; blood tests or radiology are conducted in the UHL and are therefore accessible by the clinician].

6.2.5 Randomisation

Randomisation for each participant was done after the baseline visit and once all the baseline data were collected (accelerometers returned and up-loaded into the database). Using a computer programme all participants were randomised (stratified by age, ethnicity and the use of metformin) to either a control (C) or intervention (I) group. Randomisation was set in blocks of four to ensure an even distribution of the participants in the two arms at any point during the study. This method would ensure that if the study had to be terminated for any reason SUCCESS RCT would have an even distribution of the patients in each arm. Randomisation was done by an independent administrator in the study and supervised by the study statistician who were both blind to the outcome of the randomisation.

At the baseline visits all the participants received a generic information sheet about PCOS and its management (Appendix 4.4). This leaflet included some advice on lifestyle change and weight loss. This was the information sheet written by Dr Howlett and routinely used in the Reproductive medicine clinic in LRI. The intervention group were invited to attend the SUCCESS structured education programme.

6.2.6 Intervention

The SUCCESS education programme (described in the Chapter 5) was offered to all the participants randomised to the intervention arm.

Each month, it would be ensured that at least three choices were available to each participant; whole day weekday (9:00 to 16:00), whole day Saturday (10:00 to 17:00) and three evenings on consecutive weeks (17:30 to 20:00).

The first invitation with the available dates would go out from the Study e-mail and those who did not reply would be followed by a telephone call. A potential education session would go ahead only if at least four participants registered for that day (allowing 25% non-attendance on the day).

Each education session was run by two trained educators, during the education each participant would get a resource pack (contents are attached in Appendix 4.3 – 4.7) and the results of their important blood tests or measurements including average walking steps from their accelerometers (these results would be discussed and reflected on by each individual patient during the education programme). A pedometer (Digi-Waler; SW-200 by Yamax, Japan) was also given to each participant to keep as a tool for self-regulation of their walking activity.

Control arm

Participants in the control arm received the same generic information sheet as everyone else and were told that they would be invited to the education at the end of the study.

There was no interference with medical treatment of either arm after randomisation: responsible doctors (general practitioner or specialist) were free to start any treatment or change the medication after baseline.

6.2.7 Data Collection

Data collection at the point of visits; 0, 3, 6 and 12 months (Fig 6.1.) are done by nurses and health care assistants who are blind to the participants' randomisation and independent of the study team.

6.2.8 Data Analysis

The study will be reported according to the CONSORT 2010 statement for parallel group randomised trials (340,341). Data will be analysed on an intention-to-treat basis (ITT). The base line and three months data will be analysed using STATA v10 and SPSS v16 software. Detailed analysis methods will be described in the next three chapters with the presented results.

Figure 6.1 Participants' flow chart in the SUCCESS RCT

```
                    ┌─────────────────────────┐
                    │      Recruitment        │
                    │   Outpatient/primary    │
                    │   Care/Opportunistic    │
                    └────────────┬────────────┘
                                 │
                                 ▼
                    ┌─────────────────────────┐
                    │ Check against the       │
                    │ eligibility criteria    │
                    └────────────┬────────────┘
                                 │
                                 ▼
            ┌────────────────────────────────────────┐
            │ First Visit:                           │
            │ Consent                                │
            │ Baseline measures, tests and           │
            │ Questionnaires                         │
            │ 10 days accelerometer recording        │
            └───────────────────┬────────────────────┘
                                │
                                ▼
                       ┌──────────────────┐
                       │  Randomisation   │
                       └────────┬─────────┘
                      ┌─────────┴─────────┐
                      ▼                   ▼
```

Control Arm:

Routine Care

Intervention Arm:
SUCCESS Education (Ideally within 2 weeks of baseline visit) + Pedometer to anyone attending the session

Visit 2 (3 month after baseline)
Measurements, blood test, and Questionnaire*

Visit 3 (6 month after baseline)
Measurements, blood test, and Questionnaire*

Visit 4 (12 month after baseline)
Measurements, blood test, and Questionnaire*

Control Arm:

Will be invited for education after completed RCT

*Details of the measurements, blood tests and questionnaires for each visit are presented in Table 6.1

Table 6.1 Measurements performed during each visit for participants in the SUCCESS RCT*

	0	3	6	12
Primary Outcome (Step Counts)				
Accelerometer to wear for 10 days after visit	X	X	X	X
Secondary outcome data				
Clinical History and Anthropometric data (Administered by Nurse)				
Medical History	X			X
Medication History	X	X	X	X
Menstrual History	X	X	X	X
Blood Pressure (3 measures)	X	X	X	X
Height	X	X	X	X
Weight	X	X	X	X
Body fat percentage	X	X	X	X
Waist and Hip Circumference	X	X	X	X
Hirsutism Score (self-scored)	X	X	X	X
Epworth Sleepiness Questionnaire (self-scored)	X		X	X
Biochemical data (Collected by Health care Assistant)				
Oral Glucose Tolerance Test (OGTT)	X			X
HbA1c	X	X	X	X
Lipids	X		X	X
Urea and Electrolytes	X		X	X
Liver Function Test	X		X	X
Hormone Test (details in the text)	X		X	X
Insulin Measurements	X		X	X
Biomarkers (details in the text)	X		X	X
Full Blood Count	X		X	X
Vit D levels	X		X	X
Lifestyle data				
Measure of physical activity	X	X	X	X
IPAQ (self-scored)	X	X	X	X
DINE (self-scored)	X		X	X
Quality of life/Psychological well-being/Illness perception (self-scored)				
PCOSQ	X	X	X	X
SF-12	X		X	X
EQ-5D	X		X	X
Self-efficacy	X		X	X
Illness Perception	X		X	X

IPAQ = International physical activity questionnaire, DINE = Dietary intervention in Primary care, PCOSQ = PCOS Questionnaire, SF-12 = Short Form -12 Health survey questionnaire, *Questionnaires are explained further in the text

6.3   Outcome Measures

Table 6.1 shows an outline of all the measurements performed during each visit in the SUCCESS-RCT.

6.3.1   Primary outcome

As explained earlier, step count was chosen to be the primary outcome. Physical activity and walking steps are objectively measured using a triaxial Actigraph GT3X accelerometer (Actigraph, Penascola, Florida, America). These accelerometers are the most extensively validated and accurate on the market and they are the only commercially available accelerometers to correlate with energy expenditure as measured by double-labelled water (342).

Participants are asked to wear the accelerometer on a waistband (in the right anterior auxiliary line) for ten consecutive days during waking hours. Each participant is supplied with instructions about the accelerometer as well as a log book to register their wake up time, wear time for accelerometer and the times of the day they had taken it off (Appendix 5.6). The accelerometer records movement data every one second (i.e., one second 'epoch'). Prolonged periods (at least 60minutes) of no movement, that is, strings of 'zero' activities is assumed to be non-wear time and excluded. A total of four days valid day wear is required to count as a valid recording (343) and a 'valid day' consists of at least 10 hours (600 minutes) of accelerometer movement data (344). The primary outcome (walking steps per day) is the average number of the steps taken during the valid days. Participants cannot see their step count in the accelerometer (data needs to be downloaded via a registered software).

6.3.2   Secondary outcomes and other measurements

Secondary outcomes or patient related outcome measures are grouped into four broad categories, clinical history and anthropometric data; biochemical data; lifestyle; and health related quality of life/illness perception.

6.3.2.1 Clinical History and Anthropometric data

Arterial blood pressure is measured in the sitting position (Omron, Healthcare, Henfield, UK); three measurements is obtained and the average of the last two measurements is used. Other measures include body weight and body fat percentage (Tanita TBE 611, Tanita, West Drayton, UK), waist circumference (midpoint between the lower costal margin and iliac crest), and height to the nearest 0.1 kg, 0.5% and 0.5 cm respectively.

Information on current smoking status, medication history, co-morbidities, family history and ethnicity is obtained by self-report. Menstrual history will be asked in every visit to note any change. A modified version of Ferriman-Gallwey score (181) in the format of a self-scoring scale is used to monitor hirsutism. This is the tool used in our reproductive medicine clinic at LRI (Appendix 5.7).

As discussed in Chapter 1, PCOS is associated with a high rate of sleep apnoea which is monitored in SUCCESS-RCT by using the standard Epworth questionnaire (345).

6.3.2.2 Biochemical variables

Glycaemic indices measured in the SUCCESS-RCT are haemoglobin A1c (HbA1c), fasting and 2-hour post challenge glucose, fasting insulin and the ratio of fasting glucose to insulin as a measure of insulin sensitivity (17,346). Participants are invited to attend the fasting clinical measurement sessions (0, 6 and 12 months) after an 8-hour fast. Patients are sent instructions for the oral glucose tolerance test (on baseline and 12 months visits).

In concordance with WHO recommendations (10,347) those who have a fasting or 2-hour blood glucose level in the diabetes range or HbA1c $\geq$ 6.5% (48 mmol/mol) at any clinical measurement session are called back for a confirmatory test. If diabetes is confirmed, the participant is removed from the study and referred to their general practitioner for routine diabetes care.

A set of hormones as indices of hyperandrogenaemia (sex hormone binding globulin, testosterone) and, or ovarian function (Follicular Stimulating Hormone, and Luteinizing Hormone) are checked. It should be mentioned that it was initially planned to measure the "day 21 progesterone" as an index of ovulation but due to logistic difficulties (both for participants and the staff) it proved very difficult to plan a study visit for the patients on or around day 21 of their menstruation on at least two occasions (baseline and 12 month). This test was therefore suspended after consultation in the study team and the ethics committee were informed.

In addition, fasting lipid profile, urea and electrolytes (sodium, potassium, urea, and creatinine), calcium and vitamin D levels are also measured by venous sampling. Low vitamin D level has been reported to be associated with increased insulin resistance in women with PCOS (348,349) and its treatment might improve the glucose metabolism (350). Also, an increase in walking activity may increase sun exposure and increase vitamin D levels. It was therefore decided to monitor vitamin D status in the SUCCESS-RCT.

Markers of chronic inflammation such as hsCRP, TNF alpha, IL-6, and sIL-6R, fibrinogen, and adiponectin are measured in view of the reported correlation of these biomarkers with the cardio-metabolic risks in women with PCOS (19,351-353). A spare sample for future measurements of biomarkers is taken (a separate consent was sought from participants for this sample)

All venepuncture and OGTT timings are undertaken by trained phlebotomists who are not part of the scientific advisory team for this study and who are blinded to the treatment allocation. All biochemical analyses were also conducted blinded to the randomisation group.

All participants are informed of their main blood results after each measurement session. All participants' results are sent to their GP.

6.3.2.3 Lifestyle

The two aspects of the lifestyle on which data is collected are physical activity and dietary habits.

6.3.2.3.1 Physical activity

Data on physical activity is collected in two formats; Accelerometer and international physical activity questionnaire (IPAQ).

Physical activity is objectively measured using the accelerometer as described above. Secondary outcomes include total body movement (counts per day), and time in light-, moderate- and vigorous-intensity physical activity as determined by counts per minute cut points (354). The Actigraph GT3X model incorporates an inclinometer which provides postural data. This has the advantage of allowing the research team to determine subject position (lying or sitting) and periods when the device has been removed.

The short 'last-seven-days' self-administered format of the IPAQ is used as a self-report measure of activity. This questionnaire provides a measure of walking and other moderate- to vigorous-intensity activities carried out for more than 10 continuous minutes at work, in the home, as transport and during leisure time. IPAQ has been shown to have reasonable validity compared to accelerometer data ($\rho \sim 0.4$) and test-retest reliability ($\rho \sim 0.7$) in the UK when used as a measure of total moderate- to vigorous-intensity physical activity (355). For the SUCCESS-RCT, IPAQ is used to measure total activity accumulated at work, for transport and in leisure time.

6.3.2.3.2 Diet

Food frequency questionnaires measure total fat intake, total unsaturated fat intake and total fibre intake and correlate reasonably with weighted food records.

"Dietary Instrument for Nutrition Education (DINE)[4]"(356) is the questionnaire which is used in the SUCCESS RCT.

6.3.2.4 *Quality of life, psychological well-being and illness perception*

6.3.2.4.1 *Quality of life/psychological well-being*

Several questionnaires are used to assess this group of outcomes. Health-related quality of life is measured using both the PCOSQ (357), which is a disease specific questionnaire designed for women with PCOS and validated in UK and multiple ethnicities (358-361). PCOSQ contains 26 items measuring five areas; emotions, body hair, weight, infertility problems, and menstrual problems.

Another tool to evaluate the quality of life is the EQ-5D (362,363), which is a standardised questionnaire applicable to all conditions that was developed for use as a measure of health outcomes and defines health in terms of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.

Psychological well-being is assessed by SF-12[5] which is a validated abbreviation of SF-36 (364) uses one question for each of the total eight domains (physical functioning, social functioning, physical impairment, emotional impairment, emotions, vitality, pain and global health) (365).

6.3.2.4.2 *Illness perception*

Several variables are measured to establish whether the intervention is targeting the theoretical constructs on which it is based and if so, whether they improve by behavioural change as a result of the education. An individual's perception of the illness is measured with the validated Brief Illness Perceptions Questionnaire (BIPQ) (366). This nine item instrument uses an 11 point scale (0 = no effect, 10 = complete effect) to measure five cognitive illness representations

---

[4] © Oxford University (permission sought and was granted)

[5] © Quality Metric (permission to use the questionnaire was purchased)

(consequences, timeline, personal control, treatment control, and identity), two emotional representations (concern and emotion) and illness comprehensibility (perceived knowledge). The BIPQ provides a practical and comprehensive measurement of determinants identified in Leventhal's common sense model (303,305), one of the key theoretical models underpinning the content and structure of the education programme. The BIPQ has been shown to have reasonable test-retest reliability and concurrent validity (366).

Exercise self-efficacy (367) measures participants' confidence in their ability to undertake any form of moderate- to vigorous-intensity physical activity for 10 minute periods, increasing incrementally from 10 minutes to one hour each day. Participants' confidence in their ability to self-regulate their exercise behaviour in the face of five commonly identified barriers (tired, bad mood, bad weather, lack of time and holiday) is also measured (368).

6.4   Summary of the chapter

The SUCCESS-RCT tests this hypothesis that "a structured education programme designed for women with PCOS can induce a behaviour change and increase their walking steps by an average of 2000 steps/day after one year follow up". This education programme may result in the secondary outcomes including improvement in the indices of glycaemic control and, or anthropometric indices such as weight, BMI as well as clinical and psychological aspects of PCOS. All these outcomes will be measured during the course of the study.

Chapter 7 : High rates of risk factors for cardiovascular diseases in overweight and obese women with PCOS, Baseline characteristics of the SUCCESS-RCT cohort

SUCCESS: Struct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome

In women with PCOS, the underlying insulin resistance and high prevalence of obesity increase the likelihood of a variety of metabolic complications such as diabetes, cardiovascular diseases as demonstrated in chapter 1 and 2 of this thesis.

This chapter describes the baseline characteristics of the SUCCESS cohort and their cardiovascular risk status.

7.1 Introduction

Multi-system involvement in PCOS is due to the underlying insulin resistance, which is augmented by obesity (4,17). Considering the high prevalence of the obesity in women with PCOS (68,91), they are expected to have high rates of metabolic complications. Up to 35% of women with PCOS are expected to have impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM) (4,84). Higher than average rates of hypertension (16), dyslipidemia (126), obstructive sleep apnoea (OSA) (140) and non-alcoholic fatty liver disease (20) have all been reported in PCOS and have been associated with underlying insulin resistance.

PCOS is also associated with high rates of cardiovascular risk factors (11,129). Long term follow up of a multi-ethnic cohort of women with PCOS showed high age specific rates of myocardial infarction and angina in these women as compared with the background female population (Chapter 2 of this thesis). The majority of the cardiovascular risk factors such as hypertension, hyperlipidaemia and abnormal glucose levels are modifiable (369). The SUCCESS education programme aims to improve the cardiovascular risk status in women with PCOS by increasing their walking steps.

In this Chapter, the baseline characteristics of the women in SUCCESS-RCT are examined in view of their high cardiovascular risk status.

7.2 Methods

Detailed description of methods were presented in the previous chapter, however the related sections are briefly described here.

7.2.1 Subjects

Overweight or obese women (Body Mass Index $\geq$ 23 kg/m^2 for Black and Minor Ethnicities and BMI $\geq$ 25 kg/m^2 for White Europeans) (191), aged 18-50 years with a diagnosis of PCOS (27) who were either receiving no medical treatment or had a stable treatment for at least 6 months were invited to the study. Main exclusion criteria were pregnancy, diagnosis of diabetes, use of steroids and disabling physical or mental condition.

7.2.2 Data collection

Two out of the three categories of symptoms were required for the diagnosis of PCOS (27): anovulation (reports of infertility related to female, or oligo/amenorrhoea); hyperandrogenism (declaration of excess hair and laser therapy for hair removal with a score of higher than eight in modified Ferriman-Galway scale (181,370), or evidence of hyperandrogenism in notes or baseline blood test); polycystic ovaries (reports were reviewed if available in the radiology system). A recorded confirmation of the diagnosis in the health system (primary or secondary care) was accepted if the patient was investigated previously.

Participants fasted overnight for eight hours before their baseline clinic visit. A baseline set of bloods were taken before the patients was given a glucose load of 75g [A list of the blood tests are presented in Chapter 6].

Arterial blood pressure was measured in the sitting position (Omron, Healthcare, Henfield, UK); three measurements were obtained and the average of the last two measurements were used. Information on current smoking status, medication history, family history and ethnicity were obtained by self-report, supervised by a research nurse. Ethnicity was self-declared by participants and was categorized into the following three groups: "white" (white British, and white Irish); "South Asian" (=SA, Indian, Pakistani, British Indian); "other" (any other reported ethnicity such as mixed ethnicities, Chinese, African).

Physical activity data was collected via accelerometer as described in Chapter 6.

7.2.3 Cardiovascular risk factors:

Besides age, smoking and family history of CVD in a first degree relative, the other cardiovascular risk factors were defined as (369,371,372);

Hypertension: systolic blood pressure > 140 mmHg and or diastolic blood pressure > 90 mmHg or treatment for hypertension

Hypercholesterolemia: total cholesterol > 5.0 mmol/l, and or LDL cholesterol > 3.0 mmol/l, and or Cholesterol to HDL ratio > 3.5 or treatment for hypercholesterolemia

High risk for diabetes: Impaired fasting glucose (IFG) which is fasting glucose > 6.1 mmol/l and less than 7 mmol/l and or impaired glucose tolerance (IGT) which is blood glucose ≥ 7.8 mmol/l and less than 11.1 mmol/l 2 hours after the oral glucose tolerance test. (10),

Physical inactivity: less than 150 minutes of moderate to vigorous physical activity per week (373).

7.2.4 Statistical Analysis

Normality was assessed visually by inspection of histograms and tested by probability (Q-Q) plots. Normally distributed continuous data is presented as mean (standard deviation (SD)). Where the data were non-Normally distributed, they were presented as median (Interquartile range (IQR)). Categorical data are presented as percentage

7.3 Results

In total 162 women with PCOS were included in the study. While all patients met the Rotterdam diagnostic criteria (27), 74% had the classic phenotype (the National Institute of Health = NIH phenotype) (26) with both hyperandrogenism and anovulation.

Twenty percent of the cohort was of south Asian origin, 69% white and 11% belonged to other ethnic groups. Table 7.1 presents the demographic, anthropometric and biochemical results of the baseline cohort. Mean (SD) age at the baseline visit was 33.3 (7.6) years. As per inclusion criteria all women were overweight or obese and the mean (SD) BMI was 32.7 (7.3) kg/m^2. Mean (SD) systolic 122.0 (12.3) and diastolic 78.8 (11.3) blood pressures (BP) were normal.

Family history of diabetes, hypertension and cardiovascular diseases were 32.1%, 46.9%, 37% respectively.

Mean (SD) total and, LDL cholesterol in the cohort were 5.1 (1.0) and 3.1 (0.9) mmol/l respectively. Mean (SD) cholesterol to HDL ratio was 3.7 (1.0). Mean (SD) vitamin D level was 38.0 (16.3) nmol/l and 127 (81.4%) of the participants had levels below 50 nmol/l and would be categorized as deficient or insufficient level of vitamin D (374).

Median (IQR) step count was 6259.4 (4898.0, 7824.5), only 10 participants (7%) of the cohort had step counts equal to or higher than the recommended 10000/day (375). The cohort spent 63.6% of their time in sedentary activities and only 3.1% in moderate to vigorous physical activities (MVPA). Median (IQR) time spent doing MVPA was 24 (12, 36) minutes.

7.3.1 Cardiovascular risk factors

The distribution of additional cardiovascular risk factors in the cohort of women recruited to the SUCCESS-RCT is shown in Figures 7.1 and 7.2.

Figure 7.1 shows the percentage of the cohort with each of the risk factors; 37% with a family history of CVD: 23.2% smoker, 17.7% hypertensive, 70% hypercholesterolemia, 15.2% either IFG or IGT or both, and 58.7% spent less than 150 minutes/week doing moderate to vigorous physical activity.

Almost 91% of the cohort had at least one modifiable cardiovascular risk factor in addition to their BMI (Figure 7.2).Sixty percent have more than two and 24% more than 3 additional modifiable risk factors.

Table 7.1 Characteristics of the baseline population in the SUCCESS cohort

Variable	Total Cohort 162	Variable	Total Cohort 162
Anthropometric	**Mean (SD) / %**	**Biochemical**	**Mean (SD)**
Age (years)	33.33 (7.58)	Total Cholesterol (mmol/l)	5.11 (0.97))
BMI (kg/m2)	33.65 (6.74)	HDL-C (mmol/l)	1.46 (0.43)
Weight (Kg)	89.73 (19.33)	Total Cholesterol / HDL Cholesterol	3.69 (1.01)
Waist (Cm)	103.64 (15.31)	LDL-C (mmol/l)	3.06 (0.86)
Body Fat %	42.26 (6.12)	Triglyceride (mmol/l)	1.32 (0.67)
Systolic BP	122.03 (12.32)	Fasting Glucose (mmol/l)	4.81 (0.48)
Diastolic BP	78.78 (11.34)	2-hrs Glucose (mmol/l)	5.83 (1.62)
Smoker (ever)	46.9	HbA1c (mmol/mol)	38.96 (4.07)
Smoker (Current)	23.2	HbA1c (%)	5.7 (0.37)
First degree family history	**Percent %**	Vit D levels	37.96 (16.32)
Diabetes	32.1	**Physical activity‡**	**Median (IQR)**
Hypertension	46.9	Time accelerometer worn (hr/day)	14.0 (13.2, 14.7)
CVD.	37.0	Sedentary time (hr/day)	8.8 (7.9, 9.6)
Personal History of	**Percent %**	Light physical activity (hr/day)	4.5 (3.8, 5.5)
Hypertension	7.4	MVPA (hr/day)	0.4 (0.2, 0.6)
Hypercholesterolemia	4.9	Steps / day	6259.4(4898.0, 7824.5)
History of GDM	1.9		
History of Infertility	35.2	**Percent at each activity‡**	**Median (IQR)**
Use of metformin	19.8	Sedentary time (%)	63.6(57.0, 69.5)
Anovulation	79.6	Light physical activity (%)	32.7(28.2, 39.4)
Hyperandrogenism	93.2	MVPA (%)	3.1(1.7, 4.6)

SD = Standard Deviation, BMI = Body mass index, BP = Blood pressure, GDM = Gestational Diabetes Mellitus, CVD = Cardiovascular Diseases, HDL-C = High Density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol. MVPA = Moderate to vigorous physical activity. ‡ Data is from 138 patients as 12 patients had invalid data (less than 4 days recording on accelerometer) and 12 did not return their accelerometer.

Figure 7.5 Prevalence of each cardiovascular risk factor† in the SUCCESS cohort
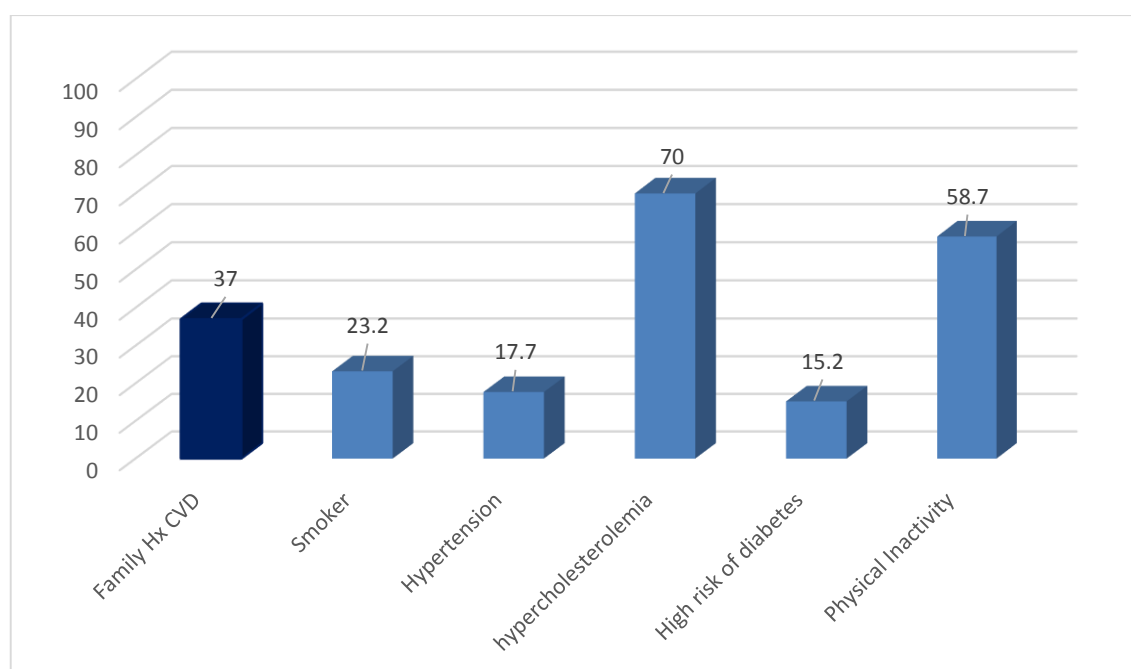
Family history as non-modifiable risk factor is shown in a darker shade.
† Current history of smoking, family history of 1st degree relatives with cardiovascular disease, hypertension (systolic blood pressure > 140 mmhg or diastolic blood pressure > 90 mmhg or treatment for hypertension), hypercholesterolemia (Total cholesterol > 5.0 mmol/l, or LDL cholesterol > 3.0 mmol/l, or Cholesterol to HDL ratio > 3.5 or cholesterol lowering drugs), high risk for diabetes (impaired fasting glucose: 6.1 < fasting glucose < 7 mmol/l or impaired glucose tolerance: 7.8 ≤ 2 hours glucose levels < 11.1 mmol/l), Physical inactivity (< 150 minutes/week of moderate to vigorous physical activity)

Figure 7.6 Distribution of modifiable cardiovascular risk factors in the SUCCESS cohort†
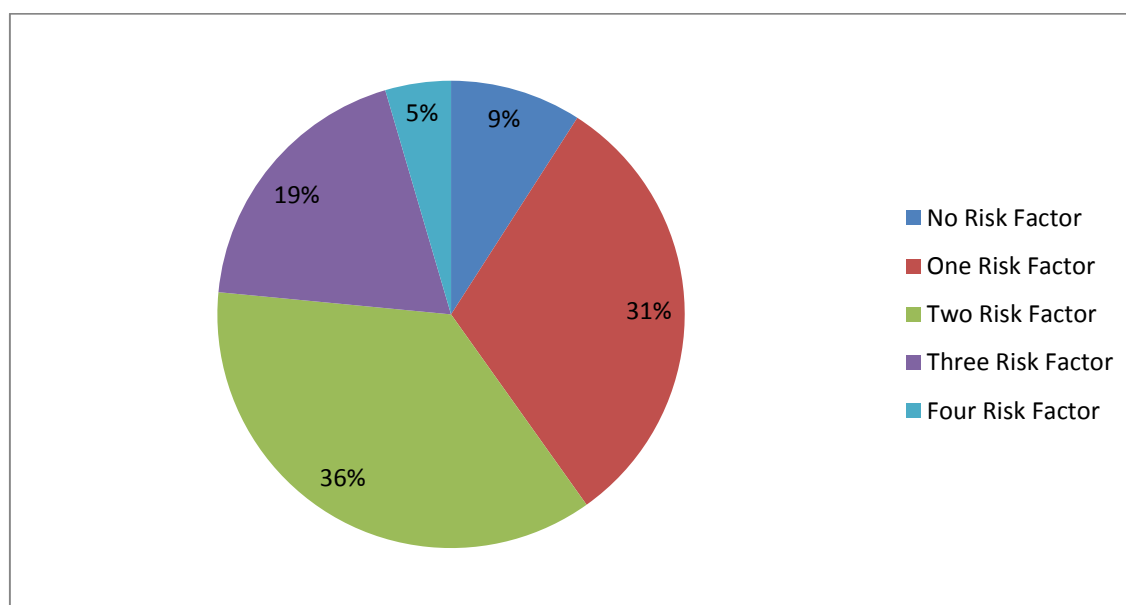
† This only includes the 138 participants who had data on all variables.

7.4 Discussion

There is a high proportion of people with cardiovascular risk factors in the cohort recruited to the SUCCESS-RCT. Sixty percent of the cohort have two or more modifiable risk factors in addition to their already higher than normal BMI.

Due to the underlying insulin resistance, it is expected to have high rates of CV risk factors in women with PCOS (4,129) . This increases when PCOS is associated with high BMI (207,376). We have already shown (Chapter 2) that obese women with PCOS had higher levels of systolic and diastolic blood pressure compared to those with normal weight adults. They also had higher rates of androgenic and anovulation symptoms (table 2.6, page 48). The classic hyperandrogenic anovulatory phenotype of PCOS (NIH phenotype) is known to be associated with higher rates of insulin resistance and metabolic complications (4,16,17) and almost 75% of women in SUCCESS cohort had the classic NIH phenotype.

It is therefore not surprising to observe high rates of associated cardiovascular risk factors in the SUCCESS cohort considering the inclusion criterion of abnormal BMI. The finding that almost a quarter of the cohort had more than 4 modifiable risk factors (including their BMI) is however, worrying and confirms the need for a preventive structured education programme for this group.

