A Retrospective Analysis Of A Community Based Weight Loss Programme In Conjunction With Group Behavioural Change Sessions In Women With Polycystic Ovary Syndrome (PCOS)

Efsevia Anastasia Nikokavoura

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Centre for Obesity Research and Epidemiology, CORE
Institute for Health and Welfare Research, IHWR
Robert Gordon University
Aberdeen, UK
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PERSONAL CONTACT DETAILS

Mrs Efsevia Anastasia Nikokavoura

E-mail: 0817136@rgu.ac.uk /enicokavoura@yahoo.com

Phone number: +44 (0) 1224 262843

Institute for Health and Welfare Research (IHWR)

Centre for Obesity Research and Epidemiology (CORE)

Robert Gordon University

Riverside East

Garthdee Road

Aberdeen

AB10 7GJ

SUPERVISOR'S CONTACT DETAILS

Principal Supervisor:

Dr Wendy Wrieden, Reader

E-mail: w.wrieden@rgu.ac.uk

Phone number: (+) 44 (0) 1224 262856

Institute for Health and Welfare Research (IHWR)

School of Pharmacy and Life Sciences

Robert Gordon University

Riverside East

Garthdee Road

Aberdeen

AB10 7GJ

Secondary Supervisor: Professor Iain Broom

E-mail: j.broom@rgu.ac.uk

Phone number: +44 (0) 1224 262895

Institute for Health and Welfare Research (IHWR)

Centre for Obesity Research and Epidemiology (CORE)

Robert Gordon University

Riverside East

Garthdee Road

Aberdeen

AB10 7GJ

Third Supervisor:

Dr. Catherine Rolland, Lecturer

E-mail: ext.rolland1@rgu.ac.uk

Phone number: +44 (0) 1224 262893

Institute for Health and Welfare Research (IHWR)

Centre for Obesity Research and Epidemiology (CORE)

Robert Gordon University

Riverside East

Garthdee Road

Aberdeen

AB10 7GJ

Fourth supervisor: Dr John G Love

E-mail: j.g.love@rgu.ac.uk

Phone number: (+) 44 (0) 1224 263228

Institute for Health and Welfare Research (IHWR)

School of Applied Social Studies

Faculty of Health & Social Care

Robert Gordon University

Garthdee Road

Aberdeen

AB10 7QG

Abstract

Polycystic Ovary Syndrome (PCOS) is variously reported to affect between 5-26 % of reproductive age women in the UK and it accounts for up to to 75% of women attending fertility clinics due to anovulation. The major symptoms include ovarian disruption, hyperandrogenism, insulin resistance and polycystic ovaries. Interestingly, at least half of the women with PCOS are obese, with the excess weight playing a pathogenic role in the development and/or progress of the syndrome. In addition, PCOS is associated with negative psycho-social symptoms and overall a poorer quality of life.

Despite the increasing prevalence of PCOS, there is still a lack of consensus over the diagnostic criteria and large scale, well planned trials are limited. The first-line treatment option for overweight/obese women with PCOS is diet and lifestyle interventions, however optimal dietary guidelines are missing. Although a number of different dietary approaches have been investigated, data on the efficacy of very low calorie diets (VLCDs) on PCOS, are still lacking and further investigations both in the short and longer term data are needed.

The aim of this project is to investigate how overweight/obese women with PCOS respond to a commercial VLCD in conjunction with group behavioural change sessions, as compared to overweight/obese women without PCOS. Weight loss was achieved via a VLCD with an average intake of 630 kcal (57g protein, 57 g carbohydrate, 18g fat , 16g fibre and ≥100% recommended daily allowances (RDA) for vitamins and minerals). Data from women recruited into LighterLife Total from 2006 to 2011, were analysed at baseline, 12 weeks and 1 year.

The baseline analysis from the overweight/obese female participants, revealed significant differences in anthropometric parameters between women with and without PCOS. Women with PCOS were younger (mean ±SD) (34.5 ±8.2 versus 41.8±11.3, $p<0.001$), had greater body weight (105.7±19.3 versus 97.8±17.0, $p<0.001$), BMI (39.01±6.6 versus 36.4±5.8, $p<0.001$ and waist circumference (115.9±15.0 versus 109.9±12.9, $p<0.001$). A subset of these participants was

matched for age and BMI, and their analysis showed no significant differences at weight change at 12 weeks and 1 year. In more detail, a completers analysis after 12 weeks of VLCD, showed that the total weight change did not differ significantly between the PCOS group (n=137) and the non-PCOS group (n=137) (-10.4kg ±10.6 versus -10.4 kg ± 10.4, p=0.938) and the percentage of weight loss achieved by PCOS women was 17.1% ±5.6 versus 18.2% ±4.4 by the non PCOS group (p=0.08). Also, there were no differences after 1 year in weight (94.2 ± 19.9, n=41, versus 90.3 ± 27.6, n=35,p=0.476) and in BMI (33.4 ± 8.5, n=41, versus 35.2 ± 7.6, n=35, p=0.476). Moreover, the percentage of weight loss achieved by PCOS women at 1 year was similar with the one achieved by the non PCOS women (-15.6%±15.6 versus -12.4% ± 13.3, p=0.35).

Overall, it appears that this commercial VLCD alongside behavioural therapy, can be an effective strategy for achieving weight reduction in cases of excess weight in women with PCOS. However, further investigations are needed to achieve a thorough way of understanding the physiology of weight loss in PCOS via a VLCD approach.

Keywords: Polycystic ovary syndrome (PCOS), very low calorie diet (VLCD), lifestyle, weight, fertility, women, behavioural, obesity

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List of Abbreviations

ASRM	American Society for Reproductive Medicine
BED	Binge Eating Disorder
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
BP	Blood Pressure
BPM	Beats per Minute
CBT	Cognitive Behavioural Therapy
CDD	600 Calorie Deficient Diet
CHO	Carbohydrates
CVD	Cardiovascular Disease
DDD	Defined Daily Dose
DHEA (S)	Dehydroepiandrosterone (Sulphate)
ESHRE	European Society for Human Reproduction and Embryology
HBA1c	Glycosylated (or glycated) Haemoglobin
HC	High Carbohydrate
HDL	High Density Lipoprotein
HP	High Protein
IGT	Impaired Glucose Tolerance
IR	Insulin Resistance
kcal(s)	kilocalorie(s)
kg(s)	Kilogram(s)
LCHP	Low Calorie High Protein
LDL	Low Density Lipopropotein
LFRE	Low Fat Reduced Energy
LH	Luteinising Hormone
LL	LighterLife
LP	Low Protein
MK-0557	orally administered neuropeptide Y receptor Y5 antagonist
NHS	National Health System
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
OCU	Ongoing Check-Up
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
QOL	Quality of Life
R&D	Research and Development office
RCT	Randomised Clinical Trial
RDA	Recommended Dietary Allowance
RS	Research Student
SHBG	Sex Hormone Binding Globulin
SPSS	Statistical Package for the Social Sciences

SQL	Structured Query Language
T2DM	Type 2 Diabetes Mellitus
TA	Transactional Analysis
TCBT	Transactional cognitive behavioural therapy
TC	Total Cholesterol
UK	United Kingdom
US	United States
VLCD	Very Low Calorie Diet
WHO	World Health Organisation
WHR	Waist to Hip Ratio
WSR	Waist to Stature Ratio

Introduction

1.2 Identification, diagnosis and prevalence of PCOS

In 1721, an Italian medical scientist , Antonio Vallisneri, gave for the first time a description of women who presented features of polycystic ovary syndrome (PCOS): "Young peasant woman, married, moderately plump, infertile, with ovaries larger than normal, like doves' eggs, lumpy, shiny and whitish" (Cooke, 1989). Then, in 1935, Stein and Leventhal were the first to investigate the association between bilateral polycystic ovaries and amenorrhea, infertility, hirsutism, acne and obesity and classify the cluster of all these symptoms as a syndrome (Stein 1935). Thus for many years, the combination of the above clinical features, was referred to as the "Stein-Leventhal syndrome". It is interesting to note that excess weight was part of the syndrome, since its first description.

Nowadays, PCOS is one of the most common female endocrine disorders, affecting 5- 26% of women of reproductive age (12-45 years old) in the United Kingdom (Michelmore et al. 1999, Hopkinson et al. 1998). This great variability observed is due to several factors. Firstly, its diagnosis is based on ultrasound and/or blood tests and as this can be quite costly, research investigating the prevalence of this syndrome is based on convenience samples, that are less than 400 individuals (March et al. 2010). Secondly, its diagnosis is mainly a "diagnosis of exclusion", implying that other causes of androgen excess or ovulatory disorders with well defined aetiologies are excluded, e.g. Cushing's syndrome, ovarian tumours, adrenal hyperplasia, thyroid dysfunction. There is, however, a lack of consensus over the diagnostic criteria used by physicians as well as a lack of robust methodology in the PCOS research, resulting in the large variability of the reported prevalence.