Considering the high concentration of CV risk factors, the 10 years CV risk status of the SUCCESS cohort was compared with the national rates. The risk score QRISK 2 (377) has been widely used to assess the 10 year CV risk status of an individual with the general population in England and Wales. Their risk score tool is readily available on line (http://www.qrisk.org/). To determine the CVD risk score in the SUCCESS cohort, the mean readings from cohort were put into QRISK2 (http://www.qrisk.org/): age (33 years), cholesterol to HDL ratio (3.69), systolic blood pressure (122 mmHg) and BMI (33 kg/m^2). With only these readings and without any other risk factors, the relative risk for cardiovascular disease in the SUCCESS cohort was 1.3 compared to a woman of the same age and ethnicity. This ratio would increase gradually by adding extra risk factors; if family history of CVD was added the relative risk would increase to 2.5 in white

women and 2.9 in south Asians (SA). The relative risk would increase to 15.1 for white women and 17.2 for SA women in SUCCESS if hypertension, family history of CVD, and smoking was added to the equation. This is just to demonstrate the high risk status of the SUCCESS cohort in comparison to the general female population, and to underline the need for a preventive intervention for this group.

The physical activity levels reported by the SUCCESS cohort were less than the healthy recommendations (373,375). The median step count was 6200 and only 7% of the cohort reached the recommended 10000 steps/day, while 58.7% had less than the 150 minutes/week of moderate to vigorous physical activity. These levels are better than other cohorts with different age and sex combination who were studied in Leicester (288,378,379). There is however, room to improve the pattern through a lifestyle change. Improving physical activity undoubtedly decreases the long term cardiovascular risk in general public (263,265) as well as women with PCOS (213,267).

7.4.1 Conclusion

Women with PCOS have a high burden of cardiovascular risk factors especially if their condition is associated with an abnormal BMI. These women would benefit from lifestyle change and increasing their physical activity. SUCCESS is a structured education programme which is tailored to this group and encourages healthy behaviour to reduce CV risk and aims at increasing step counts.

7.5   Summary of Chapter

Background: In women with PCOS, the underlying insulin resistance and high prevalence of obesity increase the likelihood of a variety of metabolic complications such as diabetes and cardiovascular diseases. This chapter describes the prevalence of cardiovascular risk factors in the participants recruited to the SUCCESS-RCT.

Methods: Participants attended the research centre after 8 hour fasting overnight. Fasting sample, and OGTT was performed, anthropometric and demographic data were collected and patients left the centre with an accelerometer fitted on their waist to record their physical activity for 10 days. Cardiovascular risk factors were defined as family history of CVD, current smoking, hypercholesterolemia, hypertension, high risk of diabetes, and physical inactivity.

Results: Mean (SD) age of the cohort was 33.3 (7.6) years, mean BMI, systolic BP, cholesterol, fasting glucose, and 2-hr glucose were; 32.7 (6.7) kg/m2, 122.0 (12.3) mmHg, 5.1 (0.9) mmol/l, 4.8 (0.5) mmol/l, 5.8 (1.6) mmol/l respectively. 91% of the cohort had at least one and 24% had four or five modifiable cardiovascular risk factor in addition to their BMI. 23.2% were smoker, 17.7% hypertensive, 70% hypercholesterolemia, 15.2% had a high risk of diabetes, and 58.7% were physically inactive.and 37% had family history of CVD.

Conclusion: A high proportion of women with PCOS have cardiovascular risk factors. These women would benefit from lifestyle change and increasing their physical activity. The SUCCESS education programme is tailored to this group and the primary outcome was an increase in step count.

Chapter 8 : Health related quality of life, illness perception and the lived experience with PCOS. Baseline data from the SUCCESS-RCT
SUCCESS: Struct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome

Design of the SUCCESS-RCT was described in Chapter 6 followed by Chapter 7 which reported the baseline biochemical and demographic characteristics of the cohort.

The current chapter presents the results of the baseline assessment of health related quality of life and illness perception in the women recruited to the SUCCESS-RCT. The education intervention especially the part of the programme which dealt with the emotional management is also explored in more detail. Finally, the feedback of the participants who participated in the education programme is analysed to see what they thought were the key messages in the programme.

8.1 Introduction

The combination of the signs and symptoms of PCOS and obesity has an impact on patients' emotions and quality of life (88). Women with PCOS have been reported to have a poorer health related quality of life (HRQoL) compared to some other chronic conditions such as diabetes, asthma, epilepsy and back pain (154).

Qualitative interviews in this study (Chapter 5) as well as other studies (157-159) report that women with PCOS feel "different", "abnormal", and "not a proper woman". They have higher rates of anxiety, depression and emotional distress (9), even after matching for BMI (161,164).

Lack of information has been shown to be associated with the poor HRQoL in this group (195). This is not surprising as Leventhal suggested that any patients with chronic condition seek information about their condition to understand the five dimensions of the illness: timeline, consequences, cure/control, identity, and cause (302,305). Women with PCOS are not different and they seek information about their condition (interviews presented in Chapter 5).

The SUCCESS education is designed to address this information gap. Participants' perception of PCOS and their HRQoL are some of the secondary outcomes in the SUCCESS-RCT. This chapter describes the results of these assessments at the baseline visit. The thoughts and feelings of the participants towards their condition as they described them in the education and their feedback on the education programme are also presented in this chapter.

8.2 Methods

Detailed procedures for the SUCCESS-RCT have been described in Chapters 6 and 7.

8.2.1 Subjects

Overweight or obese women (191), aged 18-50 years with a diagnosis of PCOS (27) were recruited to the study. Main exclusion criteria included pregnancy and

diagnosis of diabetes. Participants were randomised to either the intervention or a control arm.

8.2.2 Data collection

Information on the past medical history, and medication use was collected by trained research nurses. Participants filled in the following specific questionnaires.

8.2.2.1 Health related quality of life (HRQoL)

The validated PCOS questionnaire (PCOSQ) (357,358) was used to assess the disease specific HRQoL. The PCOSQ has 26 questions with a seven point scoring scale and assesses five domains related to PCOS. In this questionnaire scale one indicates the most severe impact and seven shows the lowest level of impact. Table 8.1 shows a sample question for each domain.

Table 8.1 Examples questions for each domains in PCOS Questionnaire

Domains	Example questions
Emotions	During the past two weeks how much of time you felt depressed as a result of having PCOS
Body Hair	Over the past two weeks, to what extent "embarrassment about excessive body hair" has been a problem for you?
Weight	During the past two weeks how much of time you felt concerned about being overweight?
Infertility	During the past two weeks how much of time you felt concerned with infertility problems?
Menstrual	In relation to your last menstruation how much "irregular menstrual period" was a problem for you?

8.2.2.2 Illness Perception

The Brief illness perception questionnaire (BIPQ) (366) was used to determine illness cognition. This nine item instrument measures cognitive illness representations (cause, consequences, timeline, control, and identity), two emotional representations (concern and emotion) and illness comprehensibility (perceived knowledge). An 11 point Likert scale (0 = no effect, 10 = complete effect) is used to score the dimensions except the "cause" which is an open

question and patients can write free text on it. (Questions are presented with the results in Table 8.2)

8.2.3 Education Intervention

Each education session was run by two trained educators as a whole day programme or over three evenings. Education consisted of three parts; the first two parts were patient and professional stories and lifestyle management. At the end of the second part, participants would be invited to make a self-management plan in an allocated time and discuss it with the group (outline of the education was shown in table 5.4 and the curriculum in Appendix 4.1).

The third part in the SUCCESS education was balancing life with PCOS; which discussed coping with PCOS and all other stresses in life. Confidentiality of the discussion in the session would be re-emphasized and participants would be invited to be as open as they could about their emotion.

In the first session of this part a blank flip chart was used with some "thought bubbles" and participants would be asked to express their thoughts and feelings about PCOS, what was in their mind in the session, what went through their mind when they were diagnosed and how have they felt over time in relation to their PCOS. Educators would facilitate a discussion in the group and help participants to describe and explore their feelings. (This is session M in the SUCCESS curriculum Appendix 4.1).

8.2.3.1 Feedback on the education

Following the education programme, all participants were asked to give anonymous free text feedback on the education programme. The feedback form (Appendix 5.4) is mainly used for further development of the education programme. However, the first two questions are designed to check what they liked in the programme ("best bits of the day") and whether they understood the main message ("key messages from the education"). Their feedback on these two questions is presented here.

168

8.2.4 Data analysis

8.2.4.1 Quantitative data

Data was presented as mean (standard deviation = SD) for continuous variables, median (Interquartile range = IQR) for ordinal (questionnaires) variables and percent for the categorical variables. Questionnaires were scored using their standard tool (357,366). Statistical tests were performed in SPSS 20.0 (Statistical Package for the Social Sciences, IBM Company, Armonk, NY, USA).

8.2.4.2 Qualitative data

There were three questions which allowed free text; the last question in BIPQ which asked participants to list three causes for their condition and the feedback from education programme on the best bits of the day and the key messages of the day. The answers to these questions were read several times. Themes were defined which would encompass the most repeated answers. The answers were then summarised into these themes for presentation in this chapter.

For example, in the last question of the BIPQ about the causes for their illness, the following answers were grouped into "Genetics":

"It is in the genes", or "*it runs in the family*", or "*hereditary*", or "*because my mother had it*".

Reviewing the answers, creating the themes, and summarising the report was performed by hand and no software was used.

The expressed emotions of participants in the "thought bubble" session were typed into an Excel sheet after each session. They were presented using the word clouds (http://www.wordle.net/create). The words which repeated most have larger font size in the cloud.

8.3 Results

8.3.1 Baseline data

In total 162 patients were recruited into the SUCCESS-RCT. Mean (SD) age at the diagnosis of PCOS was 24.1 (6.8) years. Mean (SD) duration for the diagnosis of PCOS was 9.14 (6.93) years. Reported history of depression in the cohort was 33.3% and 11.7% were on anti-depressant therapy at the baseline visit (Table 8.2).

The majority of the cohort (79%), were employed in part time or full time occupations. Ten participants (6.2%) were students. Overall, 45% had a university or postgraduate degree, 12% had finished college. Only 2% reported no education. The majority (93.8%), were either married or in a relationship.

8.3.1.1 HRQoL

PCOSQ describes the impact of the symptoms on the health related quality of life in women with PCOS in a scale of one to seven; one being the sign of the highest (=worst) impact. Table 8.2 shows the summary of the five categories of symptoms; weight had the lowest score (the highest impact on HRQoL). The median (IQR) impact of weight, body hair, menstrual problems, infertility and emotions median were; 2.2 (1.2, 3.2), 3.4 (2.2, 5.4), 3.6 (2.5, 4.7), 4.0 (2.2, 5.8), 4.4 (3.1, 5.4) respectively.

8.3.1.2 Illness perception

Out of a maximum score of 10, participants thought that the consequences of PCOS were 7.0 (4.5, 8.0). They felt that PCOS would be a permanent condition with a median (IQR) score of 10 (8.0, 10.0) and they did not think that they had personal control over the condition; 3.0 (2.0, 5.0). Table 8.2 shows the results of the first 8 questions in brief illness perception questionnaire (BIPQ).

The education and intervention arm were well balanced on all the aspects of the analyses.

Causes for PCOS:

The last question in BIPQ asked up to three causes for condition (PCOS). Similar answers were grouped together as explained in the methodology.

Dominant themes were; "problems with weight", "problems in hormones", "genetics", and "lifestyle". Nine participants mentioned "abnormalities with insulin function" as one of the causes and seven expressed that they did not know.

There were 32 other less commonly presented causes such as "irregular periods", "bad air", "bad luck", "pregnancy", and "contraceptive pills".

Table 8.2 Psychological well-being, health related quality of life and illness perception in the SUCCESS cohort at baseline by the randomisation arm

Variable	Total Cohort 162	Education N = 84	Control N = 78
Demographic	**Mean (SD) / %**	**Mean (SD) / %**	**Mean (SD) / %**
Age at diagnosis	24.1 (6.8)	25.3 (7.3)	23.6 (6.6)
Duration of PCOS	9.1 (6.9)	8.1 (6.2)	9.7 (7.4)
Body mass index (kg/m^2)	33.6 (6.7)	34.1 (7.2)	33.2 (6.2)
Reported history of depression	33.3	35.7	30.8
Use of Anti-Depressants	11.7	13.1	10.3
5 Domains of PCOS Questionnaire (Max score 7)†			
	Median (IQR)	**Median (IQR)**	**Median (IQR)**
PCOS emotions	4.4 (3.1, 5.4)	4.5 (3.4, 5.5)	4.2 (3.1, 5.3)
PCOS body hair	3.4 (2.2, 5.4)	3.1 (2.2, 5.0)	4.1 (2.3, 5.8)
PCOS weight	2.2 (1.2, 3.2)	2.2 (1.0, 3.4)	2.0 (1.2, 3.2)
PCOS infertility	4.0 (2.2, 5.8)	4.4 (2.6, 6.2)	3.5 (1.9, 5.7)
PCOS menstrual	3.6 (2.5, 4.7)	3.5 (2.5, 5.0)	3.7 (2.5, 4.5)
Brief Illness Perception (BIP) Questionnaire (Max score 10)‡			
	Median (IQR)	**Median (IQR)**	**Median (IQR)**
1- Consequences	7.0 (4.5, 8.0)	7.0 (4.0, 8.0)	7.0 (4.0, 8.0)
2- Timeline	10 (8.0, 10.0)	10.0 (8.0, 10.0)	10.0 (7.0, 10.0)
3- Personal Control	3.0 (2.0, 5.0)	3.0 (1.0, 5.0)	3.0 (2.0, 5.0)
4- Treatment Control	6.0 (5.0, 8.0)	7.0 (5.0, 8.0)	6.0 (5.0, 7.0)
5- Identity	7.0 (5.0, 8.0)	7.0 (6.0, 8.0)	7.0 (5.0, 8.0)
6- Concern	7.0 (6.0, 9.0)	7.0 (6.0, 9.0)	8.0 (6.0, 8.5)
7- Coherence	6.0 (3.2, 7.0)	6.0 (3.0, 7.0)	6.0 (4.0, 7.0)
8- Emotional Representation	7.0 (5.0, 8.0)	7.0 (5.0, 8.0)	7.0 (5.0, 9.0)

SD = Standard deviation, IQR = Interquartile range,
† In all 5 areas of PCOSQ a lower score indicates the higher (worst) impact
‡ Questions are presented here; (0 = no effect, 10 = complete effect)
1-How much does your illness affect your life? / 2- How long do you think your illness will continue? / 3- How much control do you feel you have over your illness? / 4- How much do you think your treatment can help your illness? 5- How much do you experience symptoms from your illness? / 6- How concerned are you about your illness? / 7- How well do you feel you understand your illness? / 8- How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

8.3.2 The SUCCESS Education Programme

Out of the 84 participants who were randomised into the intervention arm, 67 (80%) attended the education programme. Five withdrew before the education and 12 could not match their diary with any of the available dates.

The 67 women, who attended, received education in 14 cohorts (median number for the participants in each cohort was five). One cohort had their education in the evenings of the three consecutive weeks and the rest were in the whole day seven hours format.

8.3.2.1 Thought bubbles

In the third part of the education, participants were asked to put down their thoughts about their PCOS in thought bubbles. Figure 8.1 shows the flip charts produced in two different groups. All the expressed thoughts by the 67 participants who went through education was put in word cloud (Wordle.net) which gives weight to the font size and effect depending on the number of repetitions Figure 8.2.

After months or years of seeking information about their symptoms the sense of "relief" was the dominant feeling after diagnosis. "Anger", "frustration", "why me", worries about "infertility", and feeling "unfeminine" were some of the other dominant words.

8.3.2.2 Feedback on the education

Feedback were anonymous and voluntary; 57 patients and two family members who had attended the education filled in the feedback forms.

Best bits of the day

The most dominant theme in the "best bits of the education programme" were: "meeting others with PCOS" and "gaining knowledge about the condition and lifestyle". Examples of some of the typical comments are:

"Pleased to hear that it is not just my problem; other people face it as well"

"Gaining an understanding about how PCOS affects your life and what positive changes can be made to improve it"

Key messages of the day

"Being positive about PCOS", "benefits of the diet and exercise", and the "concept of insulin resistance" were the dominant themes reported in this part.

"Overall message was very positive: that PCOS is not the end of the world and with lifestyle change such as diet and exercise things would improve".

Figure 8.7 Thought bubbles in the SUCCESS education programme
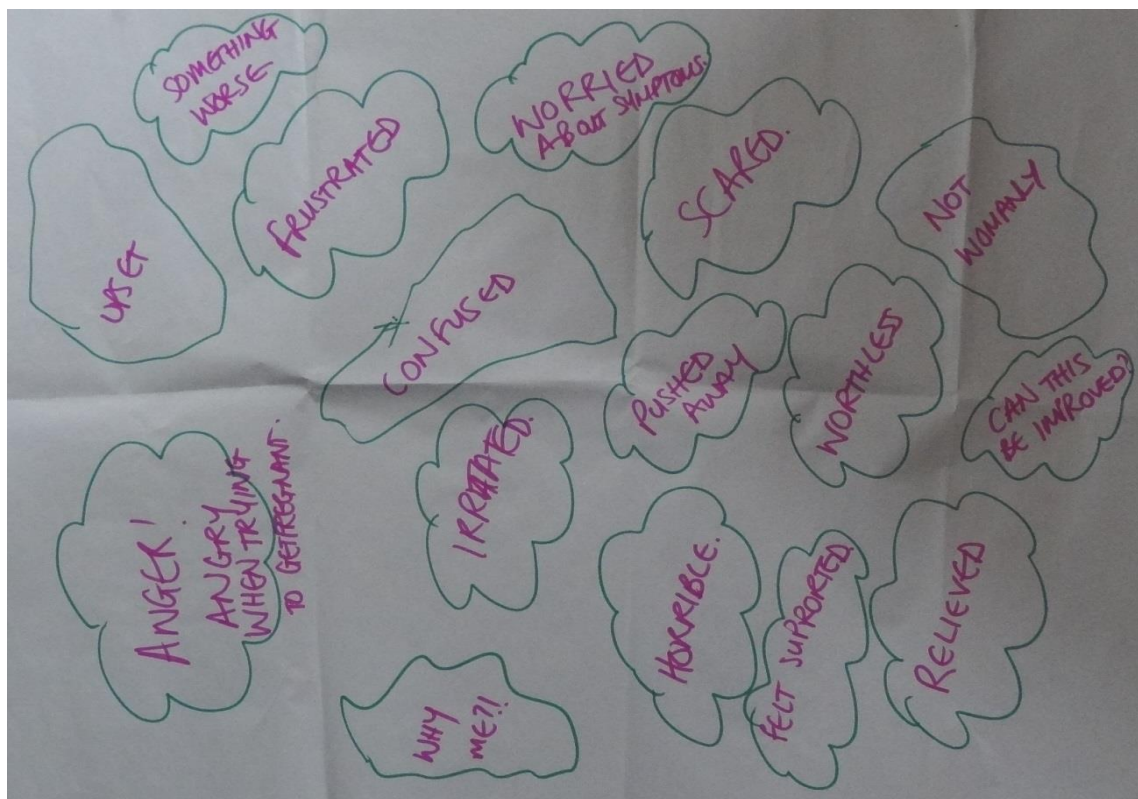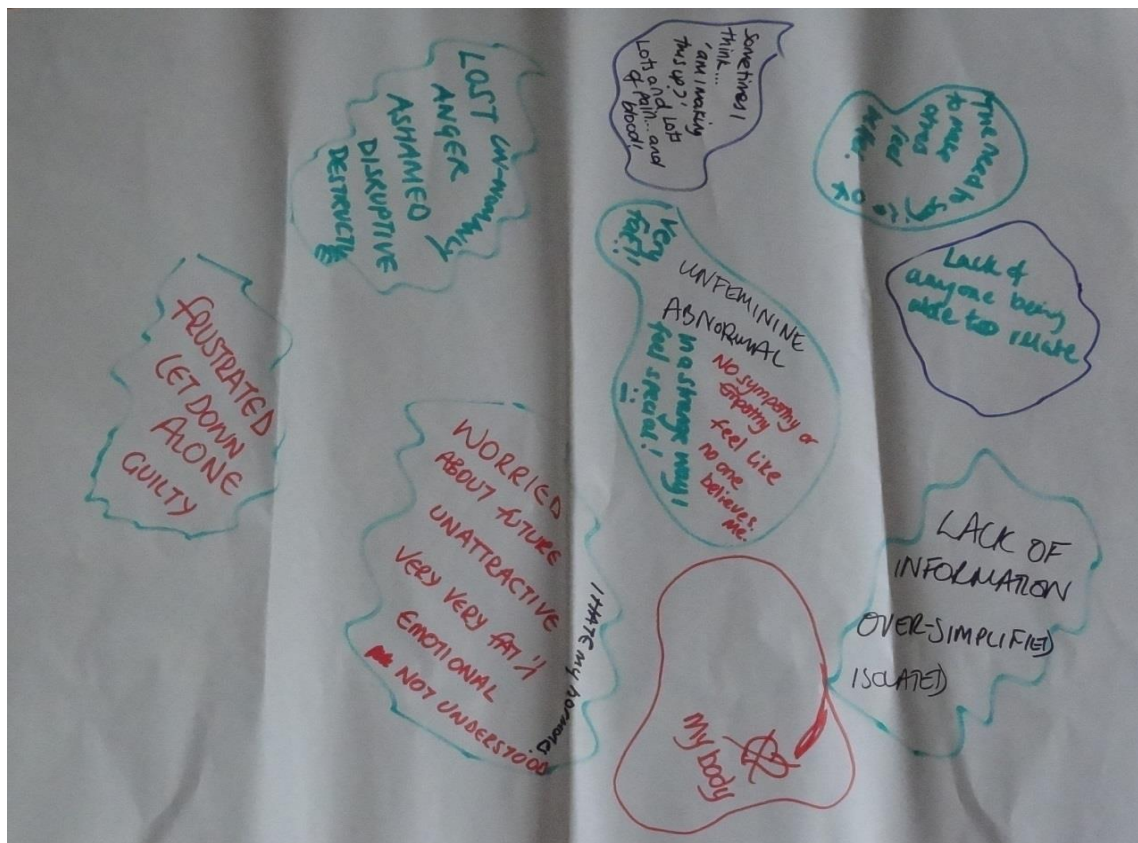
In the third part of the SUCCESS education programme, balancing life with PCOS, participants would be asked to express their feelings about their condition.

Figure 8.8 Thought bubbles of the SUCCESS education programme in a word cloud

Word cloud created using http://www.wordle.net/create

8.4 Discussion

The cohort in the SUCCESS-RCT are young women with a long history of PCOS. Their perception of their condition indicated the chronicity of PCOS with little personal control over it. Symptoms with highest impact on their quality of life were weight and body hair. The majority of the participants had strong feelings towards their PCOS; they were frustrated with their PCOS, felt angry and unfeminine.

Similar to some of the previous studies (88,154,380), weight had the highest impact on the quality of life and women were frustrated and angry with deep emotional impact from their PCOS (157,164,282). However, this study is the first to measure the illness perception in women with PCOS. Assessment of the dimensions of illness cognition as described by Leventhal (304,305), showed that women in the SUCCESS study understood the chronicity of their condition, felt there was some consequences of their PCOS but did not think they had control over the syndrome. They generally related their condition to poor lifestyle and excess weight as well as some hormonal imbalance.

The aim of the SUCCESS education programme is to improve illness perception and induce behavioural change in women with PCOS. The majority of those who attended the education programme found it appropriate and useful. They noticed that they were not alone in this condition and shared their stresses. They felt that they might be able to gain some control over their overall health through lifestyle change; namely exercise and weight management.

The SUCCESS education programme is underpinned by learning theories (Chapter 4); common sense model (304), social cognitive theory (310), implementation intention (314), and dual processing theory (319). This structured education aimed to promote a behavioural change in women with PCOS. Feedback, following the education programme, indicates that those who attended the education understood the main message about lifestyle change (dual processing theory, implementation intention); gained knowledge about PCOS and its underlying pathology (common sense model, dual processing theory); shared their experience of PCOS with other patients (social cognitive theory) and

left the education with a positive message about the possible changes in lifestyle; and intention to change.

A positive outcome in the SUCCESS-RCT depends on translation of this intention into a behavioural change and minimizing the "intention-behaviour gap" (323).

8.4.1 Conclusion

Signs and symptoms of PCOS have significant emotional impact on women with PCOS. These women attended a structured education programme (SUCCESS) to learn about PCOS and the benefits of a lifestyle changes especially increased physical activity. They left the education in a positive attitude with a message that lifestyle change can help with their general health status. The translation of this understanding into a change in their behaviour will be measured by the change in their step count as an index of change in healthy behaviour.

8.5 Summary of Chapter

Background: Women with PCOS have poor health related quality of life (HRQoL).Lack of information about PCOS has been shown to have significant impact on their HRQoL. The SUCCESS education programme provides information about PCOS and explores the benefits of lifestyle change for women with PCOS. Illness perception, HRQoL at baseline as well as, patients' feelings towards their PCOS and their feedback on the education programme were assessed.

Methods: Brief illness perception and PCOS questionnaires were used for all participants at baseline. Women who attended the education programme, expressed their feelings about PCOS, and in the format of free text feedback form summarized the key messages of the education programme.

Results: Body weight and body hair had the highest impact on HRQoL in the SUCCESS cohort. They understood the chronicity of PCOS and felt that they did not have personal control over their condition. They considered excess weight, poor lifestyle and hormonal imbalance as the main causes for PCOS. Whilst they felt relieved after receiving the diagnosis of PCOS (due to their long term efforts to make sense of their symptoms), they were very frustrated with PCOS; feeling unfeminine and confused. They left the education programme in a positive mood and understood that lifestyle change may be helpful.

Conclusion: Signs and symptoms of PCOS have significant emotional impact on women with PCOS. The cohort of women in SUCCESS who attended the education programme, found it positive with a message that lifestyle change can help with their general health status.

Chapter 9 : Effects of a structured education programme in women with polycystic ovary syndrome on step counts, 3 months interim analysis of the SUCCESS-RCT

SUCCESS: Struct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome

The high risk status of PCOS was established in chapters 1 and 2, and benefits of lifestyle interventions were discussed in Chapter 3. A structured education programme was developed for women with PCOS (Chapters 4 and 5) and a RCT was designed to test its efficacy (Chapter 6). Chapters 7 and 8 described the baseline characteristics of the cohort recruited to the SUCCESS-RCT and their feedback on the education programme.

In this chapter the three months interim results of the study are presented.

9.1 Introduction

The increased risk of long term metabolic complications such as diabetes and cardiovascular diseases in women with PCOS indicates the need for an intervention to reduce their risk. Structured lifestyle interventions have been successful in behavioural change and reducing the risk of diabetes in people at high risk of diabetes (288). Lifestyle change has been recommended as the first choice of treatment for women with PCOS (4,8,129), however there is lack of pragmatic structured education programme aimed at this patient group as discussed earlier in the Chapters 3 and 5 of this thesis.

The SUCCESS lifestyle education programme was therefore developed to address this gap and help these patients understand their condition and empower them to identify and improve their modifiable risk factors. Efficacy of this education programme to induce a behavioural change and increase the walking activity in women with PCOS has been put to test in the SUCCESS-RCT.

This is a 12 months study and this chapter presents the three months interim analysis of the results.

9.2 Methods

This is a single centre, two arm, and parallel randomised controlled trial. The primary outcome of the study is set to be 2000 steps increase in daily walking activity after 12 months following a structured education programme on lifestyle change for women with PCOS.

Secondary outcomes for the study include any change in physical activity level, glycaemic indices, weight and waist reduction, improved indices of cardiovascular risk (blood pressure and lipids), improvement in signs and symptoms of PCOS, and health related quality of life.

Calculated sample size for 2000 steps/day increase in walking activity with standard deviation of 4000 steps/day and 25 percent attrition was 160. (Chapter 6, Page 140)

9.2.1 Inclusion Criteria

Overweight or obese women (191) (Body Mass Index ≥ 23 kg/m^2 for Black and Minor Ethnicities and BMI ≥ 25 kg/m^2 for White Europeans) aged 18-50 years with a diagnosis of PCOS (27) who were either receiving no medical treatment or had a stable treatment for at least 6 months were invited to the study. Main exclusion criteria included pregnancy, diagnosis of diabetes, use of steroids and disabling physical or mental condition.

Subject were recruited from three main sources: patients with recorded diagnosis of PCOS in primary care, specialised clinics in University Hospitals of Leicester (UHL) NHS trust, and self-referral following advertisements. Diagnostic criteria for PCOS (including blood tests and imaging investigations) were reviewed by me.

9.2.2 Study procedure and Data Collection

All the study visits were performed in Leicester Diabetes Centre (LDC). Details on measurements and questionnaires for each visit are presented in Chapter 6 (Table 6.1). The clinical staff conducting and co-ordinating the clinic visits were blind to the randomisation.

At the baseline visit, after consent the participants had their fasting blood test followed by a 75 gram glucose load in the form of Lucozade (410mls of 70kcal/100ml Lucozade; GalaxoSmithKline, Middlesex, UK). Questionnaires were answered by participants in the 2-hour time interval to their second glucose test. Step counts and physical activity were objectively measured using a triaxial Actigraph GT3X accelerometer (Actigraph, Penascola Florida, America). All the participants left the study centre wearing their accelerometer which was to be returned after 10 days in a pre-paid addressed envelope.

The follow-up visit was set to be three month after the baseline visit and included assessment of the demographic and clinical measurements, HbA1c, and two questionnaires; PCOS Questionnaire (PCOSQ) (357) and international physical activity questionnaire (IPAQ) (381) Following the measurements, participants left the centre wearing their accelerometer.

9.2.2.1 Randomisation and follow up visit

A computer programme generated the randomisation table and an independent administrator conducted the randomisation for each participant after the baseline visit and once the accelerometer was returned. Randomisation was stratified for age (<35 years and > 35 years old), ethnicity (white and others), and the use of Metformin. Randomisation was set in blocks of four to ensure an even distribution of the participants in the two arms at any point during the study.

Follow up visits (three, six and 12 month) were set to be measured from the baseline visit. As a result, the participants in the intervention and control arms would come back in almost at the same time which would help with maintaining a seasonal balance between the two groups as well. Considering the primary outcome, step counts, and the potential seasonal effect on outdoor activities, there was a chance that if the follow up visits were delayed in the education arm due to the arrangements to deliver the education, then the follow up visits would fall in different un-matched seasons and this might have affected the validity of the measurements.

9.2.2.2 Intervention

The SUCCESS education programme (as detailed in chapters 5 and 8) was offered to all the participants randomised to the intervention arm as soon as randomisation had occurred. Each month, it was ensured that at least three choices were available to the participants; whole day weekday (9:00 to 16:00), whole day Saturday (10:00 to 17:00) and three evenings on consecutive weeks (17:30 to 20:00). An education day would be confirmed when at least four

participants had put their name down for that day. An education day would start with at least three participants in attendance.

The control arm received information about PCOS and benefits of lifestyle change in the form of a booklet (Appendix 4.4).

There was no interference with the medical treatment of either arm after randomisation: responsible doctors (general practitioner or specialist) were free to start any treatment or change the medications after baseline randomisation.

9.2.3   Data processing

Accelerometer: Considering that accelerometer counts movement data every one second, a prolonged period (at least 60minutes) of no movement was assumed to be non-wear time and excluded. A total of 4 days valid day wear was required to count as a valid recording (343) and a 'valid day' consists of at least 10 hours (600 minutes) of accelerometer movement data (344). Presented step counts are the average of the valid days. Each participant was given an activity log (Appendix 5.6) to document the times the accelerometer was taken off.

Accelerometer data was extracted by Dr Charlotte Edwardson using the licensed software.

International Physical Activity Questionnaire (IPAQ): Collected data was processed using the most recent guideline recommended by the IPAQ group (381). In summary: any activity with blank data or labelled as "don't know" or any participant reporting more than 960 minutes activity was deleted; the minimum accepted activity was 10 minutes and reports above 180 minutes were truncated to 180 minutes (381). Metabolic equivalent (MET) score was calculated using the following formulas (381,382)

IPAQ total MET-minutes/week = (3.3 * walking minutes * walking days) + (4.0 * moderate-intensity activity minutes * moderate days) + (8.0 * vigorous-intensity activity minutes * vigorous-intensity days)

Health related quality of life was assessed by PCOS specific questionnaire (PCOSQ) (357). Details of this questionnaire and its scoring were mentioned in earlier in Chapter 8 (page 167).

9.2.4 Statistical Analysis

Data is presented as mean (standard deviation of mean = SD) at baseline and mean change from baseline (standard error of mean = SEM) at three months. Normality was assessed visually by inspection of histograms and tested by probability (Q-Q) plots. Analysis of covariance (ANCOVA) was used to compare the mean (SEM) changes from baseline in the analysis of the three months results. Intervention effect size (95% confidence = CI) is adjusted for the stratification factors (age, ethnicity and the use of Metformin) and baseline values, as recommended (340,341). Accelerometer wearing time played an important role because increase or decrease in wear time would affect the amount of captured data. The outcome variables related to accelerometer was therefore adjusted for the change in wear time as well.

The main analysis is performed per-protocol: control group who attended their follow up visit and participants in the education arm who received the intervention before their three months visit. No imputation was done for the missing data in the main analysis. Two sensitivity analyses, however, were performed to assess the primary outcome by imputing the missing data. The first sensitivity analysis was imputing the missing data in the per-protocol analysis. An intention to treat analysis was also performed for everyone who was randomised to education or control arm.

For the sensitivity analyses, missing data were imputed and replaced with the total cohort's mean at the analysis point; i.e. the mean of observation at the baseline for missing data at baseline and mean of observation at 3 month for the missing data at three month visit (383,384). There were two reasons for the

choice of this approach over the more commonly used method, "last observation carried forward":

- ➢ Three months was the first visit after the baseline and the last observation before that would be the baseline. Carrying the baseline value to the three month outcome would automatically assume that the intervention did not make any difference. However, by using the mean of the observation at the end point a chance was given to the missing data to shift to the average outcome of the study (383,384).
- ➢ The second reason, which came in hindsight and after the flowchart of the participants was drawn, was the size of the missing data in three month visit. Carrying the baseline observation to this point of the analysis would mean that most of the participants did not have any change in the study.

Statistical tests were performed in SPSS 20.0 (Statistical Package for the Social Sciences, IBM Company, Armonk, NY, USA).

9.3 Results

9.3.1 Participants' Flow and education intervention

The flow of the participants in the study is shown in Figure 9.1. In total 184 women with PCOS consented to take part in the SUCCESS-RCT. Two women withdrew from study before randomisation; one changed her mind and one had needle phobia. Ten women were excluded at the baseline visit due to low or normal BMI. The remaining 172 participants were randomised to either receive the education intervention or to have the routine follow up in the study. Overall 10 patients should not have been randomised due to their BMI being under the ethnic specific cut points (191) and therefore excluded from the study; the final included patients were 162.

There were 11 withdrawals after randomisation; six due to pregnancy, three for work reasons, one for childcare and one did not give any reason. Seven in the control arm did not attend their follow up visit and 12 in the education arm did not

attend the follow up visit, or the education. Twenty in the education arm attended their follow up visit before coming to an education programme.

The final numbers in each arm were 67 (85%) participants in the control arm and 45 (53%) in the education arm.

None of these participants were categorically "lost to follow up", as they were all contactable and they would answer their e-mails or telephone calls, however in some occasions with long delays. Arranging a mutually convenient time for follow up visit or education intervention was difficult, while every effort was made to be flexible with the appointment time to accommodate their busy schedule. Mean (SD) time from baseline to three month visit was 108.9 (20.1) days and 112.8 (24.7) days for control and education arm respectively (P = 0.35).

The SUCCESS education was offered to all patients after randomisation to the intervention arm. However, only 45 (53% of the total education arm) managed to attend their education appointment before three month visit. Twenty (24%) attended after their three months visit and 12 (14%) have not yet been able to match their time with any of the available education programme. Three women attended the education but withdrew before their three months visit (all pregnant).

For the 45 women, who attended their education before their three months visit, the median time from education to follow up visit was 46 (IQR 20, 62.25) days.

At the three month follow up visit the only change in medication history was an increase in the number of participants who were on the Vit D supplements: 16/45 (35%) new starters in the education group and 19/67 (28%) in the control arm (P = 0.549).

Figure 9.29 Flow diagram of participants in the SUCCESS-RCT

184 Attended the baseline visit

10 Excluded
    4 Diagnosed as Diabetes†
    6 had normal BMI
2 **withdrew** after baseline visit and before returning their accelerometer

172 Randomised

86 SUCCESS Education

86 Control

2 Excluded due to normal BMI (should not have been randomised)

8 Excluded due to normal BMI (should not have been randomised)

84 invited to education

162 in baseline (Presented in Chapter 7 & 8)

78 in the Control arm

7 Withdrew (4 Pregnancy + 1 Work related + 1 Childcare + 1 No reason)

4 Withdrew (2 Pregnancy + 2 Work related)

12 lost to follow

7 lost to follow

20 had their 3 months visit before education

Education
45 **before** 3 month visit
20 **after**
12 to attend

45 (53%) Attended Education before their 3 months visit:

67 (85%) Attended their 3 months visit:

112 outcome analysis (Current Chapter)

BMI = body mass index   † Diagnosis of diabetes was by the WHO criteria (10,347). Patients diagnosed with Diabetes were referred to a diabetes related education programme (DESMOND).

9.3.2 Interim three months outcomes from SUCCESS education Intervention

Only 35/45 (78%) of the participants in the education arm and 40/67 (60%) of the control arm had valid accelerometer data at both baseline and three month. Almost 10% of the returned accelerometers did not reach the definition of validity (10 hours and minimum of four days).

Participants were asked to return their accelerometer 10 days after the clinic in a provided stamped addressed envelope. Mean (SD) time for the return of the accelerometer was 26.34 (27.56) days at baseline and 35.40 (35.98) days at 3 months visit. [The presented mean return time, excludes the 23 accelerometers which have not yet been returned].

The activity log which was returned with the monitors indicated that during the monitoring of the activities at baseline and or three month, 21/112 people had taken off their monitor during activities such as swimming, rugby, spinning class, bike riding and a party: 12/45 (26%) in the education arm and 9/67 (13%) in the control arm. Some people had taken it off without documenting the reason.

The time that accelerometer was worn had reduced in the control arm by 0.1 hr/day while it was increased in the education arm by 0.1 (0.2) hr/day. The changes in any of the outcomes related to accelerometer measurement were therefore adjusted for this variable.

9.3.2.1 Primary outcome, step counts

Although the Mean steps counts increased in the education arm by 271.2 (SEM 295.2) steps/day and decreased in the control arm by -33.7 (SEM 239.5) steps/day, the adjusted intervention effect size did not reach the statistical significance: 160.9 (95% CI, -542.7, 864.4) steps/day.

Table 9.1 demonstrates the main analysis (per-protocol without imputation) as well as the two sensitivity analyses which were performed to estimate the effect of the SUCCESS education on the primary outcome.

Table 9.1 The SUCCESS-RCT Three month interim analysis: Primary outcome

Analysis	Control			Education			Adjusted † intervention effect (95% Confidence Interval)
	N	Baseline: Mean (SD)	Change Mean (SEM)	N	Baseline: Mean (SD)	Change Mean (SEM)	
Per-Protocol (**No** imputation) ‡	40	6721.3 (2777.5)	-33.7 (239.5)	35	6029.2 (1522.0)	271.2 (295.1)	160.866 (-542.670, 864.402)
Per-Protocol (**With** imputation)	67	6687.5 (2605.3)	120.0 (220.5)	45	6065.5 (1455.9)	219.7 (239.0)	221.493 (-336.808, 779.794)
Intention to treat	78	6729.6 (2601.9)	110.9 (220.3)	84	6404.0 (1613.4)	244.9 (173.9)	17.450 (-408.302, 443.201)

N = number in the analysis, SD = Standard Deviation, SEM = Standard Error of Mean, †Adjusted for baseline stratification factors (age, ethnicity and Metformin), change in the accelerometer wear time and baseline data ‡Baseline and 3 months accelerometer data were available in 40 participants in the control arm and 35 of the education arm.

9.3.2.2 Secondary outcomes

Table 9.2 shows the baseline figures and the mean (SEM) changes from baseline and the intervention effect size (95% CI) for the secondary outcomes in SUCCESS-RCT.

Physical activity data

There was no statistically significant effect from education on any of the measured indicators of physical activity as shown in Table 9.2. Mean (SEM) sitting time was decreased by 0.15 (0.14) hr/day in the control group and increased by 0.29 (0.18) hr/day in the education arm. Similarly the education arm has a non-significant reduction in their monitored light and moderate to vigorous physical activity, -0.32 (-0.68, 0.05) and -0.04 (-0.14, 0.05) hr/day respectively.

Biochemical and demographic variables

The SUCCESS education did not have any statistically significant effect on body mass index (BMI), weight, systolic or diastolic blood pressure, or HbA1c at the three month interim analysis. BMI and weight had decreased in the education arm with mean (SEM) changes of -0.15 (0.14) Kg/m^2 and -0.42 (0.40) kg respectively, compared to no change or slight increase in the respective values of the control arm: 0.00 (0.12)kg/m^2 and 0.06 (0.30) kg.

The effects of SUCCESS education on HbA1c was a non-significant reduction of -0.81 (-2.15, 0.52) mmol/mol [=-0.07 (-0.19, 0.06) %].

Health related quality of life (HRQoL)

PCOS specific indicators of HRQoL as measured in five dimensions of PCOSQ (357), did not show any significant change as a result of SUCCESS education. There was a non-significant improvement in the emotional impact of the disease on HRQoL [0.19 (95% CI, -0.26, 0.65)] as well as the impact of infertility [0.38 (95% CI, -0.12, 0.87)] after the SUCCESS education programme.

Sensitivity analysis

There was no missing data in the biochemical, demographic and PCOSQ data. The above measurements were repeated after missing data were imputed in the physical activity indices in a per-protocol analysis. This did not make any real difference in the intervention effect sizes except for minor changes in the figures.

Table 9.2 The SUCCESS-RCT Three month interim analysis: Secondary outcomes (Per-Protocol Analysis without imputation)

Variable	Control N = 67		Education N = 45		Adjusted † intervention effect (95% Confidence Interval)
	Baseline: Mean (SD)	Change: Mean (SEM)	Baseline: Mean(SD)	Change: Mean (SEM)	
Physical Activity: Accelerometer Data ‡, and International Physical Activity Questionnaire (IPAQ)					
Sedentary time (hr/day)	8.91 (1.59)	-0.15 (0.14)	8.85 (1.16)	0.29 (0.18)	0.343 (-0.034, 0.719)
Light physical activity (hr/day)	4.61 (1.04)	0.15 (0.11)	4.65 (1.30)	-0.14 (0.16)	-0.316 (-0.677, 0.045)
MVPA (hr/day)	0.50 (0.37)	-0.02 (0.03)	0.44 (0.27)	-0.02 (0.04)	-0.043 (-0.141, 0.055)
Counts (× 1000) / day	264.02 (103.27)	1.15 (7.69)	248.33 (95.31)	-10.78 (11.46)	-20.449 (-48.866, 7.967)
IPAQTotal (Met-minutes/week)	2317.21 (245.54)	64.10 (228.88)	1907.88 (264.5)	-435.71 (282.87)	-401.903 (-1038.041, 234.234)
Demographic data					
Body mass index (Kg/m^2)	33.60(6.16)	0.00 (0.12)	35.30 (7.67)	-0.15 (0.14)	-0.228 (-0.600, 0.144)
Weight (Kg)	90.01(19.62)	0.06 (0.30)	92.91 (20.55)	-0.42 (0.40)	-0.593 (-1.571, 0.385)
Systolic Blood pressure (mmhg)	121.44 (11.11)	-3.19 (1.38)	122.40 (13.46)	-3.31 (1.50)	0.398 (-3.128, 3.924)
Diastolic Blood pressure (mmhg)	76.92 (9.81)	1.045 (0.96)	81.91 (11.49)	-2.82 (1.37)	-2.027 (-5.027, 0.973)
HbA1c (mmol/mol)	38.69 (4.29)	-1.57 (0.50)	40.00 (3.56)	-2.89 (0.56)	-0.814 (-2.152, 0.525)
HbA1c (%)	5.69 (0.39)	-0.15 (0.04)	5.81 (0.33)	-0.27 (0.05)	-0.066 (-0.190, 0.059)
Health related Quality of Life					
PCOSQ_Emotion	4.25 (1.36)	0.00 (0.17)	4.55 (1.39)	0.13 (0.16)	0.194 (-0.259, 0.647)
PCOSQ_Hair	4.05 (1.98)	0.21 (0.30)	3.73 (1.91)	-0.02 (0.12)	-0.155 (-0.613, 0.304)
PCOSQ_Weight	2.37 (1.48)	0.26 (0.16)	2.44 (1.39)	0.15 (0.22)	-0.123 (-0.614, 0.367)
PCOSQ_Infertility	4.00 (2.03)	0.11 (0.16)	4.60 (2.01)	0.39 (0.20)	0.378 (-0.115, 0.872)
PCOSQ_Menstrual	3.70 (1.45)	0.19 (0.19)	3.94 (1.38)	-0.13 (0.23)	-0.252 (-0.799, 0.295)

N = number in the analysis, SD = Standard Deviation, SEM = Standard Error of Mean, †Adjusted for baseline stratification factors (age, ethnicity and Metformin), baseline data and change in the accelerometer wear time for the related variables ‡Baseline and 3 months accelerometer data were available in 40 participants in the control arm and 35 of the education arm.

9.4 Discussion

The SUCCESS education did not increase the step count at the three month interim analysis. None of the secondary outcomes including indices of physical activity, weight, BMI, blood pressure, HbA1c, and or the dimensions of HRQoL improved within 3 months after the education intervention.

None of the parameters of physical activity reached a statistical significance, but the pattern of the results were slightly confusing. While steps counts show a trend towards increase in the education arm, the light and moderate/vigorous physical activity have reduced in this arm and the sedentary time has increased. These results are in the least puzzling and disappointing. Here in the following pages, after comparison with other similar studies, an attempt is made to explore the limitations which have possibly led to these outcomes. There are lessons to learn from these results which will also be discussed.

9.4.1 Comparison with other studies

Direct comparison of SUCCESS with other lifestyle interventions in women with PCOS is not possible as to our knowledge this is the first structured education programme in women with PCOS which aims at increasing walking steps. A single arm study (214) aimed to increase brisk walking activity in women with PCOS in order to increase the maximal oxygen concentration (VO$_2$ max). Women were instructed to walk more (20 to 60 minutes), three times a week for six months. They did not receive a structured education programme, and the study team have not reported the mean walking steps before and after their intervention. In their study nine out of 21 women (40%) did not take up the advice to do the brisk walking. Brisk walking in this study increased the fitness (Vo2 max) and had no effect on BMI, insulin and cholesterol.

Randomised controlled trials which study the effects of exercise in women with PCOS are generally supervised aerobic activities such as intensive exercise on the treadmill (385) bicycle (386) or mixture of both (211) for three to six months.

These studies generally reduced BMI in the intervention arm, and improved insulin sensitivity, but they did not involve any structured education and participants needed to attend a supervised exercise. With a small sample size (maximum 90 participants (386)) and high lost to follow up or withdrawals from study ranging from 33% (385) to 62% (211), their results are presented with very small number of the completers.

Other education interventions targeting women and not specifically those with PCOS have been successful in increasing walking activity by 2000 steps (387) and reducing weight by almost 7% (388). Their education intervention however, was very different to SUCCESS study; in one study women had a weekly 45 minute education session which included 30 minutes of exercise for the eight weeks duration of the study (387). Another study offered 30 sessions of motivational education lasting two hours in one year follow up (388). The SUCCESS study, however aimed at a larger cohort and an education programme, which would potentially be feasible to enrol in the community considering the previous similar experience (7,296).

The SUCCESS-RCT can be compared in some aspects with similar interventions developed by the Leicester Diabetes Centre: PREPARE (Prediabetes Risk Education and Physical Activity Recommendation and Encouragement) (288) and (Sedentary Time AND Diabetes = STAND) (286). PREPARE was designed as an RCT in three arms; three hours education program and a pedometer for self-monitoring the walking steps, education only and control. The combination of the education programme and pedometer increased walking activity after three month by 1720 (95% CI 368 to 3073) steps/ day. The cohort in PREPARE were very different to the women in SUCCESS; they were older (average age 65 years), and had a lower BMI (mean 29.0 kg/m^2) and of mixed gender (33% female) (288).

The STAND-RCT aimed at reducing the sedentary time through education in a cohort of young people at high risk of diabetes (Overweight or obese with at least one other risk factor for diabetes). There were some similarities and differences between the baseline characteristics of SUCCESS and STAND cohorts. The

cohort in STAND were also young (mean age 32.9 years) and obese (mean BMI = 34.2 kg/m2) like women in SUCCESS, however only 52% were female (378). Their baseline activity profile was different to the SUCCESS cohort. With a similar 14 hours monitoring time in both cohorts, participants in STAND had almost one hour more sedentary time as compared to the SUCCESS cohort (approximately 10 hours in STAND versus less than 9 hours in SUCCESS) (378). Similarly the light physical activity was higher in SUCCESS cohort (> 4.5 hours) than STAND (3.5 hours) (378). The results of STAND-RCT are yet to be published.

Lack of effect at the three months visit in this type of research might be due to the fact that it is actually too close to the education intervention. The primary outcome in SUCCESS-RCT was set to be assessed at 12 month visit. Although one study (386) achieved 4.5% reduction in BMI and 35% improvement in Vo_2 max after three months, most of the exercise interventions have reported their results at six month or later (211,213,385). In the SUCCESS-RCT, the interim analyses at three and six month were planned to help with understanding the early effects of the education. It however, seems that the three month may have been too early to show any results. The results of the six months analysis will help to test this idea.

9.4.2 Limitations and their implications on outcome analysis

Limitations could be due to the data (collection or analysis), intervention, or patient related factors.

9.4.2.1 Data

9.4.2.1.1 Collection:

Although the accelerometer is one of the best available research tools to measure physical activity, and there are little problems with the measured step counts, they have some limitations with measurements of other activities. Accelerometers do not differentiate between the lying, standing and sitting behaviour (378), and categorization is based on the level of activity which is picked up. Therefore, standing still with little fidgeting could be counted as sitting. Likewise, this

categorization does not take into account the underlying level of fitness in the participants. For example, walking could be a light physical activity for a fit and already active person, while the same level of walking could be moderate physical activity for an unfit and obese person. Both of these individuals would be labelled within the same category of physical activity in accelerometer. Accelerometers have also limited ability to capture cycling related data and do not demonstrate its accurate intensity.

On the other hand, there are situations when accelerometer is taken off either due to its limitations (swimming) or the situation itself (rugby playing) or the fact that it flashes light and some women in the SUCCESS cohort may have felt that it would be inappropriate to be worn out (party, or even possibly running in the evenings). Almost double number of participants in the intervention arm had taken their monitor off during such activities (26% versus 13%).

An iatrogenic limitation is the set point for definition of validity of data, 4 days and minimum of 600 minutes in each day (343,344), which obviously leads to an increase in the missing data. In the SUCCESS-RCT, almost 10% of the returned accelerometers had to be excluded for these criteria. This does not include the single days of data which have less than 600 minutes capture. For example, one participant had 4 valid days (>600 minutes recording) which were included in the analysis, and 2 days which did not reach the limit of 600 minutes and therefore discarded from analysis. In these two days she had 587 and 586 minutes monitoring and on each day she had more than 11000 step counts. Due to the 600 minutes limit, any data related to these two days including the walking steps had to be deleted as per set points of validity.

This was discussed with the physical activity experts in our group and it was agreed to maintain the validity criteria considering its wide international use(343).

A final limitation in this category was the return of the accelerometers. Despite providing the return envelope and many emphases and follow up telephone calls, there was a long delay in return and inevitably some lost in the post.

Cumulative effect of the missing data through any of the above options, would ultimately affect the outcome analysis. When the sample size was calculated for the SUCCESS-RCT, the 25% attrition did not account for this size of missing data.

9.4.2.1.2 Analysis

In addition to the issue with missing data, only 45 (53%) of the participants attended the education intervention before data collection at the three month follow up visit. It is therefore not a true reflection of the effect of the education in the study population.

Per-protocol approach to the analysis of the data was chosen for the same reason. There were only 75 accelerometers available to analyse the primary outcome, change in step counts, and other indices of physical activity. This means that in an intention to treat analysis, one or two data points would be imputed for the remaining 87 (54%) participants who were initially randomised into the study. Missing data happens due to either a random administrator error in data entering or due to participants' withdrawal from study or loss to follow up. Although the withdrawals happen for a reason (in SUCCESS study 10 out of 11 expressed an acceptable reason, six being pregnancy) but it can be argued that the people who stayed in the study could be different to those who withdrew or were lost to follow up. A systematic approach to impute the missing data in the RCT is to avoid this bias (383,384).

Analysis after imputing the missing data did not make a significant difference. To impute data, it was chosen to use the mean of the observation point to replace the missing data as opposed to the more conventional approach which is "last observation carried forward". As discussed earlier in the methods, this was due to the fact that only one visit had been done after the baseline appointment, and with the large number of missing accelerometer data, this approach seemed the better choice (383,384).

A more robust analysis will be performed at the six and 12 months points when most of the participants have been through education and more accelerometers have been returned.

9.4.2.2 Intervention

Considering the above argument, with lack of data, it is not appropriate to make any final conclusion as to the success of the education intervention at this time point. Contents of the SUCCESS education were evidence based, previous similar interventions have been successful (288,296), and participants' feedback indicated that the message was relayed. It is however, possible to draw some lessons from the process and the protocol in hindsight.

While there was no difference in the follow up intervals of the two groups, the logistics of arranging an education programme in the short time interval proved difficult. Almost 80% of the cohort were employed, and 93% married or in a relationship and they needed notice time to arrange time off work or childcare. There were other hurdles as well; most importantly it was necessary to have at least four participants signing up for the same date. This delayed the education intervention and consequently the median (IQR) of the time from education to three month follow up visit was 46 (IQR 20, 62.25) days. In other words, 25% of the participants in the intervention arm had attended their education within three weeks of their follow up visit.

In the SUCCESS education programme, participants receive a large amount of information especially in the one day education. Feedbacks from study, as discussed in Chapter 8, show that they understood the message about the benefits of physical activity. In the education the emphasis is on physical activity and walking but educators try to establish that each participant has to make their own plan for increased walking steps and have a realistic and achievable target. Educators use the 500 steps increment in a week as an example and make sure that there is a weekly review in the plan (page 55 of the SUCCESS curriculum Appendix 4.1). It is therefore plausible to think that some of the participants did not have enough time to achieve the 2000 steps increase before their 3 months visit.

Besides the above gradual advised increase in the step counts, it should be considered that participants' response to the advice to increase their walking steps are different as shown by the wide confidence interval in SUCCESS study and high standard deviation of up to 4000 steps/day in the reported walking steps in other studies (288). It is therefore possible that the 6 month and 12 month analysis, which will have more data and longer time to reflect the effect of the education, might show the true picture of the intervention effect.

Learning points

The logic for the interim visits and plan for analysis was to see the trend of the change. However in hindsight, three months follow up visit was too soon and led to high missing data. It is however, important to notice that although with significant delays, ultimately 80% of the intervention arm attended the education. This is equal to or higher than similar education interventions in Leicester Diabetes Centre which targeted older population and have a once per year clinical visit (7,285). The combination of 4 clinical visits and a whole day education programme in the context of the busy life of young socially active women (80% employed) might have been too much to ask.

Another learning from the process and return rates of the accelerometers is to either include that attrition rate in the sample size, or consider a measure which will be done within a visit in the department so the dependence on the participants to return is omitted from the process.

9.4.2.3 Patient related factors

9.4.2.3.1 PCOS; a mental challenge

It has been long argued that human beings are resistant to change (302). In women with PCOS there is a huge mental challenge in the background of their

mind (157,162) and the cohort in SUCCESS are not different as presented in Chapter 8.

One third of the SUCCESS cohort reported a history of depression (Chapter 8). Depression and anxiety are shown to be associated with un-healthy behaviour (389,390). Participants in SUCCESS did not feel that they had any personal control over their PCOS (results of the illness perception questionnaire presented in Chapter 8). Changing this belief and creating the sense of personal control over their condition is necessary to reduce the "intention-behaviour gap" (323). This questionnaire will be repeated again at the end of the study to evaluate the effects of the education intervention on illness perception.

Although impossible to make a direct comparison, the mental challenge, anxiety and distress caused by PCOS might be one of the reasons for the difference with PREPARE study (288) in which an older, mixed gender cohort with a different condition were involved (cohort in PREPARE were mixed gender, above 60 years old and at high risk of diabetes).

Although the HRQoL did not improve as a result of SUCCESS education in the three month analysis, all the previously mentioned limitations apply to this analysis as well. There are tools in SUCCESS (e.g; SF-12 questionnaire), which will complement the assessment of HRQoL at the end of the study.

Patients in education arm have requested reminder education session to happen every few month or once a year (there are e-mails and telephone calls as well as feedback after the education day), which may be one way to overcome some of the resistance in behaviour change. Frequent education sessions and reminders might be the reason for success in the previously discussed studies reported by Silva (388) and Clarke (387).

9.4.2.3.2 *Possible impact of dysmenorrhoea:*

Participants in SUCCESS are all women and one of the possible factors interfering with the activity, going out and walking could be the menstruation and the effect of dysmenorrhoea at the time of measurement of the primary outcome

(10 days of the accelerometer data). This is the information which is not directly collected in the SUCCESS-RCT. In each clinic visit, participants are asked to give the number of periods they have had during the last three months, and the date of their last menstrual period (LMP). However, they have not been asked to report whether they had any menstruation during the time they have the accelerometer on. Many of them have oligo/amenorrhoea, which makes it difficult to calculate their expected cycle while they had the monitor on. Dysmenorrhoea can potentially make them reduce activity level.

Dysmenorrhoea can equally happen in both arms of the study. This question can be assessed in the post intervention analysis, when the participants will be contacted to ask their opinion about the education and intervention.

This is also a learning point which can be useful in future planning of the monitoring in this patient group or any other female group.

9.5 Conclusion

The SUCCESS education programme did not increase step count in the three month interim analysis, trends were positive towards an improvement. It is possible that the analysis at three month was premature. The final analysis at 12 month follow up will inform us of the effect of the intervention on the behaviour change, full clinical and metabolic profile and women's perception of their condition. There are lessons to be learned from the process such as incorporation of the return time for the accelerometer into the design, and the missing data into the sample size for the future design of the similar studies.

A qualitative assessment of the participants view on the education and their take up from education has already been considered as part of the project and is the subject for dissertation for one of the MSc students.

The final outcomes of the SUCCESS-RCT will inform other programmes aiming at behavioural change for the cohort of women with PCOS as well as other groups at high risk of diabetes and cardiovascular diseases.

9.6 Summary of Chapter

Background Structured education programmes have proved effective in changing illness perception, increasing physical activity and improving glycaemic indices in people with diabetes or at risk of diabetes. There is a lack of pragmatic education interventions in women with PCOS. The SUCCESS–RCT was designed to test such a programme.

Methods A single centre, two arm, parallel randomised controlled trial with a primary outcome of increasing walking activity by 2000 steps/daily after 12 months following a structured education programme. Secondary outcomes were any improvement in physical activity pattern, glycaemic indices, weight, indices of cardiovascular risk (blood pressure and lipids), and health related quality of life. Per-protocol interim analysis was performed at three month point.

Results 67 out of 78 participants randomised to the control arm attended their three months visit, and 45 out of 84 in the education arm had the intervention before their three months visit. Only 75 out of the 112 participants had the baseline and follow up physical activity data. The SUCCESS education did not have a statistically significant effect on the walking activity, 160.87 (-542.67, 864.40). There were no differences in other indices of physical activity, weight, blood pressure and health related quality of life.

Conclusion Although the SUCCESS education programme did not increase walking steps in the three month interim analysis, the trends were positive towards an improvement. It is possible that the analysis at three month was premature. The final analysis at 12 month follow up will inform us of the ultimate effect of the intervention on the behaviour change, full clinical and metabolic profile and women's perception of their condition.

Chapter 10   : Discussion

Previous chapters were the scientific reports of the stages involved in the development and assessing the feasibility of the SUCCESS education programme.