The most commonly used criteria are briefly described in Table 1:

Table 1: The different diagnostic criteria of PCOS

Diagnostic Criteria	Criteria applied
The European definition (Adams, Franks et al. 1985)	(i) Polycystic ovaries identified by ultrasound plus (ii) Menstrual disturbance and/or signs of hyperandrogenism
The American definition of 1990 by the National Institutes of Health (NIH, (Zawadzki, Dunaif 1992)	(i)Clinical and/or biochemical signs of hyperandrogenism plus (ii) Oligo-ovulation or anovulation plus (iii) Exclusion of related disorders
The bridge between the European and the US definition (Homburg 2002)	Women with at least one of the following should undergo ovarian sonography: Hirsutism, acne, menstrual disturbance, anovulatory infertility. Then, if sonography depicts polycystic ovarian morphology, PCOS is confirmed. If not, further biochemical tests are needed (e.g. LH, TT, FSH, insulin homeostasis and glucose tolerance) and if any of them is abnormal, then PCOS is diagnosed.
The Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004)	PCOS diagnosis implies the existence of at least two of the following, in addition to the exclusion of related disorders: (i)Oligo-ovulation or anovulation, (ii)clinical and/or biochemical signs of hyperandrogenism, (iii) polycystic ovaries
The modified NIH criteria (Azziz 2005)	PCOS patients should have all of the following: (i)Clinical and/or biochemical signs of hyperandrogenism, (ii)ovarian dysfunction: oligo-ovulation or anovulation and/or polycystic ovarian morphology,(iii) exclusion of relative disorders

Interestingly, by using the NIH criteria (Zawadzki and Dunaif 1992), the world prevalence of PCOS in reproductive age, ranges from 5 to 12% whereas the prevalence would double or triple if the Rotterdam criteria (2004) were used. This happens due to the fact that by the use of the latter criteria, 2 new phenotypes are being created: (1) Women with polycystic ovaries and ovulatory dysfunction but without androgen excess and (2) Women with polycystic ovaries and androgen excess, but with no ovulatory dysfunction.

Additionally, the prevalence as well as the expression of the PCOS symptomatology may differ according to patient's ethnicity. For instance, it has been suggested that PCOS is more prevalent in women of South Asian origin, than in Caucasians. However, research on the prevalence of PCOS in different

ethnic groups is limited and the results can be conflicting as some reviews suggest that the expression of PCOS is different among different ethnicities and not the prevalence of PCOS (Crosignani and Nicolosi 2001). Thusthere is a need for further studies to be conducted in large populations using the same criteria.

1.2 Investigation of the Aetiology of PCOS

PCOS is said to be responsible for up to 75% of cases of infertility caused by anovulation among women who attend infertility clinics in the UK (Franks 1989, Franks 1995). However, the exact aetiology and pathophysiology of PCOS is complicated. The hormonal imbalance due to a combination of elevated androgen levels and increased insulin secretion in combination with environmental e.g. lifestyle and genetic factors contribute to the aetiology of this syndrome. The most common signs and symptoms of this syndrome are: ovulatory dysfunction, polycystic ovaries, hirsutism, obesity, raised ratio of luteinising hormone / follicle stimulating hormone, acne, androgenic alopecia and acanthosis nigricans.

Although, the aetiology of PCOS remains unclear, four main hypotheses have been identified, which are not mutually exclusive and a summary of which, is shown in Table 2.

Table 2: Summary of the hypotheses involved in the aetiology of PCOS and their physiological effects

Type of Hypothesis	Proposed mechanism involved	Physiological Effects	References
Cortisol Hypothesis	Modified cortisol metabolism, adrenal androgen production may rise up to 25%	↑ levels of cortisol → ↑ secretion of ACTH Acceleration of activity of 5α reductase: *LIVER:* cortisol → 5α - dihydrocortisol *SKIN:* testosterone → 5α-dihydrotestosterone *URINE:* 5α >5β cortisol metabolites	Ehrmann et al.1992, 1992, Moran and Azziz, 2001, Rodin et al. 1994, Stewart et al. 1990, Turner et al. 1992
Insulin Hypothesis	Positive correlation between fasting insulin and androgen levels, activity of the ovarian cytochrome P450c17α is decreased	Increased production of progesterone to androstenedione and testosterone Reduction of hepatic synthesis of SHBG	Burghen et al. 1980, Dunaif 1986, Franks et al. 1991, Holte et al. 1995, Nestler and Jakubowicz 1996, Peiris et al. 1989, Robinson et al. 1992
LH Hypothesis	An increased sensitivity of the anterior pituitary gland to GnRH stimulation may lead to LH hypersecretion	↑ LH may lead to increased ovarian androgen production as LH stimulates the ovarian theca cells together with insulin for steroid biosynthesis	Balen et al. 1995, Dunaif 1986, Ehrmann et al 1995, Yen, Vela and Rankin 1970, Venturoli et al. 1988
Ovarian Hypothesis	Increased ovarian androgen production due to upregulation of the enzymatic system of steroidogenesis	↑production of 17α-hydroxyprogesterone and androstenedione in response to ↑LH	Ehrmann et al. 1992, Nelson et al. 1999, Nelson et al. 2001, Rosenfield et al. 1990

Abbreviations: ACTH: Adrenocorticotropic Hormone, GnRH: Gonadotropin Releasing Hormone, LH: Luteinizing Hormone, P450c17α : a bifunctional cytochrome which has both 17a-hydroxylase and 17,20-lyase activities, SHBG: Sex Hormone Binding Hormone

The "Insulin Hypothesis" proposes that a defect in insulin action could result in excess secretion of androgens, an excess that disrupts the ovulation process. The "Luteinising Hormone Hypothesis" suggests that a primary defect in the hypothalamic-pituitary axis results in hyperandrogenism and anovulation. The "Ovarian Hypothesis" proposes that a defect in the ovarian synthesis and/or metabolism of sex steroids, leads to hyperandrogenism and anovulation. And finally, the "Cortisol Hypothesis",proposes that a modification of the metabolic pathway of cortisol results in increased adrenal androgen production (Tsilchorozidou et al. 2003).

To conclude, PCOS includes a cluster of symptoms and signs, and its metabolic disturbances may increase the risk of specific diseases and health conditions such as cardiovascular disease, type 2 diabetes, hypertension, gestational diabetes, spontaneous abortion, breast and endometrial cancer and infertility (Herriot et al. 2008). However, despite the proposed mechanisms suggested to explain the origin of PCOS and the increasing consensus that its core features are insulin resistance, abnormal gonadotropin dynamics and androgen excess, its exact aetiology still remains unknown. Thus, there is great need for further research to elucidate the causation of this syndrome.

1.3 PCOS associated comorbidities

PCOS has been associated not only with a variety of reproductive and skin disorders, but also with an adverse metabolic profile (Figure 1) which includes systemic dysfunctions such as insulin resistance with compensatory hyperinsulinemia, hypertension and dyslipidemia (DeUgarte et al. 2006, Escobar-Morreale et al. 2011). Interestingly, these dysfunctions mirror the ones observed in individuals with type 2 diabetes mellitus (T2DM) (Sattar, 2009). In the long term, PCOS patients may develop impaired glucose tolerance (IGT), which can eventually lead to T2DM with increased risk for cardiovascular and cerebrovascular diseases (Wild et al. 2000, Christian et al. 2003, De Groot et al. 2011). Moreover, a number of prospective studies suggest that the prevalence of both IGT and T2DM, is higher in women with PCOS when compared with weight and age matched controls without PCOS (Ehrmann et al. 1999, Legro et al. 1999). It has also been documented, that the first degree relatives of PCOS patients may be at high risk for T2DM and IGT (Colilla et al. 2001, Legro et al. 2002, Norman et al. 1996, Yildiz et al. 2003), although further large scale family studies are limited.

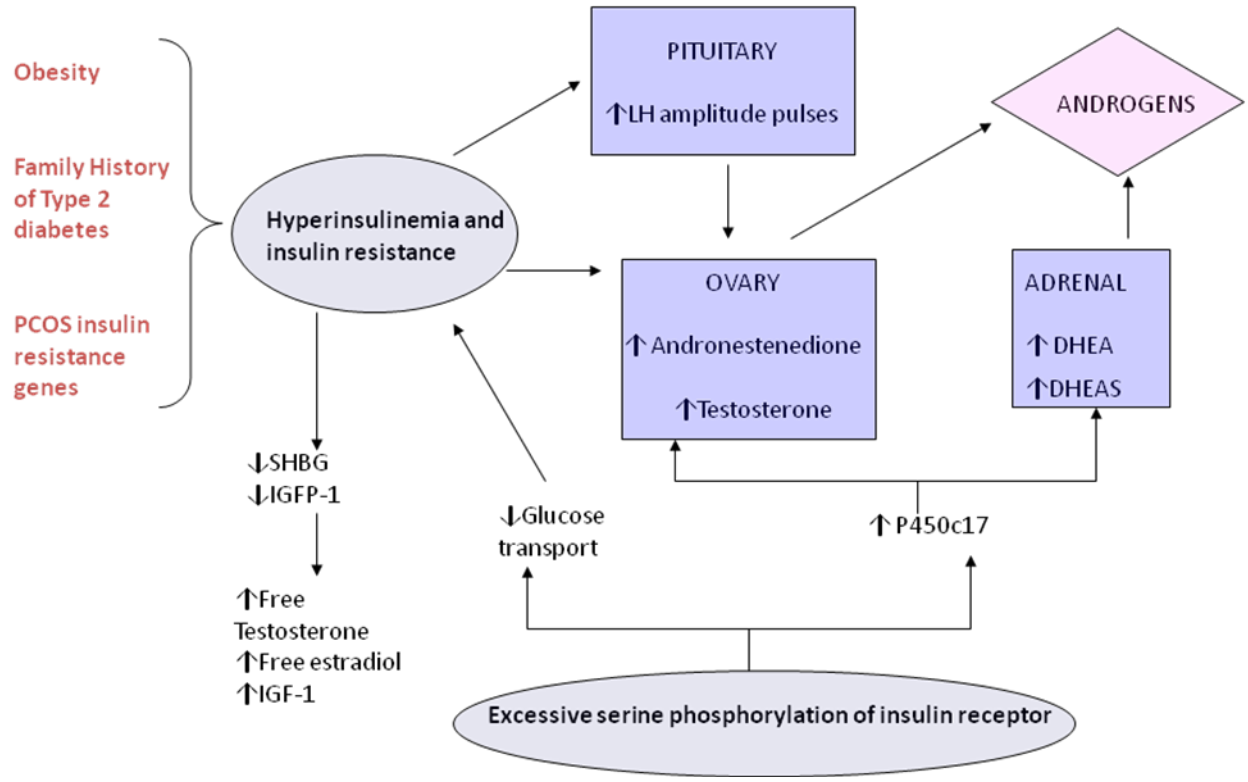

Figure 1: Biochemical and clinical abnormalities observed in PCOS, adapted from (Tsilchorozidou et al. 2004) LH: Luteinizing Hormone, SHBG: Sex Hormone Binding Globulin , IGF: Insulin Growth Factor, IGFP: Insulin Growth Factor Peptide , DHEA(S): Dehydroepiandrosterone (Sulphate)