Chapter 10 summarises all the previous chapters, clarifies my role in each stage, what I learned from this PhD, and also explores the future directions for SUCCESS after completion of this PhD project. Obviously, in all stages of this project I have had the full support and guidance of my supervisors and in each chapter, where necessary, I have described the role of others in that step. All the writings, design and structure of a step in the project have been discussed with the supervisors.

10.1 Introduction

The ultimate aim of this programme of work was to develop an evidence- based structured education programme to promote walking activity and consequently reduce cardiovascular risk in women with PCOS. This was a complex process and multiple steps were needed to make sure the programme is scientific and tailored to the target group. Figure 10.1 is a schematic representation of the multiple steps taken during this PhD project and the corresponding chapters in this thesis.

It was necessary to understand PCOS (Chapter 1), and behaviour of a local cohort of women with PCOS (Chapter 2), review the benefits and the variety of the lifestyle interventions for PCOS (Chapter 3), and understand the principles of structured education (Chapter 4). It was also crucial to listen to the women with PCOS and pilot the education programme with the target group (Chapter 5) before putting it to the test (Chapters 6 to 9).

Figure 10.30 Multiple steps taken to develop an evidence-based structured education programme and the related chapters in this thesis

Committed to Growing International Research, Education & Innovation

Understanding PCOS; epidemiology, and long term health problems

Need for preventive measures

Chapter 1

Understanding the target population: Exploring a local database of women with PCOS, high CV outcomes

Emphasizing the need for prevention

Chapter 2

Randomised Controlled Trial to test the programme

Chapters 6-9

SUCCESS: Evidence based education programme for women with PCOS

Views of the target group: interviews and pilot of the programme

Chapter 5

Lifestyle or Pharmacological interventions: Learning from a systematic review of the literature

Chapter 3

Define the principles and learning theories in a Structured education programme

Chapter4

10.2 Summary of the previous Chapters:

Chapter 1: Polycystic Ovary Syndrome (PCOS)

Aim(s): The aim of this chapter was to set the scene and understand PCOS, its epidemiology, the role of insulin resistance and obesity in the condition and its long term consequences.

Findings: PCOS is a common condition with an underlying insulin resistance. It is commonly associated with obesity and increases the risk of women with PCOS for type 2 diabetes (T2DM), hypertension, dyslipidaemia, cardiovascular diseases, as well as anxiety, depression and lower quality of life.

Strength: This chapter was a comprehensive review of the literature on PCOS emphasizing on its long tern health consequences.

Limitations: Most of the presented studies on the long term health risks associated with PCOS are retrospective observational studies.

My Role: I performed the review.

What I learned: The extent of the condition, the impact of the insulin resistance and many areas in the field which needs further exploration.

Contribution to SUCCESS / Future implications: This review informed the content of the SUCCESS education programme; PCOS stories 1 and 2 (Sessions C and G, SUCCESS curriculum Appendix 4.1) There is a need for well controlled, epidemiological follow up studies in PCOS to understand its long term consequences.

Chapter 2: Phenotypic analysis and cardiovascular outcomes in a multi-ethnic cohort of women with PCOS

Aim(s): Following the literature review, this chapter aimed to analyse a large multi-ethnic database of women with PCOS who had been seen in a local

speciality clinic who would potentially be the target group for the planned education programme. Specific aims of the analysis were to phenotype the local cohort of women with PCOS, understand the effects of ethnicity, weight and age on clinical characteristics of women with PCOS and investigate whether this local cohort had higher rates of diabetes and cardiovascular outcomes as compared to the general female population

Findings: This cohort were very young at their presentation to a speciality clinic, and their clinical and demographic characteristics changed according to their ethnicity, body weight and age at their first clinic presentation. More importantly they had a high age-specific prevalence of T2DM, myocardial infarction, and angina.

Strength: This was a large multi-ethnic local cohort of women with PCOS with over 11000 person year follow up. The results of this chapter, phenotypic and outcome analyses, had great value in informing the content of the education programme. The methodology which was used in the analysis was robust (using the age matched local population and multiple sensitivity analysis).

Limitations: This was a retrospective, observational study with some missing data. It was not possible to account for some of the important cardiovascular risk factors (such as obesity, lipids, and smoking) in the outcome analysis.

My Role: Clearing the database, and reviewing patients' electronic notes, and performing all the analyses.

What I learned: In addition to what I learned from the outcomes and the phenotypic analysis, I learned many statistical methods in this part of the thesis. I had to consider multiple options to approach to the analysis of this database, I attended different courses and statistical seminars, studied multiple references, and had in-depth and lengthy discussions with the statisticians who were involved in this project (Dr Gray, Dr Bodicoat, and Dr Bankart).

Contribution to SUCCESS / Future implications: This chapter informed the content of the SUCCESS education programme. It gave us an understanding of

what combination of signs and symptoms we would expect in our local cohort who would attend the education programme ("Your PCOS Story: session B in SUCCESS curriculum, Appendix 4.1) and also what we needed to consider to emphasize in the; PCOS stories 1 and 2 (Sessions C and G, SUCCESS curriculum Appendix 4.1). For example, this analysis showed a high rate of smoking in the cohort (especially in the white women). It was therefore decided that smoking should be added as a modifiable risk factor in the PCOS Story 2 (page 78, session G, SUCCESS curriculum) and participants' resources (page 9, "My handbook for SUCCESS", Appendix 4). These parts discuss the modifiable risk factors associated with PCOS and although smoking was not directly associated with PCOS, however the high rates of smoking in the group indicated the need to emphasize this.

The reported high rates of cardiovascular outcomes in this analysis emphasize the need for implementation of tailored preventive measures targeting this high risk group.

Chapter 3: Systematic review and meta-analysis

Aim(s): To compare the effects lifestyle and pharmacological treatments (insulin sensitizers and incretin based therapies) on body mass index (BMI).

Findings: There was no significant difference between lifestyle and Metformin, or Metformin and placebo after 6 months of treatment. There was however, a tendency to see more BMI reduction with lifestyle interventions.

Strength: The planned analysis reduced statistical heterogeneity by choosing one time point for analysis (6 month). For the first time all the lifestyle interventions and insulin sensitizers as well as incretin based therapies were compared in a single project.

Limitations: The number of involved studies and participants in each study were low and therefore the meta-analysis did not include a large number of patients. Although statistical heterogeneity was low, but there was a high chance of clinical

heterogeneity considering the wide range of phenotypic diagnosis of PCOS and the starting levels of BMI.

My Role: I wrote the initial draft of the protocol for review, performed the literature search, full text review, data extraction. Although I was involved in the process, the main statistical analysis was performed by statisticians (LG, DB and GC).

What I learned: A personal experience of performing a meta-analysis was extremely useful in view of the important points which need to be considered in the process and later on in critical analysis of the other similar papers.

I also learned the concept of network analysis which is the subject of a collaboration that came out of this PhD project.

Contribution to SUCCESS / Future implications: The results confirmed our previous understanding and added to the evidence to inform the content of the SUCCESS education programme.

The reviewed lifestyle interventions had a completely different approach to what had been planned in the SUCCESS intervention (they had multiple supervised sessions or regular weekly follow ups). The results of the SUCCESS-RCT will therefore contribute significantly to the literature as a new and pragmatic approach.

This meta-analysis became the subject of collaboration with statisticians in the Department of health sciences (University of Leicester) to perform the network analysis (LG, DB). Further analysis of this data as well as the other variables (indices of glycaemic control) using the same methodology will produce valuable information in the field.

Chapter 4 and 5: Rational, structure and development of the SUCCESS education:

Aim(s): Define the underpinning learning theories used in a structured education programme, understand the views of the women with PCOS about their condition and a potential education programme and develop and pilot the programme in the target group.

Findings: Appropriate learning theories were identified for the SUCCESS programme namely; "common sense theory", "social cognitive theory", "implementation intentions" and "dual processing theories". In the interviews, women with PCOS expressed the need for an education programme. The issue of coping with PCOS and body image was revealed and it appeared that some women had very strong feelings resulting from their PCOS.

Findings from the first three chapters, the qualitative interviews and the experience of the team in developing education programmes were put together to write the curriculum for education which was piloted twice and had good feedback from the target group and experts in the field of patient education.

Strength: The SUCCESS education programme was evidence-based and underpinned by learning theories. It was tailored to the expressed needs of the women with PCOS and piloted in two groups.

Limitations: Analysis of the qualitative data were limited, it however was enough for the development of the education programme.

My Role: With support from the experts in the team, I lead the process for development of the education programme and writing the curriculum. I performed 10/12 of the interviews, analysed the interviews and took part in delivering the education intervention.

What I learned: The whole process was full of learning for me; identification of the underpinning theories, training to become an educator in DESMOND and then leading the process of development of the education programme.

Qualitative methods were new to me and I learned the scientific approach to the analysis of the interviews. Through reading and exploring my data, I felt the importance of the qualitative research and the areas which can only be explored through this methods and not quantitative research.

The expressed feeling of the interviewees (women with PCOS) who had such an intense emotion about their condition reminded me to always bear that in mind in

my clinical duties: not only women with PCOS, but any one who steps in to the office.

Contribution to SUCCESS / Future implications: SUCCESS was developed in this phase and further analysis of the interviews planned as a collaboration with qualitative researchers in the Department of Health Sciences at the University of Leicester.

Chapter 6 - 9: A randomised controlled trial to test the efficacy of the education programme

Aim(s): To test whether a structured lifestyle intervention to promote weight loss and increasing walking activity in a self-directed programme result in a behaviour change of increasing step count and consequently affects weight, glucose tolerance, insulin resistance and other metabolic, physical, and mental health aspects in women with PCOS?

Findings: Analysis of the baseline characteristics showed that the SUCCESS cohort were at high risk of cardiovascular disease and emotionally affected by their excess hair and body weight. In an interim three month analysis, the SUCCESS education did not have a statistically significant effect on walking or other indices of physical activity, weight, blood pressure, haemoglobin A1c, and health related quality of life

Strength: This was a randomised controlled trial in a multi-ethnic cohort. Education intervention was well received by the participants and they had left the education with a positive message.

Limitations: The main limitation at this level was the point of analysis (three month) and the missing data which was as result of a multitude of factors; time point of the analysis, design of the follow up appointments, and the collection of the primary outcome data which would depend on the return of the accelerometer by the participants.

My Role: Protocol of the study was written by myself using the present examples in the department and with a benefit from my supervisors' input in the process. I was involved in all the steps of the study afterwards, starting from attending the ethics committee to recruitment, delivering the education intervention and managing the logistics of the study. In the study management (especially personnel management and liaison with the primary care), I benefited from expertise of the management team in the department.

What I learned: The experience of running a clinical trial was full of learning points; from the set up to analysis of the data. Team work, coordination and communication with colleagues and patients were among the other soft skill which I learned or practiced during this project.

As a learning point from whole project, I should add the skill of writing a scientific report to the list.

10.3 Future implications and discussion

The SUCCESS education programme is the first UK trial of a patient centred structured educational programme, underpinned by learning theories and tailored to women with PCOS. The outcomes of this intervention (negative or positive) will therefore have an impact on the future direction of such educational approach to this patient population.

Women with PCOS suffer from a chronic condition which puts them at high risk of diabetes and cardiovascular disease. It is well known that prevention is the best approach to the conditions like diabetes and cardiovascular diseases which have expensive, debilitating and sometimes devastating long term complications (2,391). Evidence shows that introduction of lifestyle interventions in the population at risk of diabetes is the most cost-effective approach in prevention of diabetes (2,392,393). Therefore planning a lifestyle intervention for a high risk population such as women with PCOS is a logical approach.

213

The SUCCESS education programme was structured based on the similar patient centred education programmes, which have been successful in increasing walking steps (288) or weight reduction (296) and illness perception even three years after a single 6 hours education programme (299). Structured education programmes like DESMOND have proved to be extremely cost effective (298) and therefore, pragmatic to implement in the health system (6). Lack of positive outcomes three month following the SUCCESS intervention is therefore, disappointing.

The major difference between SUCCESS and other similar structured education programmes is the target group. The programme followed the same structure and was delivered by the educators who had gone through the same rigorous training programmes. Participants left the education day with positive attitudes and a message to implement the lifestyle change (Chapter 8).

As discussed in Chapter 9, there are multiple issues which could have contributed to these results at this stage including the significant amount of missing data and the emotional impact of PCOS, and early analysis of the results. However, should the final results of study at the end of 12 month follow up show the same pattern, the only way forward is to analyse the possible contributing factors to the negative results.

Interviews have been planned to analyse the views of the participants who attended the education programme and assess how much information they retained 12 months after the intervention. It is important to notice that the cohort in SUCCESS were already more active with less sedentary time than another similarly young and obese cohorts recruited to a separate education intervention in our centre (378). It is therefore possible that the participants, contrary to our expectations, chose to change their food choices after the education session rather than increasing their physical activity. The effect of the education on their food choices will be assessed at the12 month follow up by repeating the DINE questionnaire (356). Detailed analysis of the post intervention interviews, together with the 12 months results will help to evaluate the ultimate effect of the SUCCESS education programme.

Since the register of the SUCCESS study on the American website (Clinical Trials register), there have been one or two patients per week who wished to be involved in the study. Currently a database is formed of patients who would want to be invited to the study should it go to their local area in UK. These patients use the common search engines (Google, or NHS choices) to find "education programme for PCOS" and the first item on their results is SUCCESS study as registered in the clinical trials website [Figure 10.2]. The fact that they search for an education programme and the high rank of the SUCCESS in the UK search engines, which happens as a result of high visit, is an indication for the need of an education programme for this patient group.

Figure 10.11 Caption from Google search (18th November 2013*)
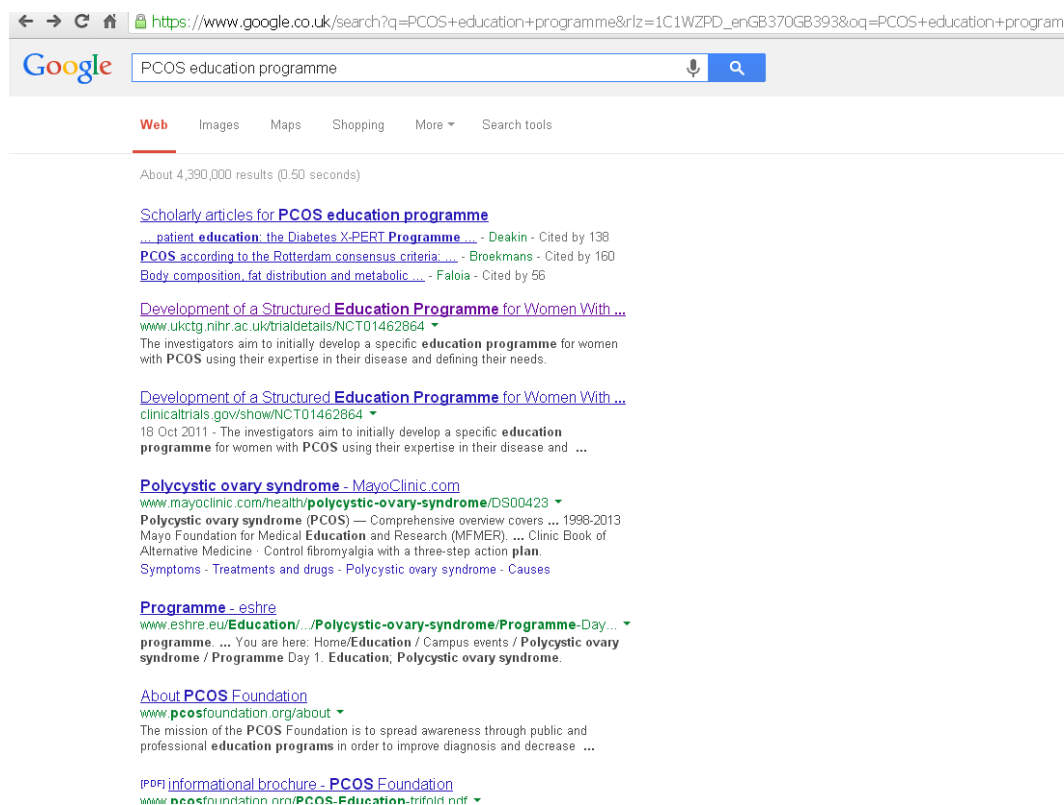
*I did not make a print screen at the time, but in October 2011 SUCCESS was at the bottom of the second page (20th item) and in November 2011 SUCCESS moved to the 7th item on the list.

10.4 In Summary

The original findings from this PhD project were

➢ There are phenotypic differences in women with PCOS of different ethnic origins, or according to their body weight. (Chapter 2)

➢ Women with PCOS have higher age-specific rates of T2DM, or myocardial infarction as compared to age matched general female population. (Chapter 2)

➢ There is no statistical difference between the effect of lifestyle interventions and Metformin on BMI at the six month follow up. (Chapter 3)

➢ Women with PCOS are keen to understand their condition and would like to have a group education programme. (Chapter 5)

➢ There is a significant body image issue (excess weight and hair) associated with this condition which has emotional impact on the patients. They had anger, felt unfeminine, and infertile. They however, felt "relief" after they were told about their condition. This was due to their long struggle to explain their condition. (Chapter 5 and 8)

➢ Obese and overweight women with PCOS have a high concentration of cardiovascular risk factors which can potentially increase their chances of cardiovascular disease. (Chapter 7)

➢ A structured education programme developed for women with PCOS, did not increase their walking steps or improve their weight, HbA1c and health related quality of life in a three month interim analysis. (Chapter 9)

Further research originated from this project

❖ Network analysis for the best treatment approach to improve BMI, indices of glycaemic control, and insulin resistance in women with PCOS comparing the insulin sensitizers, incretin based therapies, and lifestyle interventions.

❖ Further analysis of the qualitative interviews in this project in search of the emerging themes such as ethnic differences; ethical approval is already in place to conduct more interviews.

- ❖ Qualitative interviews with participants who attended the education programme to understand their attitudes to the programme, and what they gained form the programme.

- ❖ A systematic review of the "stigma and body image issues in women with PCOS"

- ❖ Similar robust statistical methods, which were used in the analysis of the cardiovascular outcomes in women with PCOS, can be applied to other chronic conditions which are registered in the same database. Ethical approval is already in place for this project.

- ❖ Final analysis of the SUCCESS-RCT will eventually lead us to the next step

10.5 Conclusion

Polycystic ovary syndrome is a common chronic condition with a multiple long term health risks. There is a need for a pragmatic education interventions for these women. The SUCCESS structured education programme was thought to be the answer to this need; it however, did not show positive results at the three month interim analysis.

The story of SUCCESS should not end here and at this point; further analysis of the results at the 12 months follow up is required for a full assessment. Positive results at the end of the study will be an indication for a bigger study involving multiple centres to evaluate its feasibility in the wider population, and finally planning for implementation in the health system. In case of negative results, the reasons for failure will be addressed and more robust intervention will have to be planned.

SUCCESS came from my heart: an after note to the thesis (and a note to the patients who may read this work)

During the course of this project I had four operations to control my eye pressure. No one knew why it happened or why it was resistant to medications and even operations. They finally put a valve, a tube and a bag in my eye which controlled the pressure, but left me with some unusual and unexplainable symptoms and only 10% sight in that eye.

I obviously spent a lot of time with my "patient hat" on, and asked a lot of questions from my consultants and I know that they did their best in the context of the time and my background to answer them. However, there were occasions when things were really frustrating. Fed up with my symptoms, I would need someone just a professional whom I could trust to explain to me what was happening and "what next"! I know, I was a very privileged patient; I could e-mail or text my consultant (a power which every time I used it, I ended up on the operation table!). Despite all this, I am still in a "what next?" state.

Therefore, I had complete sympathy with one of the patients in the education group who said: "*Obviously if patients understood their condition they would do their best to manage it in a more effective way. Why do you need to prove that? It is their body, it is their disease and surely by knowing more about it, they will try to manage it better. What is there to prove?*"

I guess, I know why:

Let me quote a paragraph from "Little Prince" (Antoine de Saint-Exupery, 1943)

If you tell grown-ups, "I saw a beautiful red brick house, with geraniums at the windows and doves on the roof…," they won't be able to imagine such a house. You have to tell them, "I saw a house worth 100,000 francs." Then they exclaim: "What a pretty house!"
[Translated by Richard Howard]

The situation is almost the same here; if I told others "I have developed an education programme for women with PCOS which has made them happy and has increased their self-confidence and they enjoyed it and all of them would like to come back and have another session" … they would immediately ask "what effect does it have on their cardiovascular outcomes? Is it cost-effective? How did you measure their happiness? Etc…" These are very valid scientific questions but at times it is really difficult to see through the patients' eye. Whatever tool we use, we may not be able to capture some of the effects of an education programme. What patients take home from an education programme is a personalized message for them.

I should refer to a an old text to explain this; almost 900 years ago a great Iranian philosopher described the "Truth of Poetry"

Think of a poem as a mirror
For a mirror has no face of its own
Whom he looks in one
He can see a face; his own

And think that a poem
Has no meaning in itself
For what one will see
Is what life has dealt him,
And how he has perfected himself

And if you say:
"The meaning of a poem is what the poet intended
And others are wrong when
They perceive it, how they will"

That is as though one would say that:
"The face of a mirror
Is the face of the craftsman
That did create it"   ***Einolqozat Hamedani***[6]

---

[6] Translated by one of the Medical Students in Leicester University: Mrs M. Yadegarfar and revised by myself.

The SUCCESS education programme and indeed any patient education, is in a way like a "poem" or a "mirror". What a patient can potentially get from this education programme depends on how they see themselves in the context of, and the interactions within the programme.

The priorities of women attending the SUCCESS education programme were different; their worries, their knowledge of the condition, and their background lifestyle were different and therefore they would leave the room with a message which was important to them. It might not have been the message we intended, but it did not matter as long as they gained something from the day and as long as they left the group in a positive way. The anonymous feedback from the education indicates that majority of them did. Maybe it was a SUCCESSful programme after all.

However, we shall have to wait and see the behavioural change and cardiovascular outcomes to be able to claim full SUCCESS.

Hamid Mani

December 2013

Bibliography

(1) Tsao CW, Vasan RS. Diagnosis: Biomarkers of cardiovascular outcomes-bonanza or bias? Nat Rev Endocrinol 2013 May 21;9(7):381-382.

(2) NICE P. Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. 2012(http://publications.nice.org.uk/preventing-type-2-diabetes-risk-identification-and-interventions-for-individuals-at-high-risk-ph38/introduction-scope-and-purpose-of-this-guidance).

(3) NICE P. **The most appropriate means of generic and specific interventions to support attitude and behaviour change at population and community levels**. NICE DSU 2007 2007;6(http://www.nice.org.uk/ph6).

(4) Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012 Jan;97(1):28-38.e25.

(5) Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009 Feb;91(2):456-488.

(6) DESMOND. **Walking Away from Diabetes**. June 2013; Available at: http://www.desmond-project.org.uk/walkingaway-280.html. Accessed 17/06, 2013.

(7) Yates T, Davies MJ, Henson J, Troughton J, Edwardson C, Gray LJ, et al. Walking away from type 2 diabetes: trial protocol of a cluster randomised controlled trial evaluating a structured education programme in those at high risk of developing type 2 diabetes. BMC Fam Pract 2012 May 29;13:46-2296-13-46.

(8) Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2011 Jul 6;(7):CD007506. doi(7):CD007506.

(9) Barry JA, Kuczmierczyk AR, Hardiman PJ. Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2011 Sep;26(9):2442-2451.

(10) WHO. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications Report of a WHO Consultation Part 1: Diagnosis and Classification of Diabetes Mellitus. 1999;WHO/NCD/NCS/99.2:https://dl-web.dropbox.com/get/Flash/Avni/WHO%201999.pdf?w=eafbd7d6.

(11) de Groot PCM, Dekkers OM, Romijn JA, Dieben SWM, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. Human Reproduction Update 2011; 17; 495-500 .

(12) Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Rev 2013 Feb;14(2):95-109.

(13) Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2010 Jul-Aug;16(4):347-363.

(14) National Institute of Health. Evidence-based Methodology Workshop on Polycystic Ovary Syndrome, 3–5 December 2012. 2012 2012(http://prevention.nih.gov/workshops/2012/pcos/docs/PCOS_Final_Statement.pdf).

(15) Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 2010 May;95(5):2038-2049.

(16) Randeva HS, Tan BK, Weickert MO, Lois K, Nestler JE, Sattar N, et al. Cardiometabolic aspects of the polycystic ovary syndrome. Endocr Rev 2012 Oct;33(5):812-841.

(17) Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012 Dec;33(6):981-1030.

(18) Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2012 Nov-Dec;18(6):618-637.

(19) Toulis KA, Goulis DG, Mintziori G, Kintiraki E, Eukarpidis E, Mouratoglou SA, et al. Meta-analysis of cardiovascular disease risk markers in women with polycystic ovary syndrome. Hum Reprod Update 2011 Nov-Dec;17(6):741-760.

(20) Baranova A, Tran TP, Birerdinc A, Younossi ZM. Systematic review: association of polycystic ovary syndrome with metabolic syndrome and non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2011 Apr;33(7):801-814.

(21) Azziz R, Marin C, Hoq L, Badamgarav E, Song P. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrinol Metab 2005 Aug;90(8):4650-4658.

(22) Hanson AE. Hippocrates: Diseases of Women1. Signs: Journal of Women in Culture and Society 1975;1(2):567-584.

(23) Rokitanski C. A manual of pathological anatomy. Philadelphia, PA: Blanchard & Lea; 1855.

(24) Achard EC, Thiers J. Le virilisme et son association a`l'insuffisance glycolytique (diabe`te des femmes a` barbe). Bull Acad Natl Med (Paris) 1921;86:51-66.

(25) Stein I, Leventhal M. Amenorrhea associated with bilaterl polycystic ovaries. Am J Obstet Gynecol 1935;29:181-185.

(26) Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome; towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, editors. Polycystic Ovary Syndrome Boston MA: Blackwell Scientific Publications; 1992. p. 377-384.

(27) Rotterdam G. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004 Jan;19(1):41-47.

(28) Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998 Sep;83(9):3078-3082.

(29) March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010 Feb;25(2):544-551.

(30) Tehrani FR, Rashidi H, Azizi F. The prevalence of idiopathic hirsutism and polycystic ovary syndrome in the Tehran Lipid and Glucose Study. Reprod Biol Endocrinol 2011 Nov 1;9:144-7827-9-144.

(31) Tehrani FR, Simbar M, Tohidi M, Hosseinpanah F, Azizi F. The prevalence of polycystic ovary syndrome in a community sample of Iranian population: Iranian PCOS prevalence study. Reprod Biol Endocrinol 2011 Mar 25;9:39-7827-9-39.

(32) Kumarapeli V, Seneviratne Rde A, Wijeyaratne CN, Yapa RM, Dodampahala SH. A simple screening approach for assessing community prevalence and phenotype of polycystic ovary syndrome in a semi-urban population in Sri Lanka. Am J Epidemiol 2008 Aug 1;168(3):321-328.

(33) Okoroh EM, Hooper WC, Atrash HK, Yusuf HR, Boulet SL. Prevalence of polycystic ovary syndrome among the privately insured, United States, 2003-2008. Am J Obstet Gynecol 2012 Oct;207(4):299.e1-299.e7.

(34) Michelmore KF, Balen AH, Dunger DB, Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. Clin Endocrinol (Oxf) 1999 Dec;51(6):779-786.

(35) Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 2000 Jul;85(7):2434-2438.

(36) Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004 Jun;89(6):2745-2749.

(37) Chen X, Yang D, Mo Y, Li L, Chen Y, Huang Y. Prevalence of polycystic ovary syndrome in unselected women from southern China. Eur J Obstet Gynecol Reprod Biol 2008 Jul;139(1):59-64.

(38) Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandra FA, Tsianateli TC, Spina GG, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab 1999 Nov;84(11):4006-4011.

(39) Gabrielli L, Aquino EM. Polycystic ovary syndrome in Salvador, Brazil: a prevalence study in primary healthcare. Reprod Biol Endocrinol 2012 Nov 22;10:96-7827-10-96.

(40) Lindholm A, Andersson L, Eliasson M, Bixo M, Sundstrom-Poromaa I. Prevalence of symptoms associated with polycystic ovary syndrome. Int J Gynaecol Obstet 2008 Jul;102(1):39-43.

(41) Moran C, Tena G, Moran S, Ruiz P, Reyna R, Duque X. Prevalence of polycystic ovary syndrome and related disorders in mexican women. Gynecol Obstet Invest 2010;69(4):274-280.

(42) Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R. Prevalence of polycystic ovarian syndrome in Indian adolescents. J Pediatr Adolesc Gynecol 2011 Aug;24(4):223-227.

(43) Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 2004 Oct;18(5):671-683.

(44) Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 2012 Mar-Apr;18(2):146-170.

(45) Wijeyaratne CN, Balen AH, Barth JH, Belchetz PE. Clinical manifestations and insulin resistance (IR) in polycystic ovary syndrome (PCOS) among South Asians and Caucasians: is there a difference? Clin Endocrinol (Oxf) 2002 Sep;57(3):343-350.

(46) Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA. Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome? Am J Obstet Gynecol 1992 Dec;167(6):1807-1812.

(47) Tena G, Moran C, Romero R, Moran S. Ovarian morphology and endocrine function in polycystic ovary syndrome. Arch Gynecol Obstet 2011 Dec;284(6):1443-1448.

(48) Polson DW, Adams J, Wadsworth J, Franks S. Polycystic ovaries--a common finding in normal women. Lancet 1988 Apr 16;1(8590):870-872.

(49) Rodin DA, Bano G, Bland JM, Taylor K, Nussey SS. Polycystic ovaries and associated metabolic abnormalities in Indian subcontinent Asian women. Clin Endocrinol (Oxf) 1998 Jul;49(1):91-99.

(50) Alsamarai S, Adams JM, Murphy MK, Post MD, Hayden DL, Hall JE, et al. Criteria for polycystic ovarian morphology in polycystic ovary syndrome as a function of age. J Clin Endocrinol Metab 2009 Dec;94(12):4961-4970.

(51) Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 2011 Apr;7(4):219-231.

(52) Abbott DH, Tarantal AF, Dumesic DA. Fetal, infant, adolescent and adult phenotypes of polycystic ovary syndrome in prenatally androgenized female rhesus monkeys. Am J Primatol 2009 Sep;71(9):776-784.

(53) Dumesic DA, Abbott DH, Padmanabhan V. Polycystic ovary syndrome and its developmental origins. Rev Endocr Metab Disord 2007 Jun;8(2):127-141.

(54) Pauli JM, Raja-Khan N, Wu X, Legro RS. Current perspectives of insulin resistance and polycystic ovary syndrome. Diabet Med 2011 Dec;28(12):1445-1454.

(55) Franks S, Berga SL. Does PCOS have developmental origins? Fertil Steril 2012 Jan;97(1):2-6.

(56) Leibel NI, Baumann EE, Kocherginsky M, Rosenfield RL. Relationship of adolescent polycystic ovary syndrome to parental metabolic syndrome. J Clin Endocrinol Metab 2006 Apr;91(4):1275-1283.

(57) Lunde O, Magnus P, Sandvik L, Hoglo S. Familial clustering in the polycystic ovarian syndrome. Gynecol Obstet Invest 1989;28(1):23-30.

(58) Zhang T, Liang W, Fang M, Yu J, Ni Y, Li Z. Association of the CAG repeat polymorphisms in androgen receptor gene with polycystic ovary syndrome: A systemic review and meta-analysis. Gene 2013 25;524(2):161-7.

(59) Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab 1980 Jan;50(1):113-116.

(60) Wijeyaratne CN, Seneviratne Rde A, Dahanayake S, Kumarapeli V, Palipane E, Kuruppu N, et al. Phenotype and metabolic profile of South Asian women with polycystic ovary syndrome (PCOS): results of a large database from a specialist Endocrine Clinic. Hum Reprod 2011 Jan;26(1):202-213.

(61) Welt CK, Gudmundsson JA, Arason G, Adams J, Palsdottir H, Gudlaugsdottir G, et al. Characterizing discrete subsets of polycystic ovary syndrome as defined by the Rotterdam criteria: the impact of weight on phenotype and metabolic features. J Clin Endocrinol Metab 2006 Dec;91(12):4842-4848.

(62) Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. Hum Reprod 2013 Mar;28(3):777-784.

(63) Ehrmann DA, Kasza K, Azziz R, Legro RS, Ghazzi MN, PCOS/Troglitazone Study Group. Effects of race and family history of type 2 diabetes on metabolic status of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005 Jan;90(1):66-71.

(64) Moghetti P, Tosi F, Bonin C, Di Sarra D, Fiers T, Kaufman JM, et al. Divergences in Insulin Resistance Between the Different Phenotypes of the Polycystic Ovary Syndrome. J Clin Endocrinol Metab 2013 98(4):E628-37.

(65) Barber TM, Wass JA, McCarthy MI, Franks S. Metabolic characteristics of women with polycystic ovaries and oligo-amenorrhoea but normal androgen levels: implications for the management of polycystic ovary syndrome. Clin Endocrinol (Oxf) 2007 Apr;66(4):513-517.

(66) Dunaif A, Graf M. Insulin administration alters gonadal steroid metabolism independent of changes in gonadotropin secretion in insulin-resistant women with the polycystic ovary syndrome. J Clin Invest 1989 Jan;83(1):23-29.

(67) Tosi F, Negri C, Perrone F, Dorizzi R, Castello R, Bonora E, et al. Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2012 May;97(5):1712-1719.

(68) Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005 24 Mar 2005;352(12):1223-12361277.

(69) Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW, Ryan KJ. Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. J Clin Endocrinol Metab 1986 May;62(5):904-910.

(70) Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab 1991 Jan;72(1):83-89.

(71) Plymate SR, Jones RE, Matej LA, Friedl KE. Regulation of sex hormone binding globulin (SHBG) production in Hep G2 cells by insulin. Steroids 1988 Oct;52(4):339-340.

(72) Chang RJ. The reproductive phenotype in polycystic ovary syndrome. Nat Clin Pract Endocrinol Metab 2007 Oct;3(10):688-695.

(73) Ciaraldi TP, Aroda V, Mudaliar S, Chang RJ, Henry RR. Polycystic ovary syndrome is associated with tissue-specific differences in insulin resistance. J Clin Endocrinol Metab 2009 Jan;94(1):157-163.

(74) Holte J, Bergh T, Berne C, Berglund L, Lithell H. Enhanced early insulin response to glucose in relation to insulin resistance in women with polycystic ovary syndrome and normal glucose tolerance. J Clin Endocrinol Metab 1994 May;78(5):1052-1058.

(75) Dunaif A, Wu X, Lee A, Diamanti-Kandarakis E. Defects in insulin receptor signaling in vivo in the polycystic ovary syndrome (PCOS). Am J Physiol Endocrinol Metab 2001 Aug;281(2):E392-9.

(76) Dunaif A, Xia J, Book CB, Schenker E, Tang Z. Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycystic ovary syndrome. J Clin Invest 1995 Aug;96(2):801-810.

(77) Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Tapanainen JS. Insulin sensitivity, insulin secretion, and metabolic and hormonal parameters in healthy women and women with polycystic ovarian syndrome. Hum Reprod 2000 Jun;15(6):1266-1274.

(78) Ciaraldi TP, el-Roeiy A, Madar Z, Reichart D, Olefsky JM, Yen SS. Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. J Clin Endocrinol Metab 1992 Aug;75(2):577-583.

(79) Dunaif A, Finegood DT. Beta-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. J Clin Endocrinol Metab 1996 Mar;81(3):942-947.

(80) Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL, Polonsky KS. Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. J Clin Invest 1995 Jul;96(1):520-527.

(81) DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril 2005 May;83(5):1454-1460.

(82) Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999 Jan;84(1):165-169.

(83) Basu R, Barosa C, Jones J, Dube S, Carter R, Basu A, et al. Pathogenesis of prediabetes: role of the liver in isolated fasting hyperglycemia and combined fasting and postprandial hyperglycemia. J Clin Endocrinol Metab 2013 Mar;98(3):E409-17.

(84) Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome--a position statement of the Androgen Excess Society. J Clin Endocrinol Metab 2007 Dec;92(12):4546-4556.

(85) Tao M, Zhou J, Zhu J, Lu W, Jia W. Continuous glucose monitoring reveals abnormal features of postprandial glycemic excursions in women with polycystic ovarian syndrome. Postgrad Med 2011 Mar;123(2):185-190.

(86) Elting MW, Korsen TJ, Rekers-Mombarg LT, Schoemaker J. Women with polycystic ovary syndrome gain regular menstrual cycles when ageing. Hum Reprod 2000 Jan;15(1):24-28.

(87) Carmina E, Campagna AM, Lobo RA. A 20-year follow-up of young women with polycystic ovary syndrome. Obstet Gynecol 2012 Feb;119(2 Pt 1):263-269.

(88) Jones GL, Hall JM, Balen AH, Ledger WL. Health-related quality of life measurement in women with polycystic ovary syndrome: A systematic review. Hum Reprod Update 2008 Jan 2008;14(1):15-25.

(89) Dokras A, Clifton S, Futterweit W, Wild R. Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril 2012 Jan;97(1):225-30.e2.

(90) Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. Obstet Gynecol 2011 Jan;117(1):145-152.

(91) Fauser BC, Bouchard P. Uncertainty remains in women with PCOS regarding the increased incidence of cardiovascular disease later in life, despite the indisputable presence of multiple cardiovascular risk factors at a young age. J Clin Endocrinol Metab 2011 Dec;96(12):3675-3677.

(92) Ching HL, Burke V, Stuckey BG. Quality of life and psychological morbidity in women with polycystic ovary syndrome: body mass index, age and the

provision of patient information are significant modifiers. Clin Endocrinol (Oxf) 2007 Mar;66(3):373-379.

(93) Glueck CJ, Dharashivkar S, Wang P, Zhu B, Gartside PS, Tracy T, et al. Obesity and extreme obesity, manifest by ages 20-24 years, continuing through 32-41 years in women, should alert physicians to the diagnostic likelihood of polycystic ovary syndrome as a reversible underlying endocrinopathy. Eur J Obstet Gynecol Reprod Biol 2005 Oct 1;122(2):206-212.

(94) Chen X, Ni R, Mo Y, Li L, Yang D. Appropriate BMI levels for PCOS patients in Southern China. Hum Reprod 2010 May;25(5):1295-1302.

(95) Zhao X, Zhong J, Mo Y, Chen X, Chen Y, Yang D. Association of biochemical hyperandrogenism with type 2 diabetes and obesity in Chinese women with polycystic ovary syndrome. Int J Gynaecol Obstet 2010 Feb;108(2):148-151.

(96) Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006 Dec 14;444(7121):840-846.

(97) Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999 Jan;22(1):141-146.

(98) Elting MW, Korsen TJ, Bezemer PD, Schoemaker J. Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. Hum Reprod 2001 Mar;16(3):556-560.

(99) Gambineri A, Patton L, Altieri P, Pagotto U, Pizzi C, Manzoli L, et al. Polycystic ovary syndrome is a risk factor for type 2 diabetes: results from a long-term prospective study. Diabetes 2012 Sep;61(9):2369-2374.

(100) Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. Clin Endocrinol (Oxf) 2000 May;52(5):595-600.

(101) Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH, Jacobs HS. Mortality of women with polycystic ovary syndrome at long-term follow-up. J Clin Epidemiol 1998 Jul;51(7):581-586.

(102) Dahlgren E, Johansson S, Lindstedt G, Knutsson F, Oden A, Janson PO, et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertil Steril 1992 Mar;57(3):505-513.

(103) Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. J Clin Endocrinol Metab 2006 Feb;91(2):492-497.

(104) Palmert MR, Gordon CM, Kartashov AI, Legro RS, Emans SJ, Dunaif A. Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. J Clin Endocrinol Metab 2002 Mar;87(3):1017-1023.

(105) Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 2006 Nov-Dec;12(6):673-683.

(106) Roos N, Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. BMJ 2011 Oct 13;343:d6309.

(107) Palomba S, Falbo A, Russo T, Rivoli L, Orio M, Cosco AG, et al. The risk of a persistent glucose metabolism impairment after gestational diabetes mellitus is increased in patients with polycystic ovary syndrome. Diabetes Care 2012 Apr;35(4):861-867.

(108) Hudecova M, Holte J, Olovsson M, Larsson A, Berne C, Poromaa IS. Diabetes and impaired glucose tolerance in patients with polycystic ovary syndrome--a long term follow-up. Hum Reprod 2011 Jun;26(6):1462-1468.

(109) Pesant MH, Baillargeon JP. Clinically useful predictors of conversion to abnormal glucose tolerance in women with polycystic ovary syndrome. Fertil Steril 2011 Jan;95(1):210-215.

(110) Legro RS, Gnatuk CL, Kunselman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab 2005 Jun;90(6):3236-3242.

(111) Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod 2001 Sep;16(9):1995-1998.

(112) Rasmussen SS, Glumer C, Sandbaek A, Lauritzen T, Borch-Johnsen K. Determinants of progression from impaired fasting glucose and impaired glucose tolerance to diabetes in a high-risk screened population: 3 year follow-up in the ADDITION study, Denmark. Diabetologia 2008 Feb;51(2):249-257.

(113) Shaw JE, Zimmet PZ, de Courten M, Dowse GK, Chitson P, Gareeboo H, et al. Impaired fasting glucose or impaired glucose tolerance. What best predicts future diabetes in Mauritius? Diabetes Care 1999 Mar;22(3):399-402.

(114) Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract 2007 Dec;78(3):305-312.

(115) Kelly CJ, Speirs A, Gould GW, Petrie JR, Lyall H, Connell JM. Altered vascular function in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2002 Feb;87(2):742-746.

(116) Paradisi G, Steinberg HO, Hempfling A, Cronin J, Hook G, Shepard MK, et al. Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation 2001 Mar 13;103(10):1410-1415.

(117) Diamanti-Kandarakis E, Spina G, Kouli C, Migdalis I. Increased endothelin-1 levels in women with polycystic ovary syndrome and the beneficial effect of metformin therapy. J Clin Endocrinol Metab 2001 2001;86(10):4666-4673.

(118) Holte J, Gennarelli G, Berne C, Bergh T, Lithell H. Elevated ambulatory day-time blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? Hum Reprod 1996 Jan;11(1):23-28.

(119) Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. Metabolism 2003 Jul;52(7):908-915.

(120) Zimmermann S, Phillips RA, Dunaif A, Finegood DT, Wilkenfeld C, Ardeljan M, et al. Polycystic ovary syndrome: lack of hypertension despite profound insulin resistance. J Clin Endocrinol Metab 1992 Aug;75(2):508-513.

(121) Cibula D, Cifkova R, Fanta M, Poledne R, Zivny J, Skibova J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. Hum Reprod 2000 Apr;15(4):785-789.

(122) Elting MW, Korsen TJM, Schoemaker J. Obesity, rather than menstrual cycle pattern or follicle cohort size, determines hyperinsulinaemia, dyslipidaemia and hypertension in ageing women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2001 2001;55(6):767-776.

(123) Glueck CJ, Morrison JA, Goldenberg N, Wang P. Coronary heart disease risk factors in adult premenopausal white women with polycystic ovary syndrome compared with a healthy female population. Metabolism 2009 May;58(5):714-721.

(124) Hoffman LK, Ehrmann DA. Cardiometabolic features of polycystic ovary syndrome. Nature Clinical Practice Endocrinology and Metabolism 2008 Apr 2008;4(4):215-222.

(125) Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 2001 Dec 1;111(8):607-613.

(126) Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril 2011 Mar 1;95(3):1073-9.e1-11.

(127) Talbott E, Guzick D, Clerici A, Berga S, Detre K, Weimer K, et al. Coronary heart disease risk factors in women with polycystic ovary syndrome. Arteriosclerosis, Thrombosis & Vascular Biology 1995 Jul;15(7):821-826.

(128) Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K, et al. Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: Results of a case-control study. J Clin Epidemiol 1998 May 1998;51(5):415-422.

(129) Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 2010 May;95(5):2038-2049.

(130) Solomon CG, Hu FB, Dunaif A, Rich-Edwards JE, Stampfer MJ, Willett WC, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. J Clin Endocrinol Metab 2002 May;87(5):2013-2017.

(131) Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health--National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. J Clin Endocrinol Metab 2008 Apr;93(4):1276-1284.

(132) Chang AY, Ayers C, Minhajuddin A, Jain T, Nurenberg P, de Lemos JA, et al. Polycystic ovarian syndrome and subclinical atherosclerosis among women of reproductive age in the Dallas heart study. Clin Endocrinol (Oxf) 2011 Jan;74(1):89-96.

(133) Iftikhar S, Collazo-Clavell ML, Roger VL, St Sauver J, Brown RD,Jr, Cha S, et al. Risk of cardiovascular events in patients with polycystic ovary syndrome. Neth J Med 2012 Mar;70(2):74-80.

(134) Schmidt J, Landin-Wilhelmsen K, Brannstrom M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metab 2011 Dec;96(12):3794-3803.

(135) Talbott EO, Zborowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzick DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004 Nov;89(11):5454-5461.

(136) Shroff R, Kerchner A, Maifeld M, Van Beek EJ, Jagasia D, Dokras A. Young obese women with polycystic ovary syndrome have evidence of early coronary atherosclerosis. J Clin Endocrinol Metab 2007 Dec;92(12):4609-4614.

(137) Orio F,Jr, Palomba S, Cascella T, De Simone B, Di Biase S, Russo T, et al. Early impairment of endothelial structure and function in young normal-weight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004 Sep;89(9):4588-4593.

(138) Pamuk BO, Torun AN, Kulaksizoglu M, Ertugrul D, Ciftci O, Kulaksizoglu S, et al. Asymmetric dimethylarginine levels and carotid intima-media thickness in obese patients with polycystic ovary syndrome and their relationship to metabolic parameters. Fertil Steril 2010 Mar 1;93(4):1227-1233.

(139) Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab 2001 Feb;86(2):517-520.

(140) Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 2001 Mar;86(3):1175-1180.

(141) Nitsche K, Ehrmann DA. Obstructive sleep apnea and metabolic dysfunction in polycystic ovary syndrome. Best Pract Res Clin Endocrinol Metab 2010 Oct;24(5):717-730.

(142) Yee B, Liu P, Phillips C, Grunstein R. Neuroendocrine changes in sleep apnea. Curr Opin Pulm Med 2004 Nov;10(6):475-481.

(143) Driver HS, McLean H, Kumar DV, Farr N, Day AG, Fitzpatrick MF. The influence of the menstrual cycle on upper airway resistance and breathing during sleep. Sleep 2005 Apr;28(4):449-456.

(144) Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. J Appl Physiol 1998 Mar;84(3):1055-1062.

(145) Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2008 Oct;93(10):3878-3884.

(146) Tasali E, Chapotot F, Leproult R, Whitmore H, Ehrmann DA. Treatment of obstructive sleep apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 2011 Feb;96(2):365-374.

(147) Williams KH, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and nonalcoholic Fatty liver disease: a pathogenic duo. Endocr Rev 2013 Feb;34(1):84-129.

(148) Gambarin-Gelwan M, Kinkhabwala SV, Schiano TD, Bodian C, Yeh HC, Futterweit W. Prevalence of nonalcoholic fatty liver disease in women with polycystic ovary syndrome. Clin Gastroenterol Hepatol 2007 Apr;5(4):496-501.

(149) Cerda C, Perez-Ayuso RM, Riquelme A, Soza A, Villaseca P, Sir-Petermann T, et al. Nonalcoholic fatty liver disease in women with polycystic ovary syndrome. J Hepatol 2007 Sep;47(3):412-417.

(150) Setji TL, Holland ND, Sanders LL, Pereira KC, Diehl AM, Brown AJ. Nonalcoholic steatohepatitis and nonalcoholic Fatty liver disease in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006 May;91(5):1741-1747.

(151) Brzozowska MM, Ostapowicz G, Weltman MD. An association between non-alcoholic fatty liver disease and polycystic ovarian syndrome. J Gastroenterol Hepatol 2009 Feb;24(2):243-247.

(152) Barfield E, Liu YH, Kessler M, Pawelczak M, David R, Shah B. The prevalence of abnormal liver enzymes and metabolic syndrome in obese adolescent females with polycystic ovary syndrome. J Pediatr Adolesc Gynecol 2009 Oct;22(5):318-322.

(153) Markou A, Androulakis II, Mourmouris C, Tsikkini A, Samara C, Sougioultzis S, et al. Hepatic steatosis in young lean insulin resistant women with polycystic ovary syndrome. Fertil Steril 2010 Mar 1;93(4):1220-1226.

(154) Coffey S, Bano G, Mason HD. Health-related quality of life in women with polycystic ovary syndrome: a comparison with the general population using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) and the Short Form-36 (SF-36). Gynecol Endocrinol 2006 Feb;22(2):80-86.

(155) Jones GL, Palep-Singh M, Ledger WL, Balen AH, Jenkinson C, Campbell MJ, et al. Do South Asian women with PCOS have poorer health-related quality of life than Caucasian women with PCOS? A comparative cross-sectional study. Health Qual Life Outcomes 2010 Dec 20;8:149-7525-8-149.

(156) Kumarapeli V, Seneviratne Rde A, Wijeyaratne C. Health-related quality of life and psychological distress in polycystic ovary syndrome: a hidden facet in South Asian women. BJOG 2011 Feb;118(3):319-328.

(157) Snyder BS. The lived experience of women diagnosed with polycystic ovary syndrome. J Obstet Gynecol Neonatal Nurs 2006 May-Jun;35(3):385-392.

(158) Kitzinger C, Willmott J. 'The thief of womanhood': women's experience of polycystic ovarian syndrome. Soc Sci Med 2002 Feb;54(3):349-361.

(159) Kowalczyk R, Skrzypulec V, Lew-Starowicz Z, Nowosielski K, Grabski B, Merk W. Psychological gender of patients with polycystic ovary syndrome. Acta Obstet Gynecol Scand 2012 Jun;91(6):710-714.

(160) Dowdy D. Emotional needs of teens with polycystic ovary syndrome. J Pediatr Nurs 2012 Feb;27(1):55-64.

(161) Jedel E, Waern M, Gustafson D, Landen M, Eriksson E, Holm G, et al. Anxiety and depression symptoms in women with polycystic ovary syndrome compared with controls matched for body mass index. Human Reproduction 2010 Feb;25(2):450-456.

(162) Deeks AA, Gibson-Helm ME, Paul E, Teede HJ. Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? Hum Reprod 2011 Jun;26(6):1399-1407.

(163) Rassi A, Veras AB, dos Reis M, Pastore DL, Bruno LM, Bruno RV, et al. Prevalence of psychiatric disorders in patients with polycystic ovary syndrome. Compr Psychiatry 2010 Nov-Dec;51(6):599-602.

(164) Veltman-Verhulst SM, Boivin J, Eijkemans MJ, Fauser BJ. Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies. Hum Reprod Update 2012 Nov-Dec;18(6):638-651.

(165) Livadas S, Chaskou S, Kandaraki AA, Skourletos G, Economou F, Christou M, et al. Anxiety is associated with hormonal and metabolic profile in women with polycystic ovarian syndrome. Clin Endocrinol (Oxf) 2011 Nov;75(5):698-703.

(166) Pastore LM, Patrie JT, Morris WL, Dalal P, Bray MJ. Depression symptoms and body dissatisfaction association among polycystic ovary syndrome women. J Psychosom Res 2011 Oct;71(4):270-276.

(167) Coulam CB, Annegers JF, Kranz JS. Chronic anovulation syndrome and associated neoplasia. Obstet Gynecol 1983 Apr;61(4):403-407.

(168) Chittenden BG, Fullerton G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed Online 2009 Sep;19(3):398-405.

(169) McGowan L, Parent L, Lednar W, Norris HJ. The woman at risk for developing ovarian cancer. Gynecol Oncol 1979 Jun;7(3):325-344.

(170) Schildkraut JM, Schwingl PJ, Bastos E, Evanoff A, Hughes C. Epithelial ovarian cancer risk among women with polycystic ovary syndrome. Obstet Gynecol 1996 Oct;88(4 Pt 1):554-559.

(171) Pasquali R, Stener-Victorin E, Yildiz BO, Duleba AJ, Hoeger K, Mason H, et al. PCOS Forum: research in polycystic ovary syndrome today and tomorrow. Clin Endocrinol (Oxf) 2011 Apr;74(4):424-433.

(172) Welt CK, Arason G, Gudmundsson JA, Adams J, Palsdottir H, Gudlaugsdottir G, et al. Defining constant versus variable phenotypic features of women with polycystic ovary syndrome using different ethnic groups and populations. J Clin Endocrinol Metab 2006 Nov;91(11):4361-4368.

(173) Zhang HY, Zhu FF, Xiong J, Shi XB, Fu SX. Characteristics of different phenotypes of polycystic ovary syndrome based on the Rotterdam criteria in a large-scale Chinese population. BJOG 2009 Nov;116(12):1633-1639.

(174) Glintborg D, Mumm H, Hougaard D, Ravn P, Andersen M. Ethnic differences in Rotterdam criteria and metabolic risk factors in a multiethnic group of women with PCOS studied in Denmark. Clin Endocrinol (Oxf) 2010 Dec;73(6):732-738.

(175) Ladson G, Dodson WC, Sweet SD, Archibong AE, Kunselman AR, Demers LM, et al. Racial influence on the polycystic ovary syndrome phenotype: a black and white case-control study. Fertil Steril 2011 Jul;96(1):224-229.e2.

(176) Koval KW, Setji TL, Reyes E, Brown AJ. Higher high-density lipoprotein cholesterol in African-American women with polycystic ovary syndrome compared with Caucasian counterparts. J Clin Endocrinol Metab 2010 Sep;95(9):E49-53.

(177) Gholap N, Davies M, Patel K, Sattar N, Khunti K. Type 2 diabetes and cardiovascular disease in South Asians. Prim Care Diabetes 2011 Apr;5(1):45-56.

(178) Dunaif A, Sorbara L, Delson R, Green G. Ethnicity and polycystic ovary syndrome are associated with independent and additive decreases in insulin action in Caribbean-Hispanic women. Diabetes 1993 Oct;42(10):1462-1468.

(179) Rowe JW, Minaker KL, Pallotta JA, Flier JS. Characterization of the insulin resistance of aging. J Clin Invest 1983 Jun;71(6):1581-1587.

(180) Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). Hum Reprod 2012 Jan;27(1):14-24.

(181) Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 1961 Nov;21:1440-1447.

(182) Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004 Jan;81(1):19-25.

(183) Stone MA, Camosso-Stefinovic J, Wilkinson J, de Lusignan S, Hattersley AT, Khunti K. Incorrect and incomplete coding and classification of diabetes: a systematic review. Diabet Med 2010 May;27(5):491-497.

(184) de Lusignan S, Sadek N, Mulnier H, Tahir A, Russell-Jones D, Khunti K. Miscoding, misclassification and misdiagnosis of diabetes in primary care. Diabet Med 2012 Feb;29(2):181-189.

(185) Ali S, Davies MJ, Taub NA, Stone MA, Khunti K. Prevalence of diagnosed depression in South Asian and white European people with type 1 and type 2 diabetes mellitus in a UK secondary care population. Postgrad Med J 2009 May;85(1003):238-243.

(186) Leicester-Council L. Area profile for city of Leicester. 2001; Available at: http://www.leicester.gov.uk/your-council-services/council-and-democracy/city-statistics/demographic-and-cultural/. Accessed May/10, 2012.

(187) Ezeh U, Yildiz BO, Azziz R. Referral Bias in Defining the Phenotype and Prevalence of Obesity in Polycystic Ovary Syndrome. J Clin Endocrinol Metab 2013 98(6):E1088-96.

(188) Erikson EH. The life cycle completed . 2nd ed. New York ; London: Norton; 1997.

(189) Levinson DJ. The seasons of a woman's life. New York: Knopf; 1996.

(190) ONS, Office of National Statistics. "Marriages in England and Wales". 26/June/2013; Available at: http://www.ons.gov.uk/ons/rel/vsob1/marriages-in-england-and-wales--provisional-/index.html. Accessed August/01, 2013.

(191) NICE P. Assessing body mass index and waist circumference thresholds for intervening to prevent ill health and premature death among adults from black, Asian and other minority ethnic groups in the UK. NICE 2013 July 2013;46(guidance.nice.org.uk/ph46).

(192) Kauffman RP, Baker VM, Dimarino P, Gimpel T, Castracane VD. Polycystic ovarian syndrome and insulin resistance in white and Mexican American women: a comparison of two distinct populations. Am J Obstet Gynecol 2002 Nov;187(5):1362-1369.

(193) Kumarapeli V, Seneviratne Rde A, Wijeyaratne C. Health-related quality of life and psychological distress in polycystic ovary syndrome: a hidden facet in South Asian women. BJOG 2011 Feb;118(3):319-328.

(194) Avery JC, Braunack-Mayer AJ. The information needs of women diagnosed with Polycystic Ovarian Syndrome--implications for treatment and health outcomes. BMC Womens Health 2007 Jun 20;7-9.

(195) Ching HL, Burke V, Stuckey BG. Quality of life and psychological morbidity in women with polycystic ovary syndrome: body mass index, age and

the provision of patient information are significant modifiers. Clin Endocrinol (Oxf) 2007 Mar;66(3):373-379.

(196) Scarborough P, Bhatnagar P, Wickramasinghe K, Smolina K, Mitchell C, Rayner M. Coronary Heart Disease Statistics 2010. 2010.

(197) Hippisley-Cox J, Ryan R. Diabetes in United Kingdom: Analysis of QRESEARCH data. 2007;DH 12.

(198) National-Health-Service H. Health Survey for England. 2010; Available at: http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles-related-surveys/health-survey-for-england. Accessed May/10, 2012.

(199) Simpson E. *The interpretation of interaction in contingency tables*. Journal of Royal Statistical Society. Series B 1951;13(2):238-241.

(200) Bland JM, Altman DG. Correlation, regression, and repeated data. BMJ 1994 Apr 2;308(6933):896.

(201) Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997 Dec;18(6):774-800.

(202) Malinas GB, John. "Simpson's Paradox" *The Stanford Encyclopedia of Philosophy*. Winter, 2012; Available at: <http://plato.stanford.edu/archives/win2012/entries/paradox-simpson/>. Accessed August, 2012.

(203) Carmina E, Chu MC, Longo RA, Rini GB, Lobo RA. Phenotypic variation in hyperandrogenic women influences the findings of abnormal metabolic and cardiovascular risk parameters. J Clin Endocrinol Metab 2005 May;90(5):2545-2549.

(204) Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Hum Reprod Update 2009 Jul-Aug;15(4):477-488.

(205) Rizzo M, Berneis K, Hersberger M, Pepe I, Di Fede G, Rini GB, et al. Milder forms of atherogenic dyslipidemia in ovulatory versus anovulatory polycystic ovary syndrome phenotype. Hum Reprod 2009 Sep;24(9):2286-2292.

(206) Nicholson F, Rolland C, Broom J, Love J. Effectiveness of long-term (twelve months) nonsurgical weight loss interventions for obese women with polycystic ovary syndrome: a systematic review. Int J Womens Health 2010 Nov 10;2:393-399.

(207) Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril 2009 Dec;92(6):1966-1982.

(208) Kassi E, Diamanti-Kandarakis E. The effects of insulin sensitizers on the cardiovascular risk factors in women with polycystic ovary syndrome. J Endocrinol Invest 2008 December 2008;31(12):1124-1131.

(209) Pasquali R, Gambineri A. Targeting insulin sensitivity in the treatment of polycystic ovary syndrome. Expert Opinion on Therapeutic Targets 2009 October 2009;13(10):1205-1226.

(210) Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. Journal of Clinical Endocrinology & Metabolism 2008 Nov;93(11):4299-4306.

(211) Brown AJ, Setji TL, Sanders LL, Lowry KP, Otvos JD, Kraus WE, et al. Effects of exercise on lipoprotein particles in women with polycystic ovary syndrome. Med Sci Sports Exerc 2009 Mar;41(3):497-504.

(212) Moran LJ, Ko H, Misso M, Marsh K, Noakes M, Talbot M, et al. Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. J Acad Nutr Diet 2013 Apr;113(4):520-545.

(213) Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. Hum Reprod Update 2011 Mar-Apr;17(2):171-183.

(214) Randeva HS, Lewandowski KC, Drzewoski J, Brooke-Wavell K, O'Callaghan C, Czupryniak L, et al. Exercise decreases plasma total homocysteine in overweight young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2002 Oct;87(10):4496-4501.

(215) Liao LM, Nesic J, Chadwick PM, Brooke-Wavell K, Prelevic GM. Exercise and body image distress in overweight and obese women with polycystic ovary syndrome: a pilot investigation. Gynecol Endocrinol 2008 Oct;24(10):555-561.