At least half of the women with PCOS are obese (Must et al. 1999; Boeka et al. 2008), which could imply that PCOS patients may have a predisposition towards obesity (Hoeger and Oberfield 2012). Interestingly, the incidence of obesity within the PCOS population is higher than the one in the general population (40.4% among women in the UK). However, since the phenotype of PCOS has been mainly based on findings in a self or otherwise referred population, and not on an unselected population, this percentage may be overestimated (Ezeh, Yildiz and Azziz 2013). Moreover, obese women with PCOS, may face additional barriers in achieving weight loss, as compared to healthy women without this condition. This could be either due to the observed decreased postprandial thermogenesis which is also statistically correlated with the degree of reduced insulin sensitivity (Robinson et al. 1992) or due to specific eating behaviours (e.g. emotional eating) and snacking patterns (cravings for sweet and savoury snacks which are high in calories and fat) that are observed among overweight/obese women with PCOS (Jeanes et al. 2010).

However, additional research is needed to compare the actual rate of weight loss between obese PCOS and non PCOS.

1.4 Quality of Life in PCOS

In addition to the metabolic and reproductive disorders, women with PCOS are at increased risk of emotional distress and poorer quality of life (QOL) (Elsenbruch et al. 2003, Himelein and Thatcher, 2006, Jones et al. 2008, McCook et al. 2005), a fact that may have either pathophysiological and/or psychosocial impact (Farrell and Antoni 2010). Chronic disease is a risk factor for depressive disorders and decreased QOL (Wilhelm et al. 2003), however many of the PCOS features, such as menstrual irregularities, difficulties in conceiving and problems with the physical appearance (e.g. acne, hirsutism, excess weight, body shape etc.), intensify the self - dissatisfaction and perceived lower QOL (Elsenbruch et al. 2003, Grogan 1999, McCook et al. 2005).

Moreover, the prevalence of depressive symptoms and anxiety among PCOS patients is high (Hahn et al. 2005, Trent et al. 2002, Weiner et al. 2004), a fact that suggests that these patients may also present with low self esteem and unhealthy eating behaviours. Furthermore, depressive and anxiety episodes appear to be significantly increased when compared to either weight-matched (Weiner et al. 2004) or aged-matched (Elsenbruch et al. 2003) healthy women. In addition, Moran et al (2010), in an observational, cross-sectional study (24 women with PCOS versus 22 women without PCOS), identified that women with PCOS perceive themselves as individuals with the increased risk of remaining overweight/obese, a belief that can influence further their relationship with food.

Overall, the psycho-social dimensions of this syndrome negatively impact on the QOL of the affected women as well as their family and friends.

1.5 Treatment for PCOS

The first-line treatment for PCOS includes diet and lifestyle interventions (Moran et al. 2009) to promote a healthy weight, especially in cases of overweight and obese patients. Certain medications are also used to manage the accompanied symptoms. For example:

- Metformin, is prescribed to regulate the ovulation rates in women with PCOS (Lord et al. 2003),
- the Combined Oral Contraceptive Pill is given to alleviate acne and hirsutism (Glueck et al. 2002), however this may lead to weight gain due to possible fluid retention and increased appetite
- Clomifene Citrate or Gonadotrophins or ovarian drilling (a specialised laparoscopic or surgical procedure) are applied specifically for ovulation induction (Saleh and Khali 2004).

Up to date, the dietary treatment is focused on weight loss in overweight/obese women with PCOS. Interestingly, lean women with PCOS are also advised to follow a healthy nutrition, due to their increased risks for type 2 diabetes and other metabolic abnormalities (Herriot et al., 2008). In cases of excess weight, even a modest weight loss of 2-5% total body weight may restore ovulation (Clark et al. 1998, Crosignani et al. 2003, Huber-Buchholz et al. 1999, Moran et al. 2006, Tolino et al. 2005), improve the reproductive hormonal profile (Jakubowicz and Nestler 1997, Kiddy et al. 1992, Mavropoulos et al. 2005, Moran et al. 2006, Tolino et al. 2005), and achieve an improvement in insulin sensitivity (Holte et al. 1995, Huber-Buchholz et al. 1999, Jakubowicz and Nestler 1997, Kiddy et al. 1992, Mavropoulos et al. 2005). However, there is still a debate over what should be considered the optimal diet composition, resulting in the lack of accurate advice given by dietitians (Herriot et al. 2008).

For example, Liepa et al (2008) proposed that patients with PCOS should consume a diet that follows the same nutritional guidelines as for patients with T2DM (Liepa et al. 2008). On the other hand, Kasim-Karakas et al (2008), after conducting a 2-month free-living randomised study at a PCOS clinic, suggested that a hypocaloric diet supplemented with an extra protein meal, results in

greater weight loss when compared to a hypocaloric diet supplemented with simple carbohydrates.

Nicholson et al (2010), attempted to present the efficacy of long term (≥12 months) non-surgical weight loss interventions and to identify behavioural strategies for obese women with PCOS in a systematic review. It was concluded that there is not enough evidence for suggesting the ideal weight loss approach in the area of PCOS. This was attributed to the heterogeneity of the interventions, poor description of the protocol in some cases and lack of comparable data. In more detail, different criteria were used for PCOS diagnosis across the studies, a variety of dietary interventions was applied (plus medications and/or behavioural change elements), the duration of the interventions was variable and in some cases there was a lack of a control group. The following table, summarises the included studies and weight loss achieved.

Table 3: Summary table of the studies included in the systematic literature review by Nicholson et al. 2010

Principal author	Intervention	Group A results	Group B results	Group C results	Group D results
Hoeger et al. 2004	Group A: Metformin (n = 9) Group B:Lifestyle change + placebo (n = 11) Group C:Metformin + lifestyle change (n = 9) Group D:Placebo (n = 9)	M: −6.5% weight	LC + Pl: −6.8% weight	LC + M: −8.9% weight	Pl: −0.2% weight
Lemay et al. 2006	Group A: rosiglitazone + diet for 6 mo (n = 15) Group B: oral contraceptive (EE/CPA) + diet for 6 mo (n = 13) At 6 mo, groups A and B commenced rosiglitazone and EE/CPA	No significant weight change	No significant weight change		
Gambineri et al. 2006	Group A: Diet + placebo (n = 20) Group B: Diet + metformin (n = 20) Group C: Diet + flutamide (n = 20) Group D: Diet + metformin + flutamide (n = 20)	D + Pl: −5 ± 16 kg	D + M: −4 ± 13 kg	D + F: −9 ± 9 kg	D + M + F: −10 ± 14 kg
Glueck et al. 2006	Group A: Metformin + diet (n = 20) Group B: Diet (n = 3)	M + D: −7.7% weight	D: −3.3% weight		
Zulian et al. 2005	Group A (BMI < 25): spironolactone for 12 mo (n = 5) Group B (BMI > 25): spironolactone + diet for 12 mo (n = 7)	No weight loss	Mean BMI: −2 ± 4.7 kg/m^2		
Glueck et al. 2003	Groups A and B: metformin for 12 mo Group A: pioglitazone for 10 mo (n = 13) Group B: metformin for 10 mo (n = 26)	No weight loss	Median: −6 kg weight		

Principal author	Intervention	Group A results	Group B results	Group C results	Group D results
Glueck et al. 2006	Metformin + dietary advice (n = 89)	Mean: (8.9% weight loss)			
Crosignani et al. 2003	Diet + physical exercise (n = 33)	76% (n = 25): ≥ −5% weight 33% (n = 11): ≥ −10% weight			

Adapted from Nicholson et al. 2010. Abbreviations: M, metformin; LC, lifestyle change; Pl, placebo; D, diet; F, flutamide; BMI, body mass index.

Interestingly, Jeanes et al (2009) aimed to evaluate the advice given by dietitians to women with PCOS specifically in the UK. The patients were recruited via "Verity" (Verity is a charity that provides support to women across the UK, diagnosed with PCOS) , and the dietitians were contacted by the British Dietetic Association and its branches. Overall, 105 dietitians completed the survey, 206 patients filled in questionnaires (the questionnaires were tailored specifically for the study and included questions related to PCOS diagnosis, self reported symptoms, body weight, height and related nutritional advice obtained) and 196 completed a 7-day food diary. According to the data received, 57% of the PCOS patients were following either a low glycaemic index diet (34%), or a weight loss diet (16%) or a combination (26%).