(216) Costello M, Shrestha B, Eden J, Johnson N, Moran L. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. The Cochrane Library 2010(11).

(217) Diamanti-Kandarakis E, Economou F, Palimeri S, Christakou C. Metformin in polycystic ovary syndrome. Ann N Y Acad Sci 2010 Sep;1205:192-198.

(218) Bailey CJ, Turner RC. Metformin. N Engl J Med 1996 Feb 29;334(9):574-579.

(219) Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med 2008 Jan 3;358(1):47-54.

(220) Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med 2008 Feb;121(2):149-157.e2.

(221) Nieuwenhuis-Ruifrok AE, Kuchenbecker WK, Hoek A, Middleton P, Norman RJ. Insulin sensitizing drugs for weight loss in women of reproductive age who are overweight or obese: systematic review and meta-analysis. Hum Reprod Update 2009 Jan-Feb;15(1):57-68.

(222) Yki-Jarvinen H. Thiazolidinediones. N Engl J Med 2004 Sep 9;351(11):1106-1118.

(223) Wilding JP. PPAR agonists for the treatment of cardiovascular disease in patients with diabetes. Diabetes Obes Metab 2012 Nov;14(11):973-982.

(224) Du Q, Yang S, Wang YJ, Wu B, Zhao YY, Fan B. Effects of thiazolidinediones on polycystic ovary syndrome: a meta-analysis of randomized placebo-controlled trials. Adv Ther 2012 Sep;29(9):763-774.

(225) Du Q, Wang YJ, Yang S, Wu B, Han P, Zhao YY. A systematic review and meta-analysis of randomized controlled trials comparing pioglitazone versus metformin in the treatment of polycystic ovary syndrome. Curr Med Res Opin 2012 May;28(5):723-730.

(226) Li XJ, Yu YX, Liu CQ, Zhang W, Zhang HJ, Yan B, et al. Metformin vs thiazolidinediones for treatment of clinical, hormonal and metabolic characteristics of polycystic ovary syndrome: a meta-analysis. Clin Endocrinol (Oxf) 2011 Mar;74(3):332-339.

(227) Katsiki N, Hatzitolios AI. Insulin-sensitizing agents in the treatment of polycystic ovary syndrome: an update. Curr Opin Obstet Gynecol 2010 Dec;22(6):466-476.

(228) Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med 1999 Apr 29;340(17):1314-1320.

(229) Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. Biochimie 2013 Oct;95(10):1811-1827.

(230) Gerli S, Mignosa M, Di Renzo GC. Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo-controlled trial. European Review for Medical & Pharmacological Sciences 2003 Nov-Dec;7(6):151-159.

(231) Galazis N, Galazi M, Atiomo W. D-Chiro-inositol and its significance in polycystic ovary syndrome: A systematic review. Gynecological Endocrinology 2011 April 2011;27(4):256-262.

(232) Nisal K, Kela R, Khunti K, Davies MJ. Comparison of efficacy between incretin-based therapies for type 2 diabetes mellitus. BMC Med 2012 Nov 30;10:152-7015-10-152.

(233) Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. Lancet 2011 Jul 9;378(9786):182-197.

(234) Jensterle Sever M, Kocjan T, Pfeifer M, Janez A. Short-term Combined Treatment with Liraglutide and Metformin Leads to Significant Weight Loss in Obese Women with Polycystic Ovary Syndrome and Previous Poor Response to Metformin. American Endocrine Meeting June 2013.

(235) Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2008 Jul;93(7):2670-2678.

(236) Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study. Int J Obes (Lond) 2013 ;37(11):1443-51.

(237) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009 Aug 18;151(4):264-9, W64.

(238) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009 Aug 18;151(4):W65-94.

(239) Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928.

(240) Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011 Jul 22;343:d4002.

(241) Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters M, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Methods Guide for Effectiveness and Comparative Effectiveness Reviews Rockville (MD); 2008.

(242) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-560.

(243) Curi DD, Fonseca AM, Marcondes JA, Almeida JA, Bagnoli VR, Soares JM,Jr, et al. Metformin versus lifestyle changes in treating women with polycystic ovary syndrome. Gynecol Endocrinol 2012 Mar;28(3):182-185.

(244) Jedel E, Labrie F, Oden A, Holm G, Nilsson L, Janson PO, et al. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomized controlled trial. Am J Physiol Endocrinol Metab 2011 Jan;300(1):E37-45.

(245) Ahmad J, Shukla N, Khan AR, Ahmed F, Siddiqui MA. Comparison of metabolic effects of metformin and rosiglitazone in the management of polycystic ovary syndrome (PCOS): A prospective, parallel, randomized, open-label study. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2008 Feb 2008;2(1):37-46.

(246) Aroda VR, Ciaraldi TP, Burke P, Mudaliar S, Clopton P, Phillips S, et al. Metabolic and hormonal changes induced by pioglitazone in polycystic ovary syndrome: a randomized, placebo-controlled clinical trial. Journal of Clinical Endocrinology & Metabolism 2009 Feb;94(2):469-476.

(247) Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertility & Sterility 2004 Oct;82(4):893-902.

(248) Jensterle M, Janez A, Mlinar B, Marc J, Prezelj J, Pfeifer M. Impact of metformin and rosiglitazone treatment on glucose transporter 4 mRNA expression in women with polycystic ovary syndrome. European Journal of Endocrinology 2008 Jun;158(6):793-801.

(249) Lam PM, Tam WH, Ma RC, Cheung LP, Tsui MH, Tong PC, et al. The reproductive and metabolic effect of rosiglitazone on Chinese women with polycystic ovarian syndrome--a double-blind randomized placebo-controlled study. Fertility & Sterility 2011 Aug;96(2):445-451.e1.

(250) Naka KK, Kalantaridou SN, Kravariti M, Bechlioulis A, Kazakos N, Calis KA, et al. Effect of the insulin sensitizers metformin and pioglitazone on endothelial function in young women with polycystic ovary syndrome: a prospective randomized study. Fertility & Sterility 2011 Jan;95(1):203-209.

(251) Onalan G, Goktolga U, Ceyhan T, Bagis T, Onalan R, Pabuccu R. Predictive value of glucose-insulin ratio in PCOS and profile of women who will benefit from metformin therapy: obese, lean, hyper or normoinsulinemic?. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2005 Dec 1;123(2):204-211.

(252) Ortega-Gonzalez C, Luna S, Hernandez L, Crespo G, Aguayo P, Arteaga-Troncoso G, et al. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic

ovary syndrome. Journal of Clinical Endocrinology & Metabolism 2005 Mar;90(3):1360-1365.

(253) Palomba S, Falbo A, Russo T, Manguso F, Tolino A, Zullo F, et al. Insulin sensitivity after metformin suspension in normal-weight women with polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism 2007 Aug;92(8):3128-3135.

(254) Romualdi D, Giuliani M, Cristello F, Fulghesu AM, Selvaggi L, Lanzone A, et al. Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Fertility & Sterility 2010 May 1;93(7):2303-2310.

(255) Yilmaz M, Karakoc A, Toruner FB, Cakir N, Tiras B, Ayvaz G, et al. The effects of rosiglitazone and metformin on menstrual cyclicity and hirsutism in polycystic ovary syndrome. Gynecological Endocrinology 2005 Sep;21(3):154-160.

(256) Jensterle M, Sebestjen M, Janez A, Prezelj J, Kocjan T, Keber I, et al. Improvement of endothelial function with metformin and rosiglitazone treatment in women with polycystic ovary syndrome. European Journal of Endocrinology 2008 Oct;159(4):399-406.

(257) Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BG, Wong JL, et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Aust 2011 Sep 19;195(6):S65-112.

(258) Nissen SE. The rise and fall of rosiglitazone. Eur Heart J 2010 Apr;31(7):773-776.

(259) Azoulay L, Yin H, Filion KB, Assayag J, Majdan A, Pollak MN, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. BMJ 2012 May 30;344:e3645.

(260) Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev 2012 May 16;5:CD003053.

(261) Mathur R, Alexander CJ, Yano J, Trivax B, Azziz R. Use of metformin in polycystic ovary syndrome. Am J Obstet Gynecol 2008 Dec;199(6):596-609.

(262) Franks S. When should an insulin sensitizing agent be used in the treatment of polycystic ovary syndrome? Clin Endocrinol (Oxf) 2011 Feb;74(2):148-151.

(263) Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. Circulation 2010 Aug 17;122(7):743-752.

(264) Boule NG, Weisnagel SJ, Lakka TA, Tremblay A, Bergman RN, Rankinen T, et al. Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. Diabetes Care 2005 Jan;28(1):108-114.

(265) Ekelund U, Franks PW, Sharp S, Brage S, Wareham NJ. Increase in physical activity energy expenditure is associated with reduced metabolic risk independent of change in fatness and fitness. Diabetes Care 2007 Aug;30(8):2101-2106.

(266) Thomson RL, Buckley JD, Lim SS, Noakes M, Clifton PM, Norman RJ, et al. Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. Fertil Steril 2010 Oct;94(5):1812-1816.

(267) Thomson RL, Buckley JD, Brinkworth GD. Exercise for the treatment and management of overweight women with polycystic ovary syndrome: a review of the literature. Obes Rev 2011 May;12(5):e202-10.

(268) Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Strauss BJ, Teede HJ. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. J Clin Endocrinol Metab 2011 Jan;96(1):E48-56.

(269) Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod 1995 Oct;10(10):2705-2712.

(270) Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 1999 Apr;84(4):1470-1474.

(271) Hollmann M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. Hum Reprod 1996 Sep;11(9):1884-1891.

(272) Domecq JP, Prutsky G, Mullan RJ, Hazem A, Sundaresh V, Elamin MB, et al. Lifestyle modification programs in polycystic ovary syndrome: Systematic review and meta-analysis. J Clin Endocrinol Metab 2013 98(12):4655-63.

(273) Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate AM, Cavazza C, et al. Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. Journal of Clinical Endocrinology & Metabolism 2006 Oct;91(10):3970-3980.

(274) Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertility & Sterility 2004 Aug;82(2):421-429.

(275) Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, et al. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism 2000 Aug;85(8):2767-2774.

(276) Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. Human Reproduction 2006 Jan;21(1):80-89.

(277) Palomba S, Falbo A, Giallauria F, Russo T, Rocca M, Tolino A, et al. Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. Human Reproduction 2010 Nov;25(11):2783-2791.

(278) Gagnier JJ, Morgenstern H, Altman DG, Berlin J, Chang S, McCulloch P, et al. Consensus-based recommendations for investigating clinical heterogeneity in systematic reviews. BMC Med Res Methodol 2013 Aug 30;13(1):106.

(279) Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health 2011 Jun;14(4):429-437.

(280) Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health 2011 Jun;14(4):417-428.

(281) Crete J, Adamshick P. Managing polycystic ovary syndrome: what our patients are telling us. J Holist Nurs 2011 Dec;29(4):256-266.

(282) Sills ES, Perloe M, Tucker MJ, Kaplan CR, Genton MG, Schattman GL. Diagnostic and treatment characteristics of polycystic ovary syndrome: descriptive measurements of patient perception and awareness from 657 confidential self-reports. BMC Womens Health 2001;1(1):3.

(283) Percy CA, Gibbs T, Potter L, Boardman S. Nurse-led peer support group: experiences of women with polycystic ovary syndrome. J Adv Nurs 2009 Oct;65(10):2046-2055.

(284) Dean E. An Analysis of Online Resources for Women with Polycystic Ovary Syndrome. Journal of Consumer Health On the Internet 2011;15(4):361-369.

(285) Gray LJ, Khunti K, Williams S, Goldby S, Troughton J, Yates T, et al. Let's prevent diabetes: study protocol for a cluster randomised controlled trial of an educational intervention in a multi-ethnic UK population with screen detected impaired glucose regulation. Cardiovasc Diabetol 2012 May 20;11:56.

(286) Wilmot EG, Davies MJ, Edwardson CL, Gorely T, Khunti K, Nimmo M, et al. Rationale and study design for a randomised controlled trial to reduce sedentary time in adults at risk of type 2 diabetes mellitus: project stand (Sedentary Time ANd diabetes). BMC Public Health 2011 Dec 8;11:908-2458-11-908.

(287) Dunkley AJ, Davies MJ, Stone MA, Taub NA, Troughton J, Yates T, et al. The Reversal Intervention for Metabolic Syndrome (TRIMS) study: rationale, design, and baseline data. Trials 2011 May 4;12:107-6215-12-107.

(288) Yates T, Davies M, Gorely T, Bull F, Khunti K. Effectiveness of a pragmatic education program designed to promote walking activity in individuals with impaired glucose tolerance: a randomized controlled trial. Diabetes Care 2009 Aug;32(8):1404-1410.

(289) NICE T6. National Institute for Clinical Excellence. *Guidance on the use of patient-education models for diabetes (Technology Appraisal Guidance 60)*. . NICE TAG 2003;60((http://www.nice.org.uk/nicemedia/live/11496/32610/32610.pdf).).

(290) NICE P. Preventing type 2 diabetes: population and community-level interventions. 2011;PH35.

(291) NICE C. National Institude of Health and Care Excellence; Type 2 Diabetes. Full Guidance. 26 January 2011; Available at: http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf. Accessed 08 August, 2013.

(292) Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. BMJ 2000 Sep 16;321(7262):694-696.

(293) Campbell NC, Murray E, Darbyshire J, Emery J, Farmer A, Griffiths F, et al. Designing and evaluating complex interventions to improve health care. BMJ 2007 Mar 3;334(7591):455-459.

(294) Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Medical Research Council; Developing and evaluating complex interventions: new guidance. . MRC 2008(www.mrc.ac.uk/complexinterventionsguidance):1-35.

(295) Bartholomew L, Parcel G, Kok G, Gottlieb N editors. *Planning health promotion programs: An intervention mapping approach*. 2nd ed. San Francisco, CA: John Wiley,; 2006.

(296) Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME, Cradock S, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. BMJ 2008 Mar 1;336(7642):491-495.

(297) Dallosso HM, Eborall HC, Daly H, Martin-Stacey L, Speight J, Realf K, et al. Does self monitoring of blood glucose as opposed to urinalysis provide additional benefit in patients newly diagnosed with type 2 diabetes receiving structured education? The DESMOND SMBG randomised controlled trial protocol. BMC Fam Pract 2012 Mar 14;13:18-2296-13-18.

(298) Gillett M, Dallosso HM, Dixon S, Brennan A, Carey ME, Campbell MJ, et al. Delivering the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cost effectiveness analysis. BMJ 2010 Aug 20;341:c4093.

(299) Khunti K, Gray LJ, Skinner T, Carey ME, Realf K, Dallosso H, et al. Effectiveness of a diabetes education and self management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. BMJ 2012 Apr 26;344:e2333.

(300) DESMOND. Future programmes. Available at: http://www.desmond-project.org.uk/upcomingmodules-281.html. Accessed 8 August 2013, 2013.

(301) Yates T, Davies MJ, Sehmi S, Gorely T, Khunti K. The Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement (PREPARE) programme study: are improvements in glucose regulation sustained at 2 years? Diabet Med 2011 Oct;28(10):1268-1271.

(302) Ogden J. Health Psychology; a textbook. 5th ed. Berkshire, England: McGrow-Hill Open University Press; 2012.

(303) Leventhal H, Meyer D, Nerenz D. The common-sense representation of illness danger. In: Rachman S, editor. *Contributions to Medical Psychology.* New York: Pergamon. 2nd ed. New York: Pergamon; 1980. p. 7-30.

(304) Leventhal H, Nerenz D. The assessment of illness cognition. In: Karoly P, editor. Measurement strategies in Health Psychology New York: Wiley; 1985.

(305) Leventhal H, Benyamini Y, Shafer C. Lay beliefs about health and illness. In: Ayers S, editor. Cambridge handbook of Psychology, Health and Medicine. Cambridge: Cambridge University Press; 2007.

(306) Leventhal H, Weinman J, Leventhal E, Philips L. Health Psychology: the serach for pathways between behaviour and health. Annals Review of Psychology 2007;59(8):1-29.

(307) Bandura A editor. *Self-efficacy: the exercise of control.* New York: W.H. Freeman and Company; 1997.

(308) Bandura A editor. *Social foundations of thought and action: A social cognitive theory.* Englewood Cliffs, NJ: Prentice Hall; 1986.

(309) Bandura A. Health Promotion by Social Cognitive Means. Health Education Behavior 2004;31:143.

(310) Bandura A. The Primacy of Self-Regulation in Health Promotion. Applied Psychology 2005;54:245-254.

(311) Bandura A. Self-efficacy: Toward a Unifying Theory of Behavioral Change . Psychological Review 1977;84(2):191-215.

(312) Bandura A. Self-efficacy in changing societies. Cambridge: Cambridge University Press; 1995.

(313) Gollwitzer P, Brandstaetter V. Implementation intentions and effective goal pursuit.
. J Pers Soc Psychol 1997;73:186-199.

(314) Gollwitzer P, Sheeran P. Self-regulation of consumer decision making and behavior: The role of implementation intentions . Journal of Consumer Psychology 2009;19:593-607.

(315) Gollwitzer PM, Sheeran P, Trotschel R, Webb TL. Self-regulation of priming effects on behavior. Psychol Sci 2011 Jul;22(7):901-907.

(316) Webb TL, Sheeran P. Mechanisms of implementation intention effects: the role of goal intentions, self-efficacy, and accessibility of plan components. Br J Soc Psychol 2008 Sep;47(Pt 3):373-395.

(317) Webb TL, Sheeran P. How do implementation intentions promote goal attainment? A test of component processes . Journal of Experimental Social Psychology 2007;43:295-302.

(318) Chaiken S. The heuristic model of persuation. . In: Zanna M, Olson J, Herman C, editors. *Social influence: the Ontaio symposium.* 5th ed., NJ: Erlbaum; 1987. p. 3-39.

(319) Chaiken S, Wood W, Eagly A. Principles of persuasion. In: Higgins E, Kruglanski A, editors. *Social psychology: Handbook of basic mechanisms and processes*; 1996.

(320) Chaiken S. Heuristic versus systematic information processing and the use of source versus message cues in persuasion. Journal of personality and Social Psychology 1980;39:752-766.

(321) Chen S, Duckworth K, Chaiken S. Motivated Heuristic and Systematic Processing. Psychological Inquiry 1999;10(1):44-49.

(322) Hagger M, Orbell S. A meta-analytic review of the common-sense model of illness representations. Psychology and Health 2003;18(2):141-84.

(323) Sheeran P. Intention-behaviour relations: A conceptual and empirical overview. In: Stroebe W, Hewstone M, editors. European Review of Social Psychology (Vol. 12), : Wiley: Chichester, UK; 2002. p. 1-36.

(324) Allan J. The intention-behaviour gap – it's all under control (executive control). European Health Psychologist 2008;10:62-64.

(325) Fennis B, Adriaanse M, Stroebe W, Pol B. Bridging the intention–behavior gap: Inducing implementation intentions through persuasive appeals . Journal of Consumer Psychology 2011;21:302-311.

(326) DiClemente CC, Prochaska JO, Fairhurst SK, Velicer WF, Velasquez MM, Rossi JS. The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. J Consult Clin Psychol 1991 Apr;59(2):295-304.

(327) Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviors. Prog Behav Modif 1992;28:183-218.

(328) Prochaska JO, DiClemente CC. Self change processes, self efficacy and decisional balance across five stages of smoking cessation. Prog Clin Biol Res 1984;156:131-140.

(329) Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. J Consult Clin Psychol 1983 Jun;51(3):390-395.

(330) Prochaska JO, DiClemente CC, Velicer WF, Ginpil S, Norcross JC. Predicting change in smoking status for self-changers. Addict Behav 1985;10(4):395-406.

(331) Prochaska JO, DiClemente CC, Velicer WF, Rossi JS. Standardized, individualized, interactive, and personalized self-help programs for smoking cessation. Health Psychol 1993 Sep;12(5):399-405.

(332) Webb TL, Sheeran P, Totterdell P, Miles E, Mansell W, Baker S. Using implementation intentions to overcome the effect of mood on risky behaviour. Br J Soc Psychol 2012 Jun;51(2):330-345.

(333) Webb TL, Ononaiye MS, Sheeran P, Reidy JG, Lavda A. Using implementation intentions to overcome the effects of social anxiety on attention and appraisals of performance. Pers Soc Psychol Bull 2010 May;36(5):612-627.

(334) BRUNER JS. On perceptual readiness. Psychol Rev 1957 Mar;64(2):123-152.

(335) Ritchie J, Spencer L. Qualitative data analysis for applied policy research . . In: Bryman A, Burgess R, editors. Analysing Qualitative Data London: Routledge; 1994. p. 173-194.

(336) Srivastava P, Hopwood N. A Practical Iteravtive Framework for Qualitative Data Analysis. International Journal of Qualitative Methodds, IJQM 2009;8(1):76-84.

(337) Moorey S. The six cycles maintenance model: Growing a "vicious flower" for depression. Behav Cogn Psychother 2010 Mar;38(2):173-184.

(338) Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002 Feb 7;346(6):393-403.

(339) Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001 May 3;344(18):1343-1350.

(340) Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010 Mar 23;340:c869.

(341) Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010 Mar 23;340:c332.

(342) Plasqui G, Westerterp KR. Physical activity assessment with accelerometers: an evaluation against doubly labeled water. Obesity (Silver Spring) 2007 Oct;15(10):2371-2379.

(343) Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. Med Sci Sports Exerc 2005 Nov;37(11 Suppl):S531-43.

(344) Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, et al. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care 2008 Feb;31(2):369-371.

(345) Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991 Dec;14(6):540-545.

(346) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function

from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985 Jul;28(7):412-419.

(347) WHO. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus available from. 2011;WHO/NMH/CHP/CPM/11.1(http://www.who.int/diabetes/publications/report-hba1c_2011.pdf).

(348) Yildizhan R, Kurdoglu M, Adali E, Kolusari A, Yildizhan B, Sahin HG, et al. Serum 25-hydroxyvitamin D concentrations in obese and non-obese women with polycystic ovary syndrome. Arch Gynecol Obstet 2009 Oct;280(4):559-563.

(349) Wehr E, Trummer O, Giuliani A, Gruber HJ, Pieber TR, Obermayer-Pietsch B. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. Eur J Endocrinol 2011 May;164(5):741-749.

(350) Wehr E, Pieber TR, Obermayer-Pietsch B. Effect of vitamin D3 treatment on glucose metabolism and menstrual frequency in polycystic ovary syndrome women: a pilot study. J Endocrinol Invest 2011 Nov;34(10):757-763.

(351) Galazis N, Iacovou C, Haoula Z, Atiomo W. Metabolomic biomarkers of impaired glucose tolerance and type 2 diabetes mellitus with a potential for risk stratification in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2012 Feb;160(2):121-130.

(352) Gonzalez F. Inflammation in Polycystic Ovary Syndrome: underpinning of insulin resistance and ovarian dysfunction. Steroids 2012 Mar 10;77(4):300-305.

(353) Duleba AJ, Dokras A. Is PCOS an inflammatory process? Fertil Steril 2012 Jan;97(1):7-12.

(354) Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc 1998 May;30(5):777-781.

(355) Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395.

(356) Roe L, Strong C, Whiteside C, Neil A, Mant D. Dietary intervention in primary care: validity of the DINE method for diet assessment. Fam Pract 1994 Dec;11(4):375-381.

(357) Cronin L, Guyatt G, Griffith L, Wong E, Azziz R, Futterweit W, et al. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). J Clin Endocrinol Metab 1998 Jun;83(6):1976-1987.

(358) Jones GL, Benes K, Clark TL, Denham R, Holder MG, Haynes TJ, et al. The Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ): a validation. Hum Reprod 2004 Feb;19(2):371-377.

(359) Jones GL, Balen AH, Ledger WL. Health-related quality of life in PCOS and related infertility: How can we assess this?. Human Fertility 2008 2008;11(3):173-185.

(360) Jones GL, Hall JM, Lashen HL, Balen AH, Ledger WL. Health-related quality of life among adolescents with polycystic ovary syndrome. J Obstet Gynecol Neonatal Nurs 2011 Sep-Oct;40(5):577-588.

(361) Bazarganipour F, Ziaei S, Montazeri A, Faghihzadeh S, Frozanfard F. Psychometric properties of the Iranian version of modified polycystic ovary syndrome health-related quality-of-life questionnaire. Hum Reprod 2012 Sep;27(9):2729-2736.

(362) Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998 Mar 7;316(7133):736-741.

(363) Gudex C, Dolan P, Kind P, Williams A. Health state valuations from the general public using the visual analogue scale. Qual Life Res 1996 Dec;5(6):521-531.

(364) Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992 Jul 18;305(6846):160-164.

(365) Ware J,Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233.

(366) Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006 Jun;60(6):631-637.

(367) Keller C, Fleury J, Gregor-Holt N, Thompson T. Predictive ability of social cognitive theory in exercise research: an integrated literature review. Online J Knowl Synth Nurs 1999 Jan 5;6:2.

(368) Marcus BH, Selby VC, Niaura RS, Rossi JS. Self-efficacy and the stages of exercise behavior change. Res Q Exerc Sport 1992 Mar;63(1):60-66.

(369) NICE P. Prevention of cardiovascular disease. NICE 2010;PH25.

(370) Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. Hum Reprod Update 2010 Jan-Feb;16(1):51-64.

(371) National Institute of Health, NHLB. What Are Coronary Heart Disease Risk Factors? 2011; Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/hd/atrisk.html. Accessed 8/10/2013, 2013.

(372) NHS Hcp. Putting Prevention First – NHS Health Check: Vascular Risk Assessment and Management Best Practice Guidance . Best Practice Guidance 2009 3 April 2009;11473.

(373) WHO. World Health Organization (2007) Global recommendations on physical activity for health. . WHO 2007(http://whqlibdoc. who.int/publications/2010/9789241599979_eng.pdf,).

(374) Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010 Jan 11;340:b5664.

(375) NHS C. Walking for health. 2012; Available at: http://www.nhs.uk/Livewell/getting-started-guides/Pages/getting-started-walking.aspx. Accessed 8/10, 2013.

(376) Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN, et al. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006 Jan;91(1):48-53.

(377) Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008 Jun 28;336(7659):1475-1482.

(378) Henson J, Yates T, Biddle SJ, Edwardson CL, Khunti K, Wilmot EG, et al. Associations of objectively measured sedentary behaviour and physical activity with markers of cardiometabolic health. Diabetologia 2013 May;56(5):1012-1020.

(379) E. G. Wilmot. Type 2 Diabetes in young adults. Leicester: University of Leicester; 2013.

(380) Guyatt G, Weaver B, Cronin L, Dooley JA, Azziz R. Health-related quality of life in women with polycystic ovary syndrome, a self-administered questionnaire, was validated. J Clin Epidemiol 2004 Dec;57(12):1279-1287.

(381) IPAQ. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms   . IPAQ 2005(http://www.ipaq.ki.se/ipaq.htm).

(382) Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000 Sep;32(9 Suppl):S498-504.

(383) White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 2011 Feb 7;342:d40.

(384) National Research Council. The prevention and treatment of missing data in clinical trials. ISBN 978-0-309-15814-5. http://www.nap.edu/catalog.php?record_id=12955; 2010.

(385) Harrison CL, Stepto NK, Hutchison SK, Teede HJ. The impact of intensified exercise training on insulin resistance and fitness in overweight and obese women with and without polycystic ovary syndrome. Clin Endocrinol (Oxf) 2012 Mar;76(3):351-357.

(386) Vigorito C, Giallauria F, Palomba S, Cascella T, Manguso F, Lucci R, et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism 2007 Apr;92(4):1379-1384.

(387) Clarke KK, Freeland-Graves J, Klohe-Lehman DM, Milani TJ, Nuss HJ, Laffrey S. Promotion of physical activity in low-income mothers using pedometers. J Am Diet Assoc 2007 Jun;107(6):962-967.

(388) Silva MN, Vieira PN, Coutinho SR, Minderico CS, Matos MG, Sardinha LB, et al. Using self-determination theory to promote physical activity and weight control: a randomized controlled trial in women. J Behav Med 2010 Apr;33(2):110-122.

(389) Strine TW, Mokdad AH, Dube SR, Balluz LS, Gonzalez O, Berry JT, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. Gen Hosp Psychiatry 2008 Mar-Apr;30(2):127-137.

(390) Benson S, Hahn S, Tan S, Janssen OE, Schedlowski M, Elsenbruch S. Maladaptive coping with illness in women with polycystic ovary syndrome. J Obstet Gynecol Neonatal Nurs 2010 Jan-Feb;39(1):37-45.

(391) Schwarz PE, Greaves CJ, Lindstrom J, Yates T, Davies MJ. Nonpharmacological interventions for the prevention of type 2 diabetes mellitus. Nat Rev Endocrinol 2012 Jan 17;8(6):363-373.

(392) Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT, et al. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. BMJ 2008 May 24;336(7654):1180-1185.

(393) Johnson M, Jones R, Freeman C, Woods HB, Gillett M, Goyder E, et al. Can diabetes prevention programmes be translated effectively into real-world settings and still deliver improved outcomes? A synthesis of evidence. Diabet Med 2013 Jan;30(1):3-15.

SUCCESS
Study

Development of a **S**truct**U**red edu**C**ation programme to improve **C**ardiovascular risk in wom**E**n with polycy**S**tic ovary **S**yndrome

Thesis submitted for the degree of

Doctor of Philosophy

University of Leicester

By

Dr Hamidreza Mani

M.D.(Shiraz, Iran) MRCP (London)

Diabetes Research Centre

and

Cardiovascular Sciences

College of Medicine, Biological Sciences and Psychology

December 2013

Appendix

List of contents

Appendix 1 People involved

Initials	Full Name	Role
BP	Mrs Bharti Patel	Research Nurse
BS	Mrs Bernie Stribling	National Operation Manager DESMOND
BW	Dr Balu Webb	Scientist
CA	Mrs Carol Akroyd	CLARHC theme manager
CE	Dr Charlotte Edwardson	Lecturer in Physical activity
DB	Dr Danielle Bodicoat (Nee Morris)	Statistician, Lecturer in Health Sciences
DR	Miss Denise Robinson	Personal Assistant to Professor Davies
DW	Dr David Webb	Senior Lecturer / Consultant
EW	Dr Emma Wilmot	Clinical Research Fellow
FB	Fiona Barker	Diabetes Specialist Nurse
FM	Mrs Frances Morris	Research Nurse
GC	Miss Gemma Clayton	MSC Student in statistics
HB	Dr Hanna Blackledge	Public Health informatics
HD	Ms Heather Daly	Nurse Consultant
HG	Mrs Harpal Ghattoraya	Diabetes Research Network, Finance Manager
IG	Mr Ismail Gangat	Clinical Workstation database manager
JB	Dr John Bankart	Statistician, Lecturer in health Sciences
JB	Mrs Jane Brela	Research assistant
JB	Mrs Janette Barnett	Diabetes Specialist Nurse, Research Assistant
JH	Mr Joe Henson	PhD student / Research Assistant
JH	Mrs Jayne Hill	Ethics advisor/Process manager
JH	Mrs Jo Howe	Senior Research Nurse
JR	Mr Jason Rigby	Administrator; Randomisation
JT	Mrs Jacqui Troughton	Senior Research Assistant
JW	Miss Jacqueline Wayte	Research Nurse
KK	Prof. Kamlesh Khunti	PhD supervisor
LB	Mrs Lesley Bryan	Research Assistant
LG	Dr Laura Gray	Statistician, Lecturer in Health Sciences
LMS	Mrs Lorraine Martin-Stacey	Senior Research Assistant
MB	Mr Michael Bonar	Creative Director
MC	Dr Marian Carey	National DESMOND director
MH	Miss Michelle Hadjiconstantinuo	Qualitative researcher
MI	Ms Michelle Izzard	Finance Administrator
MJD	Prof. Melanie Davies	PhD supervisor
ML	Dr Miles Levy	Consultant Endocrinologist
MS	Dr Margaret Stone	Qualitative researcher
MW	Mrs Margaret Whatley	Audio typist
NP	Mrs Naina Patel	Qualitative researcher
PB	Mr Paul Bray	Administrator
PJ	Dr Petra Jones	Administrator
PM	Panna Mandalia	Research Assistant (DESMOND Educator)
RK	Mrs Rose Knight	Administrator
RKG	Mrs Raj Gill	Personal Assistant to Professor Khunti
RR	Miss Rita Rathod	Administrator
SE	Mrs Sue Enright	Senior Manager Diabetes Research Network
SG	Miss Stephanie Goldby	Project Manager
SJ	Mrs Shehnaz Jamal	Website Manager
SM	Dr Samiul Mostafa	Clinical Research Fellow
SS	Mrs Sarah Sutton	Information Librrerian

TH	Dr Trevor Howlett	Consultant Endocrinologist
TY	Dr Tom Yates	PhD Supervisor
YD	Dr Yvonne Doherty	Psychologist
ZH	Dr Zin Htike	Clinical Research Fellow

Appendix 2 Sensitivity analysis

Table A2.1 Comparison of cohorts with recorded and unrecorded blood pressure

Variable	Total Cohort	Recorded BP	Un-recorded BP	P-Value (Recorded Vs Unrecorded)
Total (number)	2353	1011	1342	
Age in years; Mean (SD)	26.4 (7.6)	26.5 (7.7)	26.3 (7.5)	0.7
Smoker (%)	13.5	13.5	13.5	0.9
Acanthosis Nigricans (%)	6	10.3	3.0	<0.001
BMI, Mean (SD) kg/m^2	30.1 (7.6)	30.8 (7.7)	28.9 (7.4)	<0.001
IMD Mean (SD)	20.99 (15.13)	21.4 (15.3)	20.7 (15.0)	0.2
History of Hypertension (%)	9.3	12.8	6.7	<0.001
Systolic BP Mean (SD), mmHg	130.6 (15.7)	N/A	N/A	N/A
Diastolic BP Mean (SD), mmHg	73.7 (11.1)	N/A	N/A	N/A
Evidence of androgen excess (%)	87.5	90.1	85.7	0.001
Hirsutism	75.5	76.8	74.7	0.2
Androgenic Alopecia	4.5	6.1	3.2	0.001
Acne	21.3	23.4	19.7	0.03
Increased Androgen Excess†	5.7	6.1	5.5	0.5
Evidence of anovulation (%)	78.5	83.7	74.7	<0.001
Oligomenorrhoea	58.3	64.5	53.7	<0.001
Amenorrhoea	16.1	18.6	14.2	0.004
Infertility	15.6	16.8	14.8	0.2
polycystic ovaries (%)*	7	7.9	6.3	0.1

SD = Standard Deviation, N/A = not applicable, IMD = Index of multiple deprivation, BP = Blood Pressure

† This has not been documented for every patient as explained in the methodology. ‡ As explained in the text, imaging investigation has not been a routine practice in Leicester

Table A2.2 Comparison of cohorts with recorded and unrecorded BMI

Variable	Total Cohort	Recorded BMI	Un-recorded BMI	P-Value (Recorded Vs Unrecorded)
Total (number)	2353	1603	750	N/A
Age in years; Mean (SD)	26.4 (7.6)	26.4 (7.8)	26.4 (7.2)	0.8
Smoker (%)	13%	15.9	8.3	<0.001
Acanthosis Nigricans (%)	6%	8.2	1.7	<0.001
BMI, Mean (SD) kg/m^2	30.1 (7.6)	N/A	N/A	N/A
IMD Mean (SD)	20.99 (15.13)	21.0 (15.2)	20.9 (15.0)	0.8
History of Hypertension	9.3%	10.7	6.4	0.001
Systolic BP Mean (SD), mmHg	130.6 (15.7)	130.7 (15.7)	125.5 (20.6)	0.1
Diastolic BP Mean (SD), mmHg	73.7 (11.1)	73.8 (11.1)	70.9 (13.5)	0.3
Evidence of androgen excess (%)	87.5%	90.5	81.5	<0.001
Hirsutism	75.5%	78.0	70.4	<0.001
Androgenic Alopecia	4.5%	5.4	2.5	0.002
Acne	21.3%	22.8	18.1	0.01
Increased Androgen Excess†	5.7%	5.7	6.0	0.7
Evidence of anovulation (%)	78.5%	81.3	72.5	<0.001
Oligomenorrhoea	58.3%	61.7	51.1	<0.001
Amenorrhoea	16.1%	18.1	11.9	<0.001
Infertility	15.6%	15.4	16.1	0.6
polycystic ovaries (%)*	7%	6.4	8.3	0.1

SD = Standard Deviation, N/A = not applicable, IMD = Index of multiple deprivation, BP = Blood Pressure

† This has not been documented for every patient as explained in the methodology. ‡ As explained in the text, imaging investigation has not been a routine practice in Leicester

Appendix 3: Search terminology for Systematic Review

PCOS: Polycystic Ovary Syndrome / sclerocystic adj2 ovar* / Stein adj2 Leventhal / chronic hyperandr* anovulat / functional ovarian hyperandrogenism / ovary polycystic disease / PCOS

DESING: Random* adj2 Trial   /   Controlled Clinical Trial   /   Double-Blind Method(procedure) / Single-Blind Method(procedure, study) / Randomized methods (procedure, study) / Controlled Trials as Topic / Random Allocation / Cross-Over Studies(methodology, procedure) / Research Design / Case-Control Studies /

Pharmacological interventions: Placebo* / Drug Therapy / Metformin / Glucophage / Fortamet / Glumetza / Riomet / Thiazolidinediones / Rosiglitazone / 2,4 thiazolidinedione derivative / Pioglitazone / Actos / Avandia / avandamet / Peroxisome Proliferator-Activated Receptors / PPAR / Troglitazone / Rezulin / Resulin / Romozin / Hypoglycemic Agents / Insulin adj7 sensiti* / Dipeptidyl-Peptidase IV Inhibitors / DDP-4 / Incretin / Glucagon-Like Peptide 1 / GLP-1 / GLP / Exenatide / Byetta / Liraglutide / Victoza / Vidagliptin / Galvus / Sitagliptin / Januvia / Saxagliptin / Onglyza / Linagliptin / Tradjenta / Janumet / / Inositol Phosphates/ or exp Inositol / D-Chiro Inositol / Inositol / Bydureon / Pharmaco* / Drug* / medication* / Biguanide* / Glitazone* / Dipeptidyl-Peptidase IV" adj7 Inhibitor / DDPIV / Gliptin* / oral antidiabetic agent /

Lifestyle Interventions: Diet / Feeding Behavior / Food / Nutrition / Eat / Body Weight / Body Mass Index / BMI / Nutrition Policy / Caloric Restriction / Energy /

Exercise / Physical Exertion / Isometric Contraction / Exercise Therapy / Sports / Running / Walking / Bicycl* / Jogging / Swimming / Life Style / a*robic / isotonic / physic* adj3 behavio* / fitness. / sit* adj3 time / p*edometer / activit* adj3 train* / Mountaineering / body adj25 train* / cycling / Movement / Sedentary Lifestyle

Patient Education as Topic / Patient-Centered Care / Education* / Self Concept / Cognitive Therapy / Psychotherapy / Behavior / Primary Health Care / community adj5 intervention / Relaxation Therapy / Social Support / Social care / Self Efficacy / Adaptation / "Power (Psychology)" / Motivation / structur* / Learning/ or exp Problem-Based Learning / exp Interview / lifestyle* / Community Health Services / exp Health Education / exp Health Promotion /

Appendix 4

Content of Appendix 4 (Curriculum for the SUCCESS education programme and the education material used for patient) is subject to copyright owned by the Leicester Diabetes Centre/University of Leicester.

1st edition

© Leicester Diabetes Centre 2013

For further information regarding the SUCCESS study, please feel free to contact the author of this thesis (Dr Hamidreza Mani at Hamidreza.mani@uhl-tr.nhs.uk , postal address; Room 9, Origin, Leicester Diabetes Centre at Leicester General Hospital, Leicester, LE5 4PW).

Appendix 4.4

What is PCOS
Patient Information Sheet

Polycystic Ovary Syndrome

PCOS (Polycystic Ovary Syndrome) is a common hormonal imbalance which may cause a variety of problems. People with this condition may complain of some, or all, of a number of symptoms including excess facial and body hair (hirsutism), irregular or absent periods, and difficulty becoming pregnant. Some, but not all, patients are also overweight.

PCOS is so-called because scans of the ovaries show that they contain many small cysts, a few mm in diameter around the edge of the ovary. This does *not* mean that you have an 'ovarian cyst' which is a completely different problem.

In fact, polycystic ovaries are just the most obvious part of an imbalance in the production of several normal hormones from the ovaries, adrenal glands & the pituitary gland, and levels of insulin in the body.

PCOS is very common. Surveys have shown that perhaps a quarter of normal women, including most of those with a mild excess of facial hair and many of those with slightly irregular periods, suffer from a mild version of the condition.
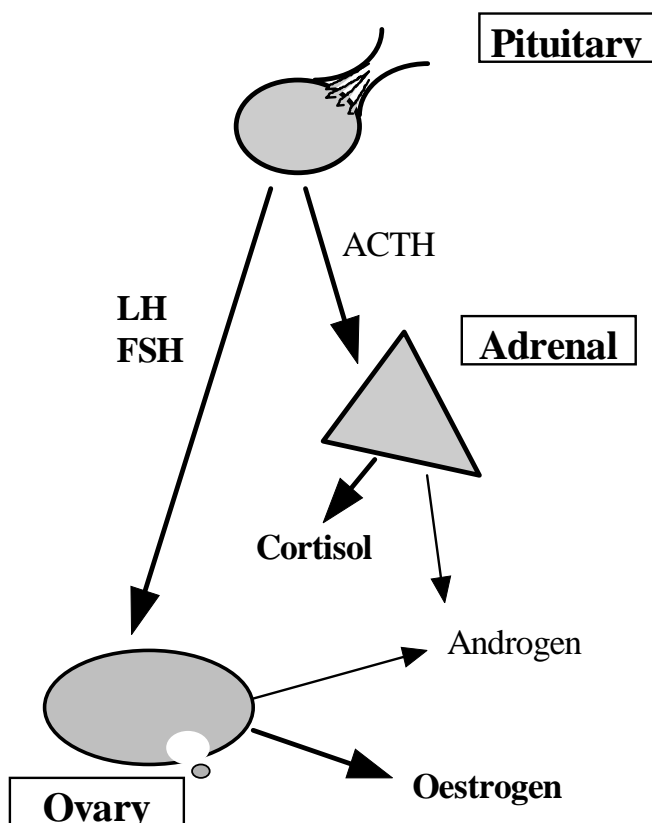
The Normal Hormone Balance:

The **pituitary gland** is connected to the underside of the brain and controls many other glands in the body by producing a variety of hormones.

The **adrenal gland** is mostly involved in producing the body's natural steroid hormone *cortisol,* under the control of the pituitary hormone ACTH

The **ovary** produces eggs for ovulation and produces the normal female hormone *oestrogen* under the control of the pituitary hormones *LH and FSH*

Both ovary and adrenal normally produce a small amount of male-like hormones, or *Androgens.*
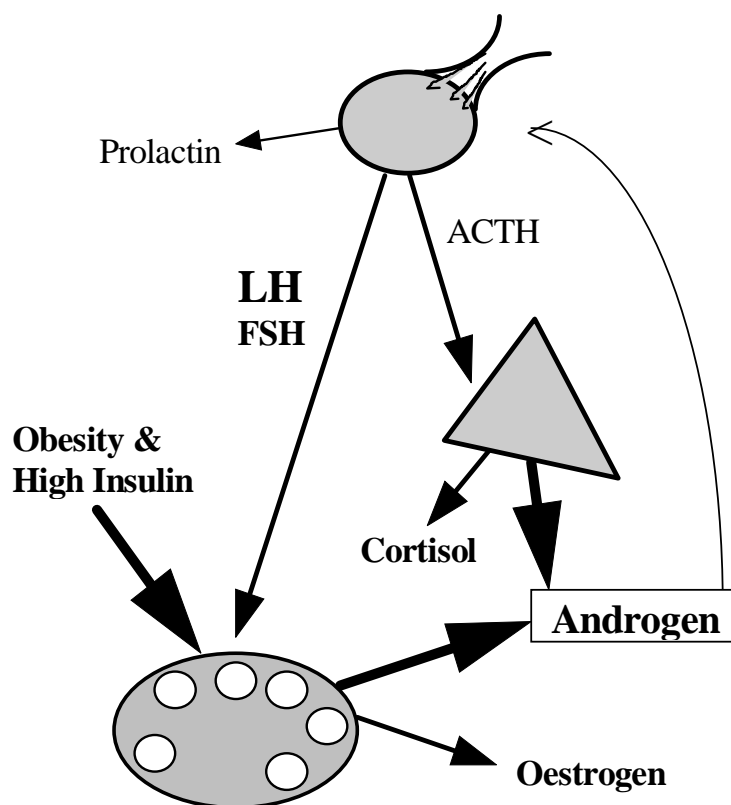
In **PCOS,** both ovaries and adrenals produce rather more of the male-like *androgens* than normal. This is responsible for the excess hair growth and interferes with the normal cycle of ovulation and periods. Ultrasound scan may show multiple small cysts around the edge of the ovaries.

As a result of the changing balance of androgens in the blood the pattern of production of pituitary hormones is also altered (more LH than FSH, and sometimes more of another hormone prolactin). This in turn causes the production of even more ovarian androgen.

High **insulin** levels, made worse by obesity, also drive more androgens from the ovary, but a high insulin also makes it easier to gain and harder to lose weight. A vicious circle is therefore set up.

It is not clear whether this vicious circle begins with the ovary, the adrenal or even the pituitary or part of the brain which controls it. What is clear is that it represents a basic part of the way your body is built and handles its hormones and energy supplies.

Treatment of Polycystic Ovary Syndrome

Dr Trevor Howlett, Leicester Royal Infirmary 2009

The various problems of PCOS can be treated in several different ways:

1. You can remove the excess hair in any way which you find convenient (plucking, waxing, threading, shaving, electrolysis, 'laser' [but beware this is expensive], removal creams etc). Removal will not itself make the hair worse – but most methods of removal won't usually stop it regrowing either.

2. Regular exercise, and appropriate diet if you are overweight, will help reduce high insulin levels in your body and reduce this part of the vicious circle.

3. Treatment with oestrogen (usually a combined contraceptive 'pill' such as *Dianette* or *Marvelon*) will switch off the ovary's excess production of androgen and will usually ensure regular periods

4. In more severe or resistant cases: Male-hormone-blocking drugs such as *Cyproterone, Spironolactone* or *Finasteride* can block the effect of androgens on the skin.

5. *Metformin* may be used in increase sensitivity to insulin

6. Occasionally adrenal hormone production can be switched off using *Prednisolone* (a steroid hormone)

7. If infertility is a problem, a number of techniques may help you produce an egg. This includes metformin and prednisolone, as well as tablets of *Clomiphene* and injections of *hCG* and *FSH.* For more complicated treatments we would refer you to the Assisted Conception Unit for closer monitoring.

More Information on Internet:
- www.PCOSupport.org
- www.verity-pcos.org.uk
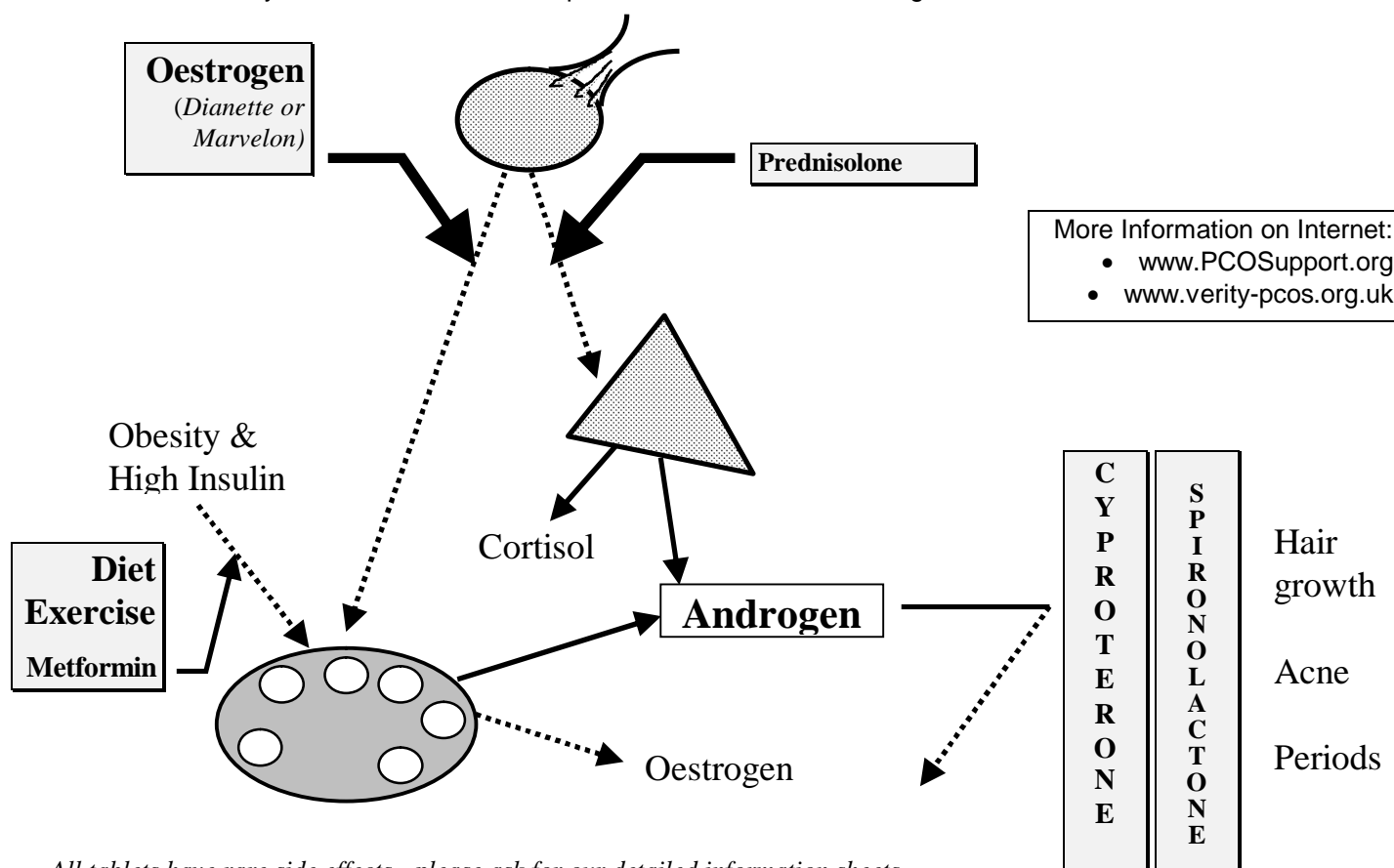
All tablets have rare side effects - please ask for our detailed information sheets

Excessive hair is usually slow to respond to treatment (remember it has also usually taken several years to develop, and has to stop getting worse before it can get better). It is unusual to notice any significant benefit in less than 6 months, and the maximum effect usually requires a year or two of treatment.

Although more complicated treatments can usually be stopped after a couple of years, many patients find they need to continue with some simple treatment (such as the 'pill') in the longer term if they wish to maintain the benefits of treatment

How to take Dianette (or Marvelon) and Cyproterone in combination:

Week 1	Week 2	Week 3	Week 4	Week 5	etc etc	
						Combined treatment is taken on a regular cycle
						Repeating the pattern every 4 weeks
						A period will normally occur in the week off treatment
1	*Days*	21	28	1	>>	**Marvelon or Dianette**: Take for Days 1 to 21 of every 28 days
1	14			1	>>	**Cyproterone**: Take for Days 1 to 14 of each Pill pack

Choice of Drugs Used in Polycystic Ovary Syndrome & other causes of Hirsutism and Possible Side Effects
Endocrinology Clinics, Leicester Royal Infirmary

- Drugs are frequently used to treat the symptoms of polycystic ovary syndrome, and in particular to treat the excessive growth of hair.
- Inevitably all drugs have some side effects, although these are usually rare. Overall we know that all the drugs we might recommend for treatment of this condition are usually effective, and completely safe in the vast majority of people who take them, but this information sheet is designed to explain more fully the effects and possible rare side effects of these tablets.
- Drugs for PCOS usually need to be taken for many months or years and this means that a small number of people may suffer long term bad effects on their health due to side effects. If we were treating some other serious medical condition, then this small 'bad-health' effect would be balanced against a large 'good-health' effect in everyone else. However, when treating PCOS or other causes of excessive hair we are usually treating a symptom (often just excessive hair growth) which will *not* in itself have any bad effects on your long-term health.
- You should also be aware that none of the drugs we use routinely actually have an official drug license to treat excessive hair problems (although they are used for this throughout the world). In every case the official license has been given to treat some other condition.
- Because of this, we believe that it is important for every patient to understand the effects, and possible side effects, of the drugs used to treat PCOS, and to be happy in her own mind that the problem being treated (and the good effect usually obtained) is 'worth' the very small risk of side effects due to the drug.

Suppression of the Ovaries using the Combined Oral Contraceptive

This is the most common treatment used to treat hair and period problems. It 'switches off' the ovary from producing its abnormal hormone levels and usually enforces a regular period cycle. Good effects on hair growth occur in most people after 6-12 months and then continue to improve for several years on treatment.

- All such 'Pills' may cause minor symptoms - such as fluid retention, slight weight gain, and changes in mood - in people who are sensitive to them.
- Migraine and high blood pressure may both be worsened, and these conditions often mean that the 'Pill' cannot be used. If you have 'hemiplegic' migraine with weakness or numbness of one side of the body during the migraine aura then you must not take the Pill (increased stroke risk)
- Patients often worry about cancer, but the news here is good - cancers of the ovary and body of the womb are much *less* common in women on the pill; cancer of the neck of the womb (cervix) is more common but this may actually be related to sex rather than the Pill itself, and in any case is picked up and treated by the cervical smear screening programme. People worry about breast cancer but the most complete study so far has concluded that the risk of breast cancer is only increased by 1% in women on the Pill, and decreases back to normal when Pill is stopped
- Risk of blood clots is the most significant problem to consider. This is a particular problem in women who are over 35 years old and who smoke or are very overweight, and we usually avoid the Pill in these women. Blood clots in the legs (which cause sudden onset of a red, painful, swollen leg) occur rarely but we now know that Pills which tend to have the best effect on hair have a slightly higher risk of blood clots compared to older Pills...

Marvelon - is a 'modern' Pill which we know improves hair problems in a majority of women. It contains a low dose of oestrogen (30 micrograms) and a newer 'progestagen' which has no male-like activity. **Yasmin** is a similar modern Pill. **Dianette** - contains a slightly higher dose of oestrogen (35 micrograms) and a small dose of an 'anti-male' hormone – cyproterone – and has been most widely used around the world. These types of Pill are now known to have a slightly higher risk of blood clots in the leg than older pills. The risk for Marvelon has been estimated as 30 per every 100,000 years taking the drug (compared to 5 per 100,000 on no treatment) - so that the absolute risk is actually very small – but about twice the risk of older 'Pills' (see below). The risk for Dianette appears to be similar. Only a minority of people who develop a blood clot would go on to get one of the more serious complications which threaten life (e.g. a pulmonary embolism). The risk of dying due to this sort of Pill has been guessed to be one in 500,000 years (which is rather less than the risk of being murdered, and compares to a risk of dying from smoking

cigarettes of 1 in 200 per year). In addition, for Dianette, rare serious side effects have been described in men taking higher doses of cyproterone (see below), but this has rarely if ever been seen on the sort of doses found in Dianette. We know that both of these Pills help hair growth, but noone has ever proven whether one is better than the other. We tend to use Dianette in the first instance since we often wish to add a higher dose of cyproterone later on. There is also a recent suggestion (as yet unproven) that Dianette may worsen depression.

Other 'Pills' - are exactly the same as Dianette or Marvelon in all side effects apart from blood clots. Older Pills (e.g. Microgynon 30, Brevinor) are now known to have a slightly lower risk of blood clots (quoted as 15 per 100,000 years) and so are preferred if the only aim is contraception or making the periods regular. However, these older pills all contain a progestagen with mild 'male-like' actions, which means that they are usually not effective in helping excessive hair or acne. These Pills cannot therefore be recommended to treat this sort of problem.

Cyproterone Acetate

Cyproterone is a drug which blocks the action of male-like hormones. It is usually our second line drug if Dianette alone has had no effect on hair problems after 6-12 months.

- Cyproterone is almost always used in combination with a contraceptive pill, usually 100mg taken for the first 14 days of every Pill pack. This is used because ...
1. This combination appears to be the most effective for improving excessive hair
2. Cyproterone is long acting and usually stops the periods completely if given alone
3. Since the drug would block the male hormones of a male baby it is essential that pregnancy is avoided
- Cyproterone usually makes the periods lighter and occur later in the week off the 'Pill'. Sometimes this means that the periods don't happen at all, and we then need to reduce the number of days of cyproterone treatment – typically to the first 12 days and then the first 10 days is still no periods. This is more likely in people who are very overweight
- A few people get a little drowsy or depressed on treatment - but this is not often a problem
- A rare serious side effect causing damage to the liver has been described. This is usually in men taking 200-300mg of cyproterone every day for prostate cancer, and it seems to be extremely rare (if it occurs at all) in women taking our normal dose. Because of this slight risk we will check your liver blood tests before and during treatment. You should stop treatment immediately if you become jaundiced (yellow skin/eyes)
- Cyproterone may encourage the growth of a type of benign brain tumour called meningioma – you should not take cyproterone if you are known to have this sort of tumour.

Spironolactone

Spironolactone is another drug which blocks male-like hormones. We normally use this is women who cannot take the Pill and/or Cyproterone. The usual dose is 200mg a day.

The drug was developed as a mild water tablet and has also been used to lower blood pressure (it also blocks another hormone in the kidney) - this may be another reason for choosing this drug.

Most people feel well on Spironolactone but potential problems include..

- Upset of the balance of salt and water in your body due to its water-tablet effects. We will check a blood test to rule this out.
- Periods may become more irregular, although many patients notice no change, and in some the periods actually seem to get better!
- Since the drug would block the male hormones of a male baby it is essential that pregnancy is avoided – which means additional care with contraception in many cases
- Bleeding stomach and duodenal ulcers may be more common (2-3x the very small normal risk)
- Substances derived from spironolactone *may* cause tumours in *rats* when given in high doses for a long time. This effect has never been proven in human beings, but has led the drug licensing authorities in this country (but not in most other countries) to suggest that it should not be the first-choice when someone needs a water tablet. There is no proof that this is a real risk, but not enough information to completely rule out this problem as a rare side effect – although it seems unlikely to be significant for short to medium term use.

Dr Trevor Howlett, Leicester Royal Infirmary, 2009

Choice of Drugs Used in Polycystic Ovary Syndrome & other causes of Hirsutism and Possible Side Effects:
2) Newer or Less common Drugs
Endocrinology Clinics, Leicester Royal Infirmary

- Drugs are frequently used to treat the symptoms of polycystic ovary syndrome, and in particular to treat the excessive growth of hair.
- Inevitably all drugs have some side effects, although these are usually rare. Overall we know that all the drugs we might recommend for treatment of this condition are usually effective, and completely safe in the vast majority of people who take them, but this information sheet is designed to explain more fully the effects and possible rare side effects of these tablets.
- Drugs for PCOS usually need to be taken for many months or years and this means that a small number of people may suffer long term bad effects on their health due to side effects. If we were treating some other serious medical condition, then this small 'bad-health' effect would be balanced against a large 'good-health' effect in everyone else. However, when treating PCOS or other causes of excessive hair we are usually treating a symptom (often just excessive hair growth) which will *not* in itself have any bad effects on your long-term health.
- You should also be aware that none of the drugs we use routinely actually have an official drug license to treat excessive hair problems (although they are used for this throughout the world). In every case the official license has been given to treat some other condition.
- Because of this, I believe that it is important for every patient to understand the effects, and possible side effects, of the drugs used to treat PCOS, and to be happy in her own mind that the problem being treated (and the good effect usually obtained) is 'worth' the very small risk of side effects due to the drug.

Finasteride
Finasteride is a drug which blocks the production of a powerful male-like hormone in the skin itself. Like most anti-male-hormone drugs, it was developed for use in men with prostate problems - but has been used to treat excessive hair problems in women.
- Studies comparing different treatments suggest that addition of finasteride to the 'Pill' causes further improvement in excessive hair - but show that overall the effect is much the same as Cyproterone and Spironolactone (with which we have greater experience).
- *We may suggest finasteride in patients who cannot tolerate cyproterone or spironolactone, or in whom these drugs have not been effective.*
- Since the drug would block the male hormones of a male baby it is essential that pregnancy is avoided (which is also why the drug pack information insert says that women should avoid it)
- There is little long-term experience of finasteride or its side effects in women, but in men relatively few side effects have been described. Patients are sometimes allergic to the tablets, which may cause lip swelling and rash - if this occurs you should stop the treatment.