Moreover, 73% of overweight women with PCOS were not following a diet to initiate weight loss. Interestingly, only 15% of the participants had seen a registered dietitian, while all the others were following a diet based on commercial diet books either prescribed or via word of mouth. In addition, the majority of the patients who were following an exercise program mentioned a significant improvement in their symptoms.

Overall, although PCOS patients recognise the importance of diet, a scientific consensus on the ideal nutritional prescription is still lacking while at the same time is very much needed (Jeanes et al. 2009).

1.5.1 Very low calorie diets (VLCDs)

A very low calorie diet (VLCD), can be defined as a nutrition plan that provides ≤800kcal per day (National Task Force 1993) and it is comprised of either conventional meals or synthetic formulas –e.g. shakes, soups, bars – or a combination of both. However, modern VLCDs should not be confused with the VLCDs used in the 1970's, the latter being associated with a number of deaths, mainly due to inadequate provision of minerals, vitamins and

protein (van Itallie, 1978, Centre For Disease Control, 1979). Modern commercial VLCDs take into consideration the maintenance of lean body mass by fortification of the formulae with high levels of good quality protein and with essential electrolytes (sodium, potassium, bicarbonate, chloride, calcium, phosphates), fatty acids, minerals and vitamins (Dhindsa et al. 2003). This approach is safe and according to the National Institute for Health and Clinical Excellence (NICE, http://guidance.nice.org.uk/CG43/), it can be used up to 3 months, in medically supervised conditions for obese patients who fail to meet their weight loss target using a standard low fat, calorie deficient diet (CDD).

A VLCD can lead to an average weekly weight loss of 1.5-2.5 kg, versus the 0.4-0.5 kg loss achieved with the CDDs (Atkinson et al. 1993). Moreover, the average weight loss at 12 weeks for an obese individual is approximately 20 kg on a VLCD, whereas it is only 8 kg on a CCD (Atkinson et al. 1993). Consequently, a VLCD could be a good alternative for obese PCOS patients - both in the short and longer term-, who may face difficulties losing weight despite following standard approaches.

However, the majority of the research around the area of weight loss in PCOS has focused on several dietary approaches: high protein diet (30% protein), monounsaturated fatty acid (MUFA) enriched diet (17% MUFA), low fat (6% fat)-high carbohydrate (81% carbohydrates, CHO) diet, healthy eating (50% CHO, 20% protein, 30% fat), very low calorie diet (VLCD), high fat diet (25% CHO, 15% protein, 60% fat). Only 3 papers have examined the effect of VLCDs on PCOS (Tolino et al. 2005, Van Dam et al. 2002, 2004). The research by Tolino et al. (2005) showed that weight loss achieved after a 7 –month caloric restriction (4 weeks VLCD and the rest duration LCD) may lead to a decrease of the free testosterone and fasting insulin levels and induce further improvement in menstrual regularities. Van Dam et al (2002), carried out an interesting study to investigate the effect of short term dieting in LH homeostasis in obese patients with PCOS. According to the observations, both basal and pulsatile secretion of LH was three times higher in PCOS patients as compared to matched individual without PCOS, implying that caloric restriction failed to normalise the LH secretion. On the contrary,

total testosterone, glucose and insulin levels were decreased. In another study, the same researchers (Van Dam et al. 2004), examined 15 obese participants with PCOS. Patients were studied at baseline (occasion 1), after a week of VLCD (occasion 2) and then after achieving 10% weight loss of their original weight via a VLCD (occasion 3). Results suggested that after the weight loss achieved, the estradiol depentant negative feedback on LH was normalised and lead to resumption of ovulation.

1.6 Summary

PCOS is one of the most common female endocrine disorders, and it has been associated with a variety of reproductive and skin disorders, as well as with an adverse metabolic profile. In addition, it is associated with negative psycho-social symptoms and overall poorer quality of life for the women involved.

However, there is still a lack of consensus over the diagnostic criteria and large scale, well planned trials investigating its prevalence among different populations are limited. Also, despite the fact that the first-line treatment option for PCOS is diet and lifestyle interventions, optimal dietary guidelines are missing. Although there is evidence supporting the efficacy and safety of VLCDs, this approach has not been adequately investigated in the area of PCOS and both short and longer term data are still needed.

2. Aim

The aim of this project was to investigate how overweight and obese women with PCOS respond to a commercial VLCD with a behavioural component as compared to women without PCOS.

2.1 Objectives

1) To identify the baseline characteristics of women with PCOS undertaking a commercial VLCD in conjunction with a behavioural component
2) To determine whether women with PCOS present differently to women without PCOS following the same approach
3) To assess and compare the weight loss achieved at 12 weeks by women with PCOS versus women without PCOS
4) To assess and compare the weight loss achieved at 12 months by women with PCOS versus women without PCOS

3.Methodology

3.1 Project design

This project involved a retrospective analysis of a subset of the original LighterLife (LL) database which contained observations and measurements for every client that followed this commercial approach. The subset included anonymised data from women 18-75 years of age, with BMI≥28kg/m^2, who followed the LL Total approach from January 2006 until December 2011. The parameters that were originally planned to be analysed are: Age (yrs), Weight (kg), Stature (m), BMI (kg/m^2), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Smoking Status, Ethnicity (self reported), Attendance Rates, Foodpacks Consumed, Waist Circumference (cm), Hip Circumference (cm), Bust Circumference (cm), Medications.

However, information was either not available or available in an unsuitable for analysis format, thus the final analysis included the parameters in the following figure (Figure 2).

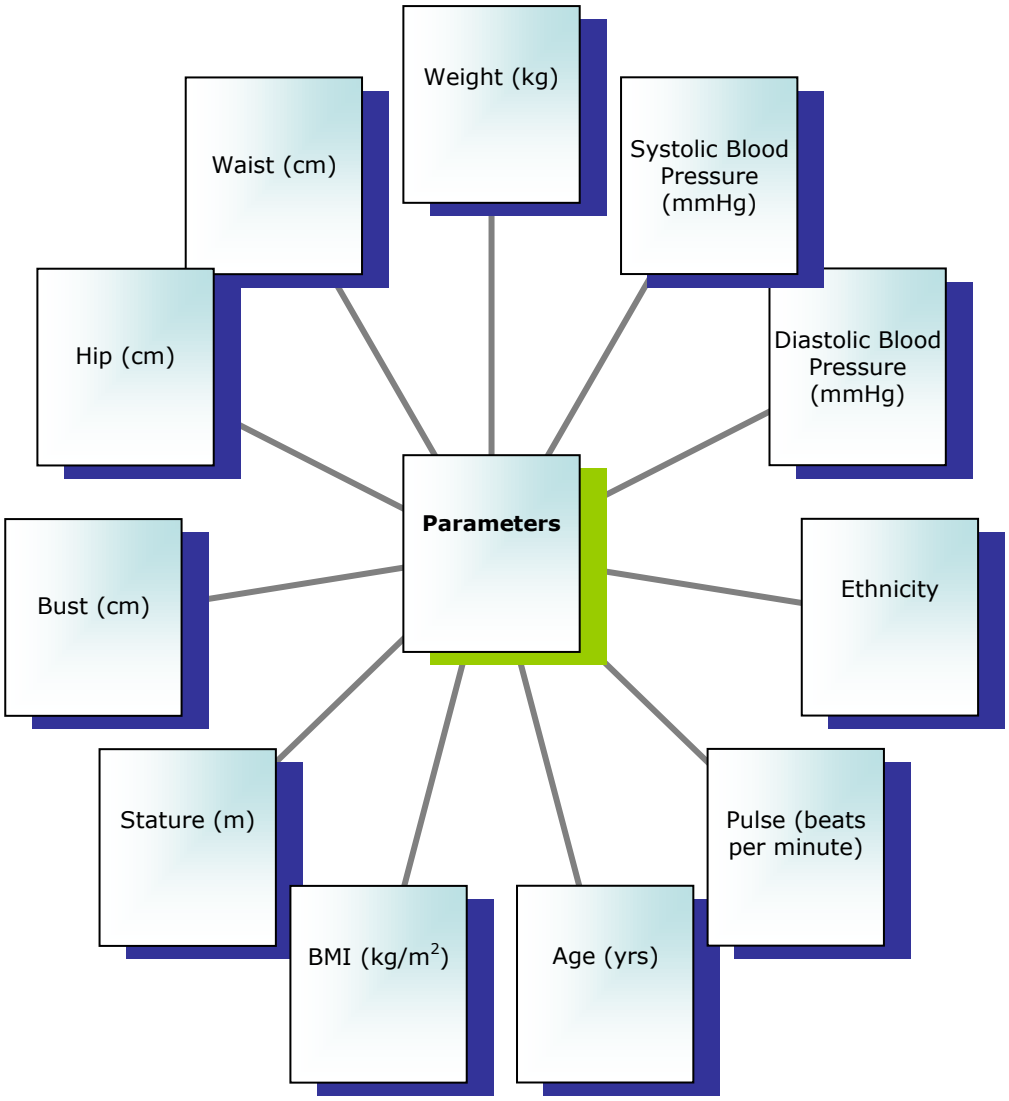

Figure 2: Parameters used for the epidemiological analysis of the LL database

The project was divided into 3 main parts (Figure 3):

i) The first part focused on the comparison of the baseline presentation of overweight/obese women with and without PCOS. Moreover, the prevalence of PCOS among the different ethnic groups was investigated.

ii) The second part examined whether overweight/obese participants with PCOS patients lose different amounts of total weight and at a different rate as compared to obese non-PCOS after they had all followed the LL programme for 12 weeks.

iii) The third part investigated whether the total weight loss differs between overweight/obese women with and without PCOS, at 12 months after the initiation of the VLCD.

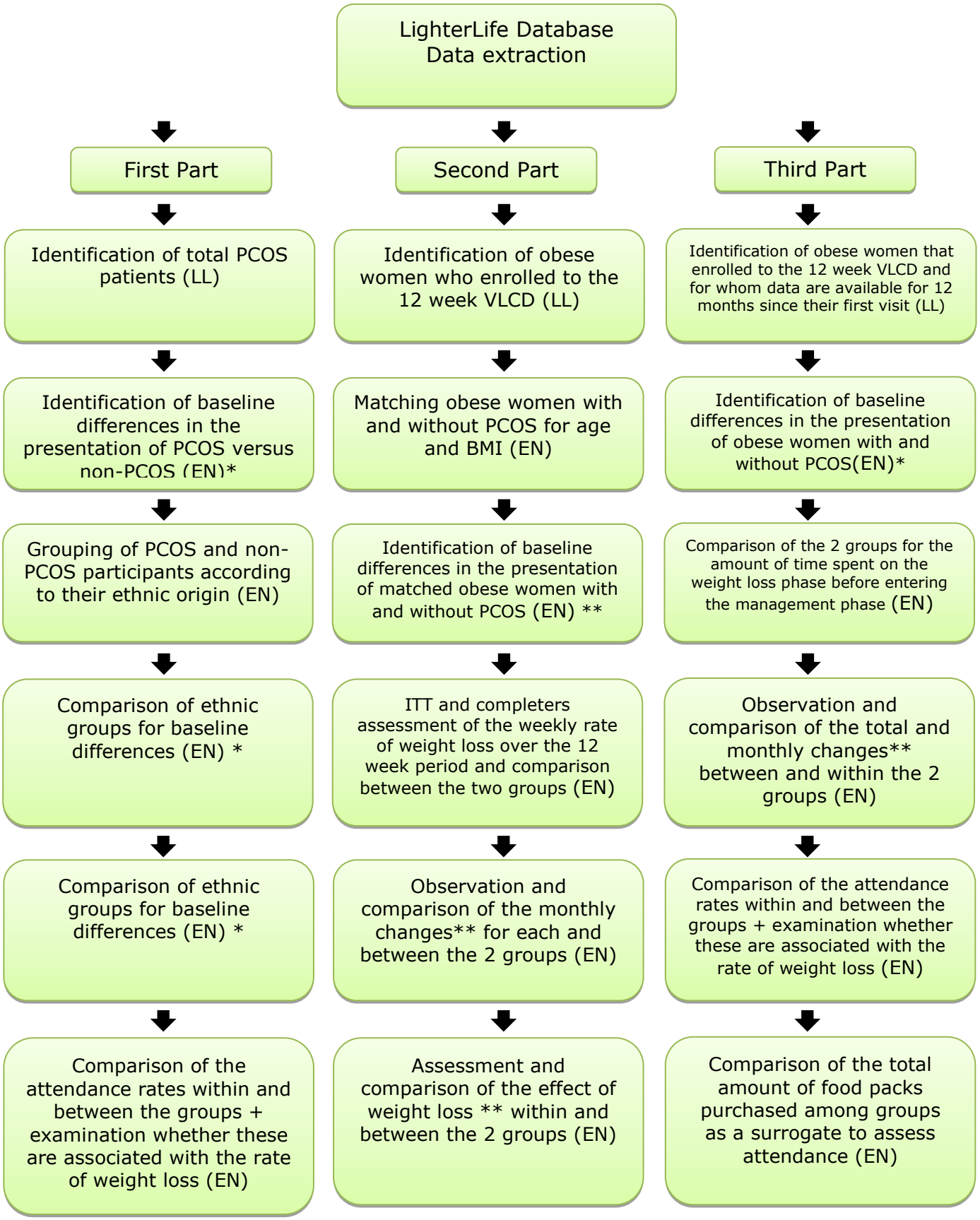

Figure 3: Schematic presentation of the database analysis (EN implies that the specific task was done by the research student, LL implies that the specific task was done by the data analyst of LighterLife)

*age (yrs), stature (m), body weight (kg), BMI (kg/m^2), waist circumference (cm), hip circumference (cm), bust circumference (cm), waist to hip ratio (WHR), stature to waist ratio (SHR), systolic and diastolic blood pressure (mmHg)

**body weight (kg), BMI (kg/m^2), waist circumference (cm), hip circumference (cm), bust circumference, waist to hip ratio (WHR), stature to waist ratio (SHR), systolic and diastolic blood pressure (mmHg) and medications (Defined Daily Dose)

3.2 The LighterLife Total Approach

The LighterLife Total is a nutritionally balanced VLCD combined with a behavioural programme and it is one of the several approaches used by LighterLife. Potential clients (both men and women) can follow LL Total if they either have BMI≥30 kg/m^2 or BMI ≥28-29.9kg/m^2 plus a waist circumference >88cm in women and >102 cm in men.

Initially, for the prospective client to enrol, a self - declared medical history needs to be filled in, which is later assessed by the LighterLife (LL) weight management counsellor. Then, the individual completes the Client Information Form (CIF, appendix), which will be checked by the medical department of the company. If any of the exclusion criteria are applicable (see section of Study Participants), the potential client will not be allowed to enrol. On the other hand, if the potential participant appears to be suitable, the Health Questionnaire (HQ, appendix) will be completed by their general practitioner or practice nurse, to confirm their self-declared information on the previously submitted forms. This questionnaire also includes details on past medical history, current blood pressure values and medications. After this step, and if all the inclusion criteria are met, the participant can start the LighterLife Total Programme. Then, throughout the active weight loss phase, an ongoing check up (OCU, appendix) is performed every 28 days, by a general practitioner or a practice nurse, where blood pressure is checked and medications may be adjusted. Below is a summary on patient's data acquisition (Table 4).

Table 4: Data Acquisition for LL clients

Data	Method of Acquisition
Information regarding ethnicity, smoking status and age (yrs)	Health Questionnaire submitted to the central LL database by the LL counsellors
Data on body weight (kg), stature (m), BMI (kg/m^2), waist circumference (cm), bust circumference (cm), hip circumference (cm) and smoking status	Submitted to the central LL database by the LL counsellors
Information on medications, blood pressure (mmHg) and disease status (PCOS).	Extracted from the medical form and then submitted to LL database
Updated every 28 days on any changes regarding medications, blood pressure and health status	Submitted through the ongoing check up form to the central LL database by the LL counsellors

According to the protocol of the LL Total, participants replaced conventional food with Foodpacks (soups, shakes, bars). These provide a daily average intake of 550kcal, 50g protein, 50g carbohydrate, mean 17g fat, 10-17gr fibre and at least 100% of RDAs for vitamins and minerals. Participants were advised to stay adequately hydrated while on the programme.

The LL Total Programme has two distinctive stages: active weight loss and weight management. Time spent on the weight loss period depends on the starting weight. However, in accordance with the National Institute for Health and Clinical Excellence (NICE, http://guidance.nice.org.uk/CG43/), participants were following the VLCD approach for up to 3 months. In case that further time was required, then the clients resumed the VLCD, after following a 7-day low calorie diet.

During each stage, the clients attend weekly group meetings of 4-12 people delivered by a trained LL counsellor, utilising group support and counselling to encourage long term behavioural modification and weight management. The behaviour change techniques applied, borrow elements from the

principles of Cognitive Behavioural Therapy (CBT) and Transactional Analysis (TA) -which form the transactional cognitive behavioural therapy (TCBT®)- and from the addiction/change theory (Buckroyd and Rother 2007, Chaston and Dixon 2008, Cooper et al. 2003). Following the active weight loss period, participants are gradually reintroduced to conventional food, following a standardised protocol (management), where foodpacks are gradually decreased while the consumption of the conventional food is increased (Appendix).

3.3 Study Participants

Women aged between 18-75 years, with BMI≥28kg/m^2, who followed the LighterLife Total approach from January 2006 until December 2011, were included in the analysis. Moreover, due to the LighterLife protocol, the following exclusion criteria were applicable:

- type 1 diabetes
- porphyria
- total lactose intolerance
- major cardiovascular or cerebrovascular disease
- history of renal disorder or hepatic disease
- active cancer
- currently suffering from thrombosis or have taken medication for this condition within the last six months
- serious illness, injury, trauma and/or surgery in the last 3 months
- epilepsy, seizures, convulsions, major depressive disorder, psychotic episodes, schizophrenia, bipolar disorders, delusional disorders
- current suffering from anorexia, bulimia or undergoing treatment for any other eating disorder
- due to undergo serious treatment /surgery
- are pregnant or breastfeeding
- have given birth or had a miscarriage in the last 3 months

3.4 Acquisition of Data from LighterLife

The research student composed a script for data extraction according to the study objectives. The script was later translated into standard system commands (Structured Query Language (SQL)) and then appropriate software (Microsoft Access) was used to generate data. When the new database was generated, the data analyst at LighterLife performed a process known as database cleansing. This involved visual inspection to investigate eligibility, validity and integrity of the records. For example it was checked whether all the data were consistently formatted, if there were any duplicates, missing values, if there was an increase or decrease in the weekly body weight >10kg etc. Due to the confidential nature of database cleansing –the data analyst occasionally needed to check the original participant files or to contact the LL counsellor of a participant-, the research student was not allowed to perform this procedure.

After the database cleansing, a subset of the original LL database (women 18-75 years of age, with BMI≥28kg/m^2, who followed the LL Total approach from January 2006 until December 2011) was sent to the research student and then the subset was checked by the student for any outliers before proceeding to further statistical analysis. This involved sorting cases using Microsoft Excel and searching for any extreme values that were outwith an expected range. In cases of extreme values, the LL data analyst was consulted before their removal.

The initial number of PCOS participants that were identified in the database was 574, but after data cleansing and checking for outliers 59 clients with PCOS were removed (515 remained). Regarding the non-PCOS clients, the original number was 109,412 but 7,317 were removed, leaving 102,095 participants for further analysis.

3.5 Statistical Analysis

Analysis of the individual parameters was performed by the use of descriptive statistics (e.g. mean, standard deviation). Then, all variables were assessed for normality using the Kolmogorov-Smirnov test. As the parameters were either normal or very close to being normally distributed, a set of appropriate parametric tests were executed. Specifically, differences of continuous variables between groups were assessed using an unpaired two-tailed t-test and differences within groups, were assessed via a paired t-test. If more than 2 groups were compared, analysis of variance (ANOVA) and other post hoc tests were used (Bonferroni). For categorical outcomes, non-parametric tests were used. All P-values were 2-sided, and a P-value of < 0.05 was considered as statistically significant. Analyses were performed with SPSS (SPSS Inc., Chicago, Illinois).

To avoid any potential biases stemming from the comparison of the large population in the non PCOS group (n=102,095) versus the much smaller sample of PCOS women (n=515), all the analyses were repeated for a randomly selected sample of 515 non PCOS women through a specific function on using SPSS. This process involves drawing a random sample from the whole population via the random selection procedure that is available on SPSS.

4.Results

4.1 Baseline Characteristics of LighterLife clients with PCOS versus without PCOS

There were 515 participants with PCOS and 102,095 who did not have PCOS (non-PCOS), out of a total sample of 102,610. The detailed baseline characteristics of the above groups are shown in Table 5.

Table 5: Comparison of baseline characteristics between PCOS (n=515) and non PCOS (n=102,095) participants

Parameter	All (n=102,610)	Non PCOS (n=102,095)	PCOS (n=515)	P†
Age (yrs)	41.8±11.3	41.9±11.3	34.5±8.2	<0.001*
Height (m)	1.64±0.07	1.64±0.07	1.65±0.07	0.018*
Weight (kg)	97.9±16.9	97.8±17.0	105.7±19.3	<0.001*
BMI (kg/m^2)	36.4±5.8	36.4±5.8	39.01±6.6	<0.001*
Bust (cm)	117.2±10.9 (n=25,248)	117.2±10.9 (n=25,137)	122.5±12.1 (n=111)	<0.001*
Hip (cm)	125.1±12.3 (n=25,119)	125.05±12.3 (n=25,009)	130.5±12.1 (n=110)	<0.001*
Waist (cm)	109.9±12.9 (n=25,247)	109.9±12.9 (n=25,136)	115.9±15.0 (n=111)	<0.001*
WHR	0.88±0.07 (n=25,101)	0.88±0.07 (n=24,991)	0.89±0.09 (n=110)	0.335
Pulse/min	75.8±9.3 (n=101,951)	75.8±9.3 (n=101,440)	76.6±8.8 (n=511)	0.067
Systolic BP (mmHg)	128.9±15.1 (n=101,951)	129.0±15.13 (n=101,440)	127.5±12.6 (n=511)	0.007*
Diastolic BP (mmHg)	81.1±10.6 (n=101,951)	81.1±10.6 (n=101,440)	81.4±10.2 (n=511)	0.536
Total Medications	1.0±1.6	1.0±1.6	2.5±1.6	<0.001*

Values are means ± standard deviation. Abbreviations: BMI, Body Mass Index; WHR, Waist to Hip Ratio.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

To avoid any potential biases stemming from the comparison of the large population in the non PCOS group (n=102,095) versus the much smaller sample

of PCOS women (n=515), the analysis was repeated for a randomly selected sample of 515 non PCOS women through SPSS. According to GPower 3.1, the choice of 515 participants in each group, would allow us to identify both small and medium effect size differences on weight, with the statistical power of 89% and 100% accordingly.

This analysis gave similar results except for height, where there was no longer a statistical difference between the groups (1.65±0.07 versus 1.64±0.07, p=0.054).

Table 6 : Comparison of baseline characteristics between PCOS (n=515) and randomly selected non PCOS (n=515)

Parameter	All (n=1,030)	Non PCOS (n=515)	PCOS (n=515)	P†
Age (yrs)	38.4±10.7	42.40±11.5	34.5±8.2	<0.001*
Height (m)	1.64±0.07	1.64±0.07	1.65±0.07	0.054
Weight (kg)	101.5±18.6	97.4±16.9	105.7±19.3	<0.001*
BMI (kg/m^2)	37.7±6.4	36.3±5.8	39.01±6.6	<0.001*
Bust (cm)	119.5±11.5 (n=233)	116.7±10.1 (n=122)	122.5±12.1 (n=111)	<0.001*
Hip (cm)	127.8±12.2 (n=232)	125.4±11.9 (n=122)	130.5±12.1 (n=110)	0.001*
Waist (cm)	113.2± 14.4 (n=233)	110.8±13.4 (n=122)	115.9±15.0 (n=111)	0.007*
WHR	0.89±0.07 (n=232)	0.88±0.07 (n=122)	0.89±0.09 (n=110)	0.684
Pulse/min	76.2±9.02 (n=1,022)	75.8±9.3 (n=511)	76.6±8.8 (n=511)	0.148
Systolic BP (mmHg)	128.7±13.4 (n=1,022)	129.8±14.2 (n=511)	127.5±12.6 (n=511)	0.006*
Diastolic BP (mmHg)	81.6±10.5 (n=1,022)	81.8±10.8 (n=511)	81.4±10.2 (n=511)	0.556
TotalMeds	1.7±1.7	0.9±1.3	2.5±1.6	<0.001*

Values are means ± standard deviation. Abbreviations: BMI, Body Mass Index; WHR, Waist to Hip Ratio.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

4.1.1 BMI Categories

In Table 7, the different BMI groups encountered in both the PCOS and the non-PCOS group are presented. Then, the differences between PCOS and non PCOS for each BMI group were assessed. Proportions were compared using Chi-square.

Table 7: The different BMI groups encountered in the PCOS and non PCOS category

BMI values	BMI groups	Non PCOS (%)	PCOS (%)
28-29 kg/m^2	**0**	7,913 (7.8%)	22 (4.3%)
30-34.9 kg/m^2	**1**	41,388 (40.5%)	127 (24.7%)
35-39.9 kg/m^2	**2**	29,514 (28.9%)	159 (30.9%)
40-44.9 kg/m^2	**3**	14,489 (14.2%)	116 (22.5%)
45-49.9 kg/m^2	**4**	5,769 (5.7%)	55 (10.7%)
>50.0 kg/m^2	**5**	3,022 (3.0%)	36 (7.0%)

The following table shows comparisons between the PCOS and non PCOS groups, using combined BMI groups this time (overweight, obesity class I and II, obesity class III).

Table 8: Combined BMI groups encountered in the PCOS and non PCOS category

BMI values	BMI groups	Non PCOS (%)	PCOS (%)
28-29 kg/m^2	**1**	7913 (7.8%)	22 (4.3%)
30-39.9 kg/m^2	**2**	70,902 (69.4%)	286 (55.5%)
≥40.0 kg/m^2	**3**	23,280 (22.8%)	207 (40.0%)

4.1.2 Blood Pressure

Values for blood pressure (mmHg) and pulse (beats per minute, bpm) were also compared between the PCOS and non PCOS categories and within the different BMI groups (both unmerged and merged -overweight, obesity class I and II, obesity class III-). This was done to identify possible differences within the different groups, because of the established association between high BMI and high blood pressure.

Table 9: Comparison of Systolic and Diastolic Blood Pressure and Pulse, between PCOS and non PCOS participants at **BMI group=0,** *(BMI= 28-29kg/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP (mmHg)	non PCOS	7,837	124.1±14.2	0.427
	PCOS	22	126.5±17.8	
Diastolic BP (mmHg)	non PCOS	7,837	78.0±10.3	1.0
	PCOS	22	78.0±11.3	
Pulse (bpm)	non PCOS	7,837	74.3±8.9	0.712
	PCOS	22	75.0±8.1	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 10: Comparison of Systolic and Diastolic Blood Pressure and Pulse between PCOS and non PCOS participants at **BMI group=1** *(BMI= 30-34.9kg/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP (mmHg)	non PCOS	41,121	126.7±14.5	0.09
	PCOS	126	124.9±11.9	
Diastolic BP (mmHg)	non PCOS	41,121	79.7±10.2	0.49
	PCOS	126	79.1±11.0	
Pulse (bpm)	non PCOS	41,121	75.1±9.1	0.90
	PCOS	126	75.2±8.5	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 11: Comparison of Systolic and Diastolic Blood Pressure and Pulse between PCOS and non PCOS participants at **BMI group=2** *(BMI= 35-39.9 kg/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP (mmHg)	non PCOS	29,341	129.9±15.0	0.07
	PCOS	159	128.3±11.3	
Diastolic BP (mmHg)	non PCOS	29,341	81.8±10.5	0.04*
	PCOS	159	83.5±10.2	
Pulse (bpm)	non PCOS	29,341	76.1±9.3	0.241
	PCOS	159	77.0±8.9	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 12: Comparison of Systolic and Diastolic Blood Pressure and Pulse between PCOS and non PCOS participants at **BMI group=3** *(BMI= 40-44.9 kg/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP (mmHg)	non PCOS	14,411	132.3±15.2	0.001*
	PCOS	115	127.5±12.6	
Diastolic BP (mmHg)	non PCOS	14,411	83.3±10.5	0.017*
	PCOS	115	80.9±8.6	
Pulse (bpm)	non PCOS	14,411	76.9±9.4	0.725
	PCOS	115	76.6±8.7	

Values are means ± standard deviation..
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 13: Comparison of Systolic and Diastolic Blood Pressure and Pulse between PCOS and non PCOS participants at **BMI group=4** *(BMI= 45-49.9 kg/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP (mmHg)	non PCOS	5,726	134.9±12.0	<0.001*
	PCOS	54	127.2±13.1	
Diastolic BP (mmHg)	non PCOS	5,726	84.5±8.6	0.004*
	PCOS	54	80.3±9.7	
Pulse (bpm)	non PCOS	5,726	77.7±9.3	0.88
	PCOS	54	77.9±7.8	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 14: Comparison of Systolic and Diastolic Blood Pressure and Pulse PCOS and non PCOS participants at **BMI group=5** *(BMI>50.0/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP(mmHg)	non PCOS	3,004	137.0±15.8	0.32
	PCOS	35	134.3±16.2	
Diastolic BP(mmHg)	non PCOS	3,004	85.3±11.1	0.77
	PCOS	35	85.9±11.8	
Pulse (bpm)	non PCOS	3,004	77.9±9.5	0.65
	PCOS	35	78.60±10.6	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 15: Comparison of Systolic and Diastolic Blood Pressure and Pulse between PCOS and non PCOS at **Combined BMI Group 1** *(BMI:28-29 kg/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP(mmHg)	non PCOS	7,837	124.1±14.2	0.427
	PCOS	22	126.5±17.8	
Diastolic BP(mmHg)	non PCOS	7,837	78.0±10.3	1
	PCOS	22	78.0±11.3	
Pulse (bpm)	non PCOS	7,837	74.3±8.9	0.712
	PCOS	22	75.0±8.1	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 16: Comparison of Systolic and Diastolic Blood Pressure between PCOS and non PCOS at **Combined BMI Group 2** *(BMI: 30-39.9 kg/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP(mmHg)	non PCOS	70,462	128.1±14.8	0.065
	PCOS	285	126.8±11.7	
Diastolic BP(mmHg)	non PCOS	70,462	80.6±10.4	0.114
	PCOS	285	81.6±10.7	
Pulse (bpm)	non PCOS	70,462	75.5±9.2	0.220
	PCOS	285	76.2±8.8	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test

* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 17: Comparison of Systolic and Diastolic Blood Pressure between PCOS and non PCOS at **Combined BMI Group 3** *(BMI: ≥40.0 kg/m^2)*

Parameter	PCOS category	N	Mean±SD	P†
Systolic BP(mmHg)	non PCOS	23,141	133.5±15.4	<0.001*
	PCOS	204	128.6±13.0	
Diastolic BP(mmHg)	non PCOS	23,141	83.8±10.7	0.01
	PCOS	204	81.6±9.3	
Pulse (bpm)	non PCOS	23,141	77.2±9.4	0.926
	PCOS	204	77.3±8.8	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

4.1.3 Ethnic Categories within the PCOS and non PCOS sample

The prevalence of different ethnic categories among the PCOS and non PCOS particpants. are shown at Table 18.

Table 18: Prevalence of the different ethnicities in the PCOS and non PCOS group

	Ethnicity							
PCOS Category	**Caucasian**	**Indian**	**Bangladeshi**	**Pakistani**	**Black African**	**Black Caribbean**	**Black other**	**Chinese**
Non PCOS	9,411	2,308	1,733	1,127	1,733	1,561	677	69
PCOS	437	34	9	19	9	7	51	0

Due to low numbers encountered in the PCOS group, the different ethnic groups were combined: Asian (Indian, Pakistani, and Bangladeshi) and African (Black African, Black Caribbean and Black Other). The Chinese subgroup was not included, as it appeared only in the PCOS sample.

Table 19: Prevalence of combined ethnicities in the PCOS and non PCOS group

	Ethnicity		
PCOS Category	**Asian**	**African**	**Caucasian**
PCOS	11.1%	4.1%	84.9%
Non PCOS	3.8%	3.9%	92.3%

As it can be seen from the above table, the prevalence of Asians in the PCOS category is almost 3 times more, than in the non-PCOS category. Also, an attempt to note any differences in the expression of the PCOS phenotype among the different combined ethnic groups was carried out by ANOVA.

The same analysis was repeated for the random sample that was selected through SPSS.

Table 20 : The different ethnic categories observed between PCOS (n=515) and randomly selected non PCOS (n=515)

Ethnic Group	Non PCOS	PCOS	Total
Caucasian	484	437	921
Indian	8	34	42
Pakistani	10	19	29
Black African	5	9	14
Black Caribbean	3	7	10
Bangladeshi	2	4	6
Black Other	3	5	8
Chinese	0	0	0
Total	**515**	**515**	**1,030**

As it can be seen from the table below, the prevalence of Asians in the PCOS category is again approximately 3 times more, than in the non-PCOS category.

Table 21: The combined ethnic categories observed between PCOS (n=515) and randomly selected non PCOS (n=515)

Ethnic Group	Non PCOS (%)	PCOS (%)	Total (%)
Caucasian	484 (94.0%)	437(84.9%)	921 (89.4%)
Asian	20 (3.8%)	57(11.1%)	77 (7.8%)
Africans	11 (2.1%)	21(4.1%)	32 (3.1%)
Total	**515 (100%)**	**515 (100%)**	**1,030**

Table 22: Baseline characteristics among the different ethnic categories of the PCOS participants

Parameter	Ethnicity	N	Mean±SD
Age (yrs)	Asian	57	31.2±7.1
	African	21	35.6±8.2
	Caucasian	437	34.9±8.2
	Total	515	34.5±8.2
Height (m)	Asian	57	1.62±0.06
	African	21	1.65±0.08
	Caucasian	437	1.65±0.07
	Total	515	1.65±0.07
Weight (kg)	Asian	57	97.6±16.6
	African	21	114.3±24.0
	Caucasian	437	106.3±19.1
	Total	515	105.7±19.3
BMI (kg/m^2)	Asian	57	37.2±5.9
	African	21	41.9±7.0
	Caucasian	437	39.1±6.7
	Total	515	39.0±6.6
Waist (cm)	Asian	13	111.3±14.3
	African	7	121.9±15.9
	Caucasian	91	116.1±15.0
	Total	111	115.9±15.0
Hip (cm)	Asian	13	124.2±9.6
	African	7	132.9±13.04
	Caucasian	90	131.2±12.2
	Total	110	130.5±12.1
WHR	Asian	13	0.89±0.07
	African	7	0.91±0.04
	Caucasian	90	0.89±0.09
	Total	110	0.89±0.08

WSR	Asian	13	0.68±0.09
	African	7	0.73±0.08
	Caucasian	91	0.71±0.10
	Total	111	0.70±0.09
Bust (cm)	Asian	13	115.9±11.2
	African	7	131.4±16.7
	Caucasian	91	122.7±11.5
	Total	111	122.5±12.1
Systolic BP (mmHg)	Asian	57	123.3±13.1
	African	20	129.4±11.9
	Caucasian	434	128.0±12.4
	Total	511	127.5±12.6
Diastolic BP (mmHg)	Asian	57	80.2±10.4
	African	20	82.5±10.8
	Caucasian	434	81.5±10.2
	Total	511	81.4±10.2
Pulse (bpm)	Asian	57	78.2±9.3
	African	20	76.2±8.9
	Caucasian	434	76.4±8.7
	Total	511	76.6±8.8

The above table shows the descriptive characteristics of the combined ethnic groups of PCOS participants, as determined by one-way ANOVA. Bonferroni post-hoc tests revealed that:

- Asian women with PCOS were younger (yrs) than Caucasian women with PCOS (34.9±8.2 versus 31.2±7.1, p=0.004),
- Asian women with PCOS were presented with less weight(kg) than the African (97.6±16.6 versus 114.3±24.0, p=0.002) and the Caucasian (97.6±16.6 versus 106.3±19.1 p=0.004),
- Asian women with PCOS had lower BMI (kg/m^2)than the African (37.2±5.9 versus 41.9±7.0, p=0.016),
- Asian women with PCOS had smaller bust (cm) than African women (115.9±11.2 versus 131.4±16.7, p=0.018),
- Asian women had decreased values of systolic blood pressure (mmHg) when compared to Caucasian (115.9±11.2 versus 122.7±11.5, p=0.023)

The same analysis was performed for the combined ethnic groups of the non PCOS participants (Table 23).

Table 23: Baseline characteristics among the different ethnic categories of the non-PCOS participants

Parameter	Ethnicity	N	Mean±SD
Age (yrs)	Asian	3,855	36.6±10.4
	African	3,971	38.4±9.6
	Caucasian	94,200	42.2±11.3
	Total	102,026	41.9±11.3
Height (m)	Asian	3,855	1.61±0.06
	African	3,971	1.64±0.07
	Caucasian	94,200	1.64±0.06
	Total	102,026	1.6±0.07
Weight (kg)	Asian	3,855	91.1±15.0
	African	3,971	100±18.1
	Caucasian	94,200	98±16.9
	Total	102,026	97.8±17.0
BMI (kg/m^2)	Asian	3,855	35.2±5.1
	African	3,971	37.0±6.2
	Caucasian	94,200	36.4±5.8
	Total	102,026	36.4±5.8
Waist (cm)	Asian	708	106.9±12.1
	African	890	110.0±12.9
	Caucasian	23,521	110.0±12.9
	Total	25,119	109.9±12.9
Hip (cm)	Asian	706	121.5±10.2
	African	885	124.9±12.0
	Caucasian	23,402	125.2±12.3
	Total	24,993	125.1±12.3
WHR	Asian	706	0.88±0.07
	African	885	0.88±0.08
	Caucasian	23,384	0.88±0.07
	Total	24,975	0.88±0.07
WSR	Asian	708	0.67±0.08
	African	890	0.67±0.08
	Caucasian	23,521	0.67±0.08
	Total	25,119	0.67±0.08
Bust (cm)	Asian	709	112.1±10.01

	African	890	116.3±11.8
	Caucasian	23,521	117.4±10.9
	Total	25,120	117.2±11.0
Systolic BP (mmHg)	Asian	3,842	124.4±14.5
	African	3,935	126.7±15.1
	Caucasian	93,595	129.3±15.1
	Total	101,372	129.0±15.1
Diastolic BP (mmHg)	Asian	3,842	79.5±10.3
	African	3,935	80.8±11.3
	Caucasian	93,595	81.2±10.5
	Total	101,372	81.1±10.6
Pulse (bpm)	Asian	3,842	76.9±9.3
	African	3,935	76.7±9.6
	Caucasian	93,595	75.8±9.3
	Total	101,372	75.8±9.3

The Bonferroni post-hoc tests showed that the differences between the ethnic categories were more eminent in the non PCOS group.

Age

- Asian women were younger (yrs) than African and Caucasian (36.6±10.4 versus 38.4±9.6, p<0.001 and 36.6±10.4 versus 42.2±11.3, p<0.001)
- African women were younger (yrs) than Caucasian (38.4±9.6 versus 42.2±11.3, p=0.009

Weight and BMI

- Asian women were presented with less weight (kg) than Caucasian (91.1±15.0 versus 98±16.9, p<0.001)
- African were presented with more weight (kg) than Caucasian and Asian (100±18.1 versus 98±16.9, p<0.001 and 100±18.1 versus 91.1±15.0, p<0.001)

Waist, Hip and Bust circumferences

- Both African and Caucasian had wider waistline (cm) (110.0±12.9 versus 106.9±12.1, p<0.001 and 110.0±12.1 versus 106.9±12.1, p<0.001) and hip circumference (cm) than the Asians (124.9±12.0 versus 121.5±10.2, p<0.001 and 125.2±12.3 versus 121.5±10.2, p<0.001)

- Asian had smaller bust size (cm) than both Africans and Caucasians (112.1±10.01 versus 116.3±11.8, p<0.001 and 112.1±10.01 versus 117.4±10.9, p<0.001)

Systolic and Diastolic BP

- Caucasian had higher systolic pressure (mmHg) than Asians and Africans (129.3±15.1 versus 124.4±14.5 ,p<0.001 and 129.3±15.1 versus 126.7±15.1, p<0.001)

- Asian had lower systolic blood pressure (mmHg) than African (124.4±14.5 versus 126.7±15.1, p<0.001)

Pulse

Asians and Africans had higher pulse (bpm) than Caucasians (76.9±9.3 versus 75.8±9.3, p<0.001 and 76.7±9.6 versus 75.8±9.3, p<0.001).

At the following tables, an ANOVA was performed to analyse for the differences between PCOS and non PCOS, within the same ethnic group.

Table 24: Baseline characteristics in the Asian Subgroup between the PCOS and non PCOS participants

	PCOS Category	N	Mean± SD	P†
Age (yrs)	non PCOS	3,855	36.61±10.4	<0.001 *
	PCOS	57	31.16±7.1	
	Total	3,912	36.53±10.3	
Height (m)	non PCOS	3,855	1.61±0.06	0.108
	PCOS	57	1.62±0.06	
	Total	3,912	1.61±0.06	
Weight (kg)	non PCOS	3,855	91.1±15.0	0.001*
	PCOS	57	97.6±16.6	
	Total	3,912	91.2±15.1	
BMI (kg/m^2)	non PCOS	3,855	35.2±5.1	0.005*
	PCOS	57	37.2±5.9	
	Total	3,912	35.23±5.2	
Systolic BP (mmHg)	non PCOS	3842	124.4±14.5	0.545
	PCOS	57	123.3±13.1	
	Total	3,899	124.4±14.5	
Diastolic BP (mmHg)	non PCOS	3,842	79.5±10.3	0.632
	PCOS	57	80.2±10.4	
	Total	3,899	79.5±10.3	
Pulse (bpm)	non PCOS	3842	76.9±9.3	0.270
	PCOS	57	78.3±9.3	
	Total	3899	76.9±9.3	

Values are means ± standard deviation. Abbreviations: BMI, Body Mass Index
†Significance level of the difference between PCOS and non PCOS groups at each time point, calculated using an independent t-test
* marks the significant difference between the 2 groups, $p < 0.05$

Table 25: Baseline characteristics in the African Subgroup between the PCOS and non PCOS participants

	PCOS Category	N	Mean± SD	P†
Age (yrs)	non PCOS	3,971	38.4±9.6	0.190
	PCOS	21	35.6±8.2	
	Total	3,992	38.4±9.6	
Height (m)	non PCOS	3,971	1.64±0.07	0.676
	PCOS	21	1.65±0.08	
	Total	3,992	1.64±0.07	
Weight (kg)	non PCOS	3,971	100.0±18.1	<0.001 *
	PCOS	21	114.3±	
	Total	3,992	100.1±18.2	
BMI (kg/m^2)	non PCOS	3,971	37.040±6.2	<0.001 *
	PCOS	21	41.878±7.0	
	Total	3,992	37.065±6.2	
Systolic BP (mmHg)	non PCOS	3,935	126.7329±15.1	
	PCOS	20	129.4±11.9	0.431
	Total	3,955	126.7±15.0	
Diastolic BP (mmHg)	non PCOS	3,935	80.8±11.3	0.509
	PCOS	20	82.5±10.8	
	Total	3,955	80.9±11.3	
Pulse (bpm)	non PCOS	3,935	76.7±9.6	0.849
	PCOS	20	76.3±8.9	
	Total	3,955	76.7±9.5	

Values are means ± standard deviation. Abbreviations: BMI, Body Mass Index
†Significance level of the difference between PCOS and non PCOS groups at each time point, calculated using an independent t-test
* marks the significant difference between the 2 groups, $p < 0.05$

Table 26: Baseline characteristics in the Caucasian Subgroup between the PCOS and non PCOS participants

	PCOS Category	N	Mean± SD	P†
Age (yrs)	non PCOS	94,200	42.2±11.3	<0.001*
	PCOS	437	34.9±8.2	
	Total	94,637	42.2±11.3	
Height (m)	non PCOS	94,200	1.64±0.07	0.05*
	PCOS	437	1.65±0.07	
	Total	94,637	1.64±0.07	
Weight (kg)	non PCOS	94,200	98.0±16.9	<0.001*
	PCOS	437	106.3±19.1	
	Total	94,637	98.1±17.0	
BMI (kg/m^2)	non PCOS	94,200	36.4±5.8	<0.001*
	PCOS	437	39.1±6.7	
	Total	94,637	36.4±5.8	
Systolic BP (mmHg)	non PCOS	93,595	129.2±15.1	0.068
	PCOS	434	128.0±12.4	
	Total	94,029	129.3±15.1	
Diastolic BP (mmHg)	non PCOS	93,595	81.2±10.5	0.521
	PCOS	434	81.5±10.2	
	Total	94,029	81.2±10.5	
Pulse (bpm)	non PCOS	93,595	75.8±9.3	0.158
	PCOS	434	76.4±8.7	
	Total	94,029	75.8	

Values are means ± standard deviation. Abbreviations: BMI, Body Mass Index
†Significance level of the difference between PCOS and non PCOS groups at each time point, calculated using an independent t-test
* marks the significant difference between the 2 groups, $p < 0.05$

4.2 Comparison of participants with and without PCOS after 12 weeks on the LighterLife Total programme

After the baseline investigation of the database, the PCOS participants were matched for age (age ±1 unit) and BMI (BMI ± 1 unit) with the non PCOS participants in order to proceed to the 12 week analysis. The 12 week part included both a Baseline Carried Forward analysis (BOCF) on the Intention to Treat sample (ITT) (n=508 for PCOS and n=508 for non PCOS) and a Completers (n=137 for PCOS and n=137 for non PCOS) analysis.

4.2.1 BOCF Analysis

There were no differences between the PCOS and non PCOS women in age (yrs) (34.5±8.2 versus 34.5±8.2, p=0.948), height (m) (1.65±0.1 versus 1.65±0.1, p=0.937), weight (kg) (105.4±18.9 versus 105.3±19.0, p=0.892) and BMI (kg/m^2)(38.9±6.4 versus 38.8±6.4, p=0.831), as they were all matched at baseline.

The weekly weight loss as well as the weekly reduction in BMI, were similar for both groups, with no significant statistical differences (Table 27 and Table 28).

Table 27: Comparison of weekly weight between PCOS (n=508) and matched non PCOS individuals (n=508)

Parameter	Category	Mean±SD	P†
Baseline Weight (kg