Metformin
Metformin is a drug which has now been used for over 10 years in the treatment of PCOS, but which has been used from very many years in the treatment of diabetes. It works by increasing the sensitivity of the body to insulin - women with PCOS are often ' insulin resistant', and we now know that this resistance contributes to the hormonal imbalance which causes the symptoms of PCOS.
- Although metformin has been available for many years our experience in PCOS is still relatively short term. Several studies have suggested that metformin improves the irregularity of the periods, increases the chance of ovulation ('releasing an egg') and therefore increases the chance of falling pregnant in PCOS – particularly when overweight. Metformin is less effective in helping the excessive hair growth, although it does appear to help in a significant proportion of cases.

- You may have heard the metformin helps weight loss. This certainly seems to be true for some people but it seems not for everyone and, although the effect can occasionally be dramatic, for most it is only a matter of a few pounds.
- <u>Metformin can cause stomach upsets (nausea, vomiting, diarrhoea) so that we recommend that the dose is slowly increased to the usual dose of 1 tablet (500mg) three times a day over a couple of weeks and taken with the main meals - if this is done then most people can take the tablet without problems.</u> If you are unable to take ordinary metformin due to these side effects then we usually recommend trying the 'slow-release' form of the medication.
- Metformin is not recommended in people with liver or kidney problems, and we will check this before starting the drug. Metformin is not usually recommended in pregnancy <u>in diabetics</u> (since insulin treatment is always recommended in such cases in the UK), but even in diabetes has been used without problems in some parts of the world. In PCOS there is still relatively little information, but no evidence of harm, in patients who become pregnant - however it is sensible to stop the drug as soon as pregnancy is confirmed. The only exception to this is if there have previously been multiple miscarriages – when we occasionally recommend continuing he drug.
- Overall, in our experience, metformin seems to be a great help to some people, but doesn't help everyone.
- *We often suggest use of metformin in our clinic in patients who are overweight, especially with irregular periods and/or trying to fall pregnant.*

Clomiphene

Clomiphene is used to stimulate the ovaries to produce eggs and is usually the next step if someone is having difficulty becoming pregnant. This is usually supervised by the Fertility clinic. The usually dose is 50mg-100mg from days 2 to 6 of the menstrual cycle.
- Clomiphene rarely causes disturbances of vision (the drug should be stopped)
- The risk of multiple pregnancy is slightly increased, but anything more than twins is very rare
- If the ovaries are over-stimulated then they may become swollen and painful - contact your doctor if you get severe pain in the lower part of your abdomen.
- The Committee on Safety of Medicines has warned that there might be an increased chance of ovarian cancer if the drug is used for a long time and have recommended no more than 6 cycles of treatment (but this needs to be balanced against the fact that becoming pregnant considerably *reduces* your risk of ovarian cancer)

Steroid Hormones

Steroid hormones (Prednisolone or Dexamethasone) improve the hormone imbalance of PCOS. They do not seem to have very much effect on the hair problems, but can improve acne, make the periods more regular and help fertility.
- Giving more steroid hormone than the body usually produces would cause a large number of side effects - and you may well read about these. However, these are only seen with doses much higher than those we would recommend for PCOS
- We aim to give the same dose of steroid which your body normally makes, and give it in a special way to switch off your natural steroid hormones and 'swap one for the other'. It is hard to get this dosage perfect, so steroids are rarely used as a long-term treatment, but may occasionally be helpful.
- If we use these drugs, you should carry a steroid card and will need to increase the dose if you suffer from another stressful illness (e.g. diarrhoea or 'flu'). Be sure that you have a copy of our 'Steroid replacement' information sheet if you are taking these tablets

Dr Trevor Howlett, Leicester Royal Infirmary, 2009

Appendix 5.1

REC Letter

NRES Committee East Midlands - Leicester

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839425
Facsimile: 0115 8839294

20 June 2011

Professor Melanie Davies
Professor of Diabetes Medicine
Unversity of Leicester
Diabetes Research Group
Level 0, Victoria Building
Leicester Royal Infirmary
LE1 5WW

Dear Professor Davies,

Study title:	**StructUred eduCation programme to improve Cardiovascular Risk in womEn with polycyStic ovary Syndrome; SUCCESS study**
REC reference:	**11/EM/0141**

Thank you for your letter of 31 May 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

This Research Ethics Committee is an advisory committee to the East Midlands Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

271

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Evidence of insurance or indemnity		13 August 2010
Interview Schedules/Topic Guides: Phase 1	1	20 February 2011
Interview Schedules/Topic Guides: Phase 2	1	20 February 2011
Interview Schedules/Topic Guides: RCT	1	20 February 2011
Investigator CV		23 February 2010
Letter from Sponsor		21 February 2011
Letter from Statistician		
Letter of invitation to participant: Phase 1	1	20 February 2011
Letter of invitation to participant: Phase 2	1	20 February 2011
Letter of invitation to participant: Phase 3	1	20 February 2011
Other: CV - Student		20 February 2011
Other: Phase 3 GP Invitation Letter	1	20 February 2011
Other: NIHR		14 December 2010
Other: Peer Review - Alison Goodall		03 September 2010
Other: Peer Review - David Jones		18 August 2010
Other: Peer Review - Professor Williams		11 September 2010
Other: Patient Journey		
Other: Participants Flowchart in Success		
Other: Phase 3 recruitment email	1	20 February 2011
Other: Instruction Sheet	1	20 February 2011
Other: Phase 3 GP results letter end of study non diabetes	1	20 February 2011
Other: Phase 3 GP results letter end of study diabetes	1	20 February 2011
Other: Phase 3 Paticipant results letter non diabetes end	1	20 February 2011

of study		
Other: Phase 3 participant results letter diabetes non of study	1	20 February 2011
Other: Phase 3 GP result letter diabetes	1	20 February 2011
Other: Phase 3 GP results letter non diabetes	1	20 February 2011
Other: Phase 3 participant results letter non diabetes	1	20 February 2011
Other: Phase 3 participant results letter diabetes	1	20 February 2011
Other: Phase 3 participant results letter re-screening	1	20 February 2011
Other: Phase 1 participant appointment letter	1	20 February 2011
Other: Phase 2 participant appointment letter	1	20 February 2011
Other: Phase 3 participant appointment letter	1	20 February 2011
Other: Phase 3 participant re-screening appointment letter	1	20 February 2011
Other: Confirmation of address by GP	1	20 February 2011
Other: Covering Letter to P/O		31 May 2011
Participant Consent Form: Phase 1	2	24 May 2011
Participant Consent Form: Phase 2	2	24 May 2011
Participant Consent Form: Phase 3	2	24 May 2011
Participant Information Sheet: Phase 1	2	24 May 2011
Participant Information Sheet: Phase 2	2	24 May 2011
Participant Information Sheet: Phase 3	2	24 May 2011
Protocol	1	20 February 2011
Questionnaire: Polycystic Ovary Syndrome Questionnaire		
Questionnaire: SF-12		
Questionnaire: EuroQol		
Questionnaire: International Physical Activity Questionnaire		
Questionnaire: Brief Illness Perception Questionnaire		
Questionnaire: Exercise and Barrier self - efficacy		
Questionnaire: Eating Habits (DINE)		
Questionnaire: Epworth Sleepiness Scale		
Questionnaire: Hair Scoring		
Questionnaire: Scoring of excess hair		
REC application	66901/204757/1/492	07 April 2011
Response to Request for Further Information		31 May 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

Notifying substantial amendments
Adding new sites and investigators
Progress and safety reports
Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/EM/0141	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Carl Edwards
Chair

Email: jessica.chatrie@nottspct.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Student - Dr Hamidreza Mani*

   R&D Contact - Mrs Carolyn Maloney

Topic guide for the SUCCESS Study

Version 3

1. **Introduction to interview:** The researcher will reassure the participants taking part in the interview that:

   - The research team is interested in finding out about their views, experiences and understanding of PCOS

   - There is no intention of 'testing' participants

   - Participants are free to say as much or as little as they wish in response to any line of questioning

   - The content of the interview will not be divulged to any healthcare professional involved in their care.

2. **Background information:** In order to be able to describe the sample of patients who contribute to the study, the interviewer will invite the person being interviewed to provide information about:

   Age at time of interview

   Ethnicity

   Can you tell at what age when you finished your full time education?

   When were you **diagnosed** with PCOS?

3. **Can you tell me about how you were diagnosed with this condition?**

   Probe; How did you **feel/what did you think** when you were given the diagnosis

4. **What did you experience which you think was associated with this condition? (Symptoms)**

   Probe; Is any of them **more important** to you?

   If interviewee does not come up with anything;
   There are lots of symptoms associated with this diagnosis which some people experience. Don't you mind if I read out a few of them? I should emphasize that this does not mean that you are going to have these symptoms (interviewer to go through the list)

   - Hirsutism
   - Menstrual irregularity/Infertility
   - Polycystic ovaries

- Weight gain
- Acne

Probe; Is any of them more important to you?

5. **What treatment / advice have you been offered or you have done?**

   Prompt if any of the following not mentioned:
   - Medication
   - Lifestyle
     - Diet
     - Exercise
   - Any other things that you do to help manage this condition?

   Probe: **How successful** do you think the treatments have been?

6. **Understanding, knowledge, beliefs and attitudes about the condition**
   - What do you think **caused the condition**? (**Why do you think you had this condition**?)

   - Why do you think it **started**?   **Probe**: e.g. **family history/wt gain**

   - Are you aware of any **long term effect** of this condition?
     Prompt: for example
     - Diabetes/ Insulin resistance?

7. **Can you describe your experience of living with this condition?**

   Probe: Has your experience of living with this condition **changed over time** or not?
   Probe: What effects has this condition had on **your job**, **social interaction**?
   Probe; Have you felt it difficult (at anytime) to **cope** with this condition?
   Probe: If yes, **what kinds of things have made it difficult to cope / manage this condition**?

8. **How do you feel about managing it?**

9. **Do you think people's cultural background (Ethnicity), makes any difference to how you cope with PCOS or get support?**

10. **If you wanted to find more information to help you manage your condition, where would you go?**
    Prompt:
    - Other people with the condition
    - Healthcare professional
    - Internet
    - Charity (Verity)

11. **How do other people in your life support you with this condition?**

2

Prompt:

- Family
- **Friends**
- Colleagues
- Wider networks extended family, community, neighbourhood

Probe;
- **What support** they have offered?

- **How do you find their interactions and feelings**?

12. **How did you find the support and care that was given to you by the doctor/nurse?**

   Probe: **What** kinds of things they did or said which **helped** you?
   What kinds of issues in relation to the care and support given by them was not

   helpful?

13. I am going to read two sentences to you. Please tell me which one do you agree more?

   Overall I have **control** over my PCOS

   Overall it is the PCOS which **controls** me

14. A part of this research will involve us developing and delivering education sessions to help manage the condition and reduce their risk of complications. This will include providing knowledge to increase their understanding of the condition and what is it besides talking about how changes to diet and physical activity can help.

Education intervention;

   Probe: Is this something that **you would be interested in taking part** in? (Explore **why**)

   Besides diet and physical activity is there anything else you think should also be included?

   How would you like the education to be delivered, at the moment, for other conditions   like diabetes, we invite people to group education sessions. Prompt: If not mentioned:

   - DVD
   - Internet forums-twitter, forum, face book

   What do you think are some of **things that may prevent people from attending these education sessions**?

3

277

What do you think are some of **that might motivate people to attend** education?

If you were to attend; would you prefer a **3.5 hours session** with a break **or 2 sessions of 2 hours** after work/ weekend / early morning?

15. In our education programme we offer the participants to **attend with a family member or friend** if they wish to. What would you feel if you were in the session and someone else had come with a relative/friend who does not have PCOS? **Probe**; **What if this person was a male**?

16. Who else do you think needs to be educated and how?

Prompt;
- Could this be part of the sex education at school?
- Do you think both sexes need to be educated about the condition? (boys and girls)
- Just general posters at e.g. GP surgeries?
- If that public education was available, would that reduce the embarrassment, shyness about the symptoms and signs?

17. Thinking back to when you were **first diagnosed** what do you feel **would have better prepared you for managing PCOS**?

18. Is there **anything else** that you may wish to discuss that we might not covered but feel is important?

19. Would **want to be invited to the trial running** of the trial which we develop based on these interviews?

Thanks.

PHASE 2 PROCESS EVALUATION TOPIC GUIDE

Notes: The detailed version of the topic guide will be developed by the research team, as part of the study. The areas listed below indicate likely broad topics to be covered by the questionnaire;

The focus is on **gathering experiences of participants to the intervention**.

- Experience of attending the workshop/meeting/teaching sessions

- Key messages taken away from the workshop

- Most/Least helpful part

- Help with understanding PCOS?

- Message delivered

- Impact; Change as a result of the education

- Suggestions

Your thoughts on the workshop………….

Best bits

☺ ....

☺ ....

☺ ....

What do you think was the key message(s) of the workshop?

IDEAS for improving

✏ ....

✏ ....

✏ ....

What I didn't enjoy

☹ ....

☹ ....

☹ ....

Thank you for your time.

The level of the workshop was…	too easy ☐	about right ☐	too difficult ☐
The length of the workshop…	too short ☐	about right ☐	too long ☐
What do think about the venue?			
What is the best time to hold a workshop?			

Other comments and any other topics you'd like to know more about

Thank you for your time.

Your thoughts on "more walking/exercise" ……….

When do you think it will be easiest to do more walking/exercise?

☺ ....

☺ ....

☺ ....

IDEAS for helping others in the future to walk more/exercise

✏ ....

✏ ....

✏ ....

When do you think it will be more difficult to do some walking activity (exercise)?

☹ ....

☹ ....

☹ ....

Other comments on being asked to walk more/exercise

Thank you for your time.

Appendix 5.5:

SUCCESS
Study

Struct**U**red edu**C**ation programme
to improve **C**ardiovascular risk in
wom**E**n with polycy**S**tic ovary **S**yndrome;
SUCCESS study

PHASE 3
SUCCESS Study Randomised Controlled Trial:
PARTICIPANT INFORMATION SHEET

Professor Melanie Davies Professor of Diabetes Medicine, University of Leicester and University Hospitals of Leicester NHS Trust
Professor Kamlesh Khunti Professor of Primary Care Diabetes and Vascular Medcine, University of Leicester
Dr Hamidreza Mani Clinical Research fellow, University Hospitals of Leicester

Invitation to participate:

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it involves. This information sheet is designed to help you decide whether you would like to participate in this study. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

As you may already know, PCOS is the most common hormonal disorder which affects up to 1 in 5 women in the population. Studies have shown that half of these women have some problems in controlling (metabolism) of their blood sugar and therefore are at increasing risk of developing Diabetes. This problem gets worse if the patient is overweight as well.
Studies have shown that if women with PCOS make change to their liftesyle (diet and activity), they may reduce their risk of getting diabetes and heart diesase in the future.
We have developed an educational programme that can be run in groups (Structured education) to support women with PCOS make the lifestyle changes needed to improve their PCOS and prevent health problems in future.
We are keen to find out whether this programme works and is it effective in improving the glucose metabolism in PCOS. This study is designed to test this programme and answer our question.

Why have I been chosen? Can anyone take part?

You have been invited to take part in the study because you have a diagnosis of Polycystic Ovary Syndrome (PCOS), you are aged between 18-50 years old and you have a recorded body mass index (BMI) of

Body Mass Index ≥ 23 kg/m^2 for Black and Minor Ethnicities

Body Mass Index ≥ 25 kg/m^2 for White Europeans

In order to take part we also need you to have a good grasp of spoken English because this study is designed around an educational programme which will be delivered in English. In addition, if you are taking steroid medication for any long-term medical complication you may not be eligible to take part.

It is also required that you have not been started on any new medication for treatment of your PCOS in the past 6 months.

Do I have to take part?

It is up to you to decide; participation is voluntary. We will describe the study and go through the information sheet. We will then ask you to sign a consent form to show that you have agreed to take part. You will be given a copy of the signed consent form. You are free to withdraw at any time without giving a reason. The treatment and standard of care you receive from the NHS will not be affected if you decide not to take part or to withdraw.

What will happen to me if I take part?

This study will last for 1 year and we will meet up with you at the start of the study, after 3 and 6 month and then at the end of the study at 12 months. At the first visit you will be invited to visit the diabetes research team at a local venue and this visit will take around 3 hours. You will have the chance to meet the friendly members of our team, and to ask any questions you might have before signing our consent form. You will be asked to fast for this visit (water only from midnight the night before). When we meet you, we will record information about your medical history, any tablets you take and any family history of any medical conditions. We will check your blood pressure, weight, height and waist measurement. Blood tests will be taken. You will then be given Lucozade to drink and your blood tests will be repeated after 2 hours. These blood tests help us assess your risk of diabetes.

During the 2 hour wait between blood tests, you will be asked to complete some questionnaires about your activity and diet, and also on your past medical history. We will also use this time to introduce the activity monitor, known as the 'Actigraph'. This small device is worn on your waist and records your movement during waking hours. We will demonstrate how to use the device and provide written instructions. After this study visit we would like you to wear the device for 10 days during waking hours. We do this to assess how active you are and how much time you spend sitting. Once you have worn the device for 10 days, it is returned to us in the post so we can download information about how active you have been. Once your 2 hour blood test has been taken you are free to leave. We will give you tea and biscuit but we will not serve any food after the test, however you can bring your own light snack and food for after the test. We will send a copy of your blood results to your GP.

What happens next?

Taking part in the study involves being randomly entered into one of two study groups. The groups will be randomly selected by computer (a bit like tossing a coin), so you cannot choose which group you are in. You will *not* know which group you are in before consenting to take part in the study. Randomisation will happen after we have received the "Actigraph" monitor in the post but before we look at your data.

Group 1 is what we call the **'control' group**. If you are in this group, you will receive some useful leaflets informing you about PCOS and about how exercise can be used to help in treatment of this condition. At the end of the study period (one year) we will offer you the chance of attending the same 3.5 hour educational programme that is being given to Group 2 (see below).

Group 2 is the education group. If you are randomly assigned to be in the education group, we will invite you to the 3.5 hour SUCCESS education session. At this visit you, along with 4 to 9 other individuals like you, will be seen by two educators who will deliver an interactive seminar focusing on what it means to have PCOS, what are the effects of diet and exercise on it and how can we take control of our life with PCOS. During this visit we will discuss your blood results, blood pressure and weight with you and discuss ways of improving your results, one of which is increasing your physical activity. During the next year you will have the opportunity to be in regular contact with a healthcare professional with a wide range of resources to help you.

At the end of the course you will be given a pedometer to help you monitor your walking activity. This will let you set goals to help you increase your physical activity. It is our hope that this increase in physical activity will improve all aspects of PCOS and your general well being.

Regardless of which group you are in at 3, 6 and 12 months, we will ask you to visit us for a further fasting and 2 hour glucose blood test. This will help us keep an eye on your diabetes risk and your general well-being. During these visits we will also take a blood sample to measure your cholesterol levels and some key hormones that we measured before. We will also measure your:

- Height
- Weight
- Hip and Waist Measurements
- Blood Pressure

We will ask you to complete a questionnaire at each visit, just as you did when you joined the study and we will ask you to wear the same small 'Actigraph' physical activity monitor for ten days after each visit.

Optional additional assessments

We would also like to collect some further important measurements from you. However these measurements are optional – it is for you to decide whether or not you would like to have them done.

We would like to give you the option of attending Glenfield Hospital (Leicester) to have the muscle and fat content of your body assessed by a dual energy X-ray absorptiometry (DEXA) scan and an abdominal magnetic resonance imaging (MRI) scan. These scans will give you and us a detailed picture of the amount of muscle and fat you have in your body. In particular these scans will be able to measure how much fat you have stored around your vital organs, such as your liver and kidneys. This type of fat is particularly harmful and is strongly linked to your future risk of both type 2 diabetes and heart problems. DEXA and MRI scans are routine clinical tests but carry a small risk. DEXA involves exposure to radiation. The level of radiation exposure is exceedingly small (20μSv per scan) in comparison to the natural background radiation we are all exposed to (approximately 3000 μSv per year). The same level of radiation exposure would be received during a 2 hour intercontinental flight from radiation arising in outer space. MRI scans can be of concern for individuals who are highly claustrophobic (uncomfortable in confined spaces) and may be unsuitable if you have certain medical conditions. Both scans require you to lie still for up to 30 minutes. It is important to stress that these scans are optional and will not affect your participation in the study. If you have these scans performed at the start of the study, we would like to invite you have them repeated at 12 months, the end of the study. This will help us to evaluate the effect of the study on body fat.

What do I have to do if I want to take part in this study?

If you decide to take part in the study you will be asked to sign a consent form when you come for your first visit. You will be given a copy of the patient information sheet and a copy of the signed consent form to keep for your own records.

What are the possible benefits of taking part?

By taking part in the study you and your GP will find out information about your diabetes risk, your cholesterol, your hormones, and your kidney and liver function from the blood tests. At the end of the study you will also be provided with information about how much activity was recorded at the four points over the year on the 'Actigraph' activity monitor. You are unlikely to directly benefit from participating in the study. The results of this study will be used to improve future assessment and care for patients like you who have polycystic ovary syndrome. The results of this study will also help inform future guidance on the activity levels required for health.

What if I change my mind after taking part in the study and wish to withdraw my consent?

As explained before, your taking part in the study is your choice and you are free to withdraw from study without giving any explanation, and your care will not be affected in any way.
Your name will be removed from the study. Data collected from you in the study up to that point can also be removed on your request. You can also ask for you blood samples to be removed from storage and destroyed.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Data will be stored either in locked filing cabinets' or in password protected databases which are only accessible by members of the research team. Any information about you which is disseminated will have your name and address removed so that you cannot be recognised from it. Information collected will not be used for any other purpose than that explained here. Your GP will be informed that you are taking part in this study.

What are the side effects of any treatment received when taking part?

You will not be given any medication as part of this study. However you may suffer slight discomfort while the blood samples are being taken from your arm and some people do experience bruising after blood samples have been taken.

What are the risks of taking part?

Taking part involves minimal risk for you, just the inconvenience of taking the time to participate in the study. The aim of this study is to develop an understanding of the impact of an educational programme and increase in physical activity on PCOS. This will allow us to develop a fuller understanding of the role of lifestyle change in this condition.
This study itself may not be of direct benefit to you but it will contribute to the ongoing work aimed at the improvement in care for PCOS.
The tests in the study are not designed for clinical diagnosis, but in the unlikely event that we may find an abnormality (eg diabetes) this will be discussed directly with you. With your permission, we will pass this information to your GP and any relevant specialist(s) with the aim of organising prompt and appropriate investigation and treatment.

Will my taking part in this study be kept confidential?

Absolutely! All information that is collected about you during the course of the research will be kept strictly confidential in secure locations within Leicester Royal Infirmary.

Will my GP be informed of my results?

Yes, your family doctor will be informed of all the results of the tests taken as part of this study. When the study stops your GP will become the main point of contact for any ongoing concern. After the end of the study your care in regard to your diagnosis of PCOS will continue as it has always been. We will ask for your consent to contact your GP.

Will I get study and travelling expenses?

Parking charges and travelling expenses up to £25 per visit can be reimbursed.

What will happen to the results of the research study?

The results of the study may be published in a professional journal, but you will not be identified by name in any publications. You will be informed about the results of the study when it has finished.

Who is organising and funding the research?

This study is being organised and co-ordinated by the University Hospitals Leicester and Diabetes Research Group in University of Leicester. The funding is Diabetes Research Group and British Endocrine Society.
.

What if something goes wrong?

It is very unlikely that you will come to any harm during this study. However, if you do come to harm through your direct participation this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the patient information and liaison service (PILS) are available to provide independent help, advice and support. They can be contacted at:

Patient Information and Liaison Service
Gwendolen House
Gwendolen Road
Leicester LE5 4QF

08081 788337 (free phone number)

Your legal rights to claim compensation for injury where you can prove negligence are not affected.

Who has reviewed the study?

This study was reviewed by the "Leicestershire, Northamptonshire & Rutland Research Ethics Committee".

Contact for Further Information

Thank you for taking the time to read this information sheet. The doctors involved in this study will be pleased to discuss any questions or concerns that you may have. If you have any further questions about this research please contact Dr Mani on 0116 2047981 or email him at Hamidreza.mani@uhl-tr.nhs.uk

INSTRUCTION SHEET: ACTIVITY MONITOR

- Wear the activity monitor everyday for the **next 10 days**

- Put the activity monitor on every morning when you get up and take it off when you go to bed.

- Wear the monitor on your waistband above the right hip.

- If using the belt attachment please remember to keep the belt a 'snug' fit

- Do not get the activity monitor wet so please take it off if you are bathing or showering or doing watersports activities (eg swimming). It is, however, alright to wear the activity monitor if it is raining.

- Please record the time you put the accelerometer on and off and the time you got up and went to bed on the record sheet provided. If you take the monitor off during the day please also note the time and reason it was off.

- Make sure the activity monitor is the right way up. The black button should be at the top.

- You do not need to do anything with the activity monitor - just wear it

- Please return the activity monitor as discussed with the research team.

- If you have any questions or difficulties with the monitor please contact Dr Hamid Mani on 01162047981 *or* hamidreza.mani@uhl-tr.nhs.uk

RECORD SHEET ACTIVITY MONITOR

NAME: _____

Over the next 10 days please use this sheet to record:
a) the time you woke up at
b) the time you actually got up out of bed
c) the time you first put the activity monitor on in the morning
d) the time you last took the accelerometer off in the evening
e) any other times during the day when you took the monitor off and the reason why you took the monitor off during the day
f) the time you went to bed at (fill this in the following morning)
g) the time you actually fell asleep at (fill this in the following morning)

Day Date	Woke up at (a)	Got up at (b)	Monitor on (morning) (c)	Monitor off (evening) (d)	Other times when I took the monitor off and why (e)	Bedtime (f)	Went to sleep at (g)
Mon 17th Dec	0700	0720	0740	2210	1500-1600 (swimming)	2230	2300

Please bring this completed record sheet to your next project visit – Thanks.

Day & Date	Woke up at	Got up at	Monitor on (morning)	Monitor off (evening)	Other times when I took the monitor off and why	Bedtime	Went to sleep at

SCORING OF EXCESS HAIR
Gynae-Endocrine Clinic
Department of Diabetes & Endocrinology
Leicester Royal Infirmary   **Date: /   / 200**

For each area of your face and body, **please tick the box which best describes you**
Use the picture to help you decide if you are uncertain

A	✓	**Upper Lip**	B	✓	**Chin**:
0		No hair	0		No hair
1		Few scattered hairs	1		Few scattered hairs
2		Several hairs at the outer margins of the lip	2		Several hairs with small thicker patches
3		Full cover with sparse, thin or light hair	3		Full cover with sparse, thin or light hair
4		Full cover with thick, dark coarse hair	4		Full cover with thick, dark coarse hair *or* "5 o'clock shadow"

C	✓	**Sideburns**:	D	✓	**Chest**:
0		No hair	0		No hair
1		Few scattered hairs	1		Few hairs around the nipples only
2		Several hairs with small thicker patches	2		Many hairs around nipples *and* in middle of chest
3		Full cover with sparse, thin or light hair	3		Sparse, thin or light hair all over chest
4		Full cover with thick, dark coarse hair	4		Thick, dark coarse hair all over chest

E	✓	**Upper abdomen**: (Upper stomach)	F	✓	**Lower abdomen**: (Lower stomach)
0		No hair	0		No hair
1		Few hairs in midline	1		Few hairs in midline
2		Many hairs in midline *only*	2		Many hairs in midline *only*
3		Sparse, thin or light hair all over upper abdomen	3		Thick dark hair in midline, extending from pubic hair with or without sparse, thin or light hairs elsewhere
4		Thick, dark coarse hair all over upper abdomen	4		Thick, dark coarse hair all over lower abdomen

G	✓	**Upper Back**:	H	✓	**Lower Back**:
0		No hair	0		No hair
1		Few scattered hairs	1		Small tuft of hair at bottom of back
2		Several hairs with small thicker patches	2		Large tuft of hair at bottom of back
3		Full cover with sparse, thin or light hair	3		Full cover with sparse, thin or light hair
4		Full cover with thick, dark coarse hair	4		Full cover with thick, dark coarse hair

I	✓	**Upper Arms**:	J	✓	**Legs**:
0		No hair	0		No hair
1		Few scattered hairs	1		Few hairs on insides of legs, extending from pubic hair
2		Several hairs with small thicker patches	2		Thick hairs on insides of legs, extending from pubic hair
3		Full cover with sparse, thin or light hair	3		Full cover with sparse, thin or light hair
4		Full cover with thick, dark coarse hair	4		Full cover with thick, dark coarse hair

SUCCESS STUDY Self scoring excess hair   Version 1 20/2/2011

REMOVAL OF HAIR FROM FACE AND BODY

Please tick the appropriate boxes

How often do you remove the hair from each area? **What do you use to remove the hair?**

		Face	Body	Legs
0	Never			
1	Every few weeks			
2	Every week			
3	Several times a week			
4	Every day			

	Face	Body	Legs
1. Bleaching			
2. Pluck/Clip/Cut/Thread			
3. Removing cream			
4. Wax / Sugar			
5. Electrolysis			
6. Shave			

Please draw a line across each of the lines below to show how bad you feel that your hair problem is at the moment..

The whole hair problem overall *Best Possible* |————————————————————| *Worst Possible*

The hair on my FACE *Best Possible* |————————————————————| *Worst Possible*

The hair on my BODY *Best Possible* |————————————————————| *Worst Possible*

The hair on ARMS/LEGS *Best Possible* |————————————————————| *Worst Possible*

Appendix 6.1

Review article published in Diabetes Management

Appendix 6.2

Cardiovascular outcome paper in Clinical Endocrinology

The following published article has been removed from the electronic version of this thesis (pp. 309-317) due to copyright restrictions:

Mani H, Levy MJ, Davies MJ, Morris DH, Gray LJ, Bankart J, et al. Diabetes and cardiovascular events in women with polycystic ovary syndrome: a 20-year retrospective cohort study. Clinical Endocrinology, 2013, 78 (6), 926-934.
http://dx.doi.org/10.1111/cen.12068

The unabridged version can be consulted at the University of Leicester Library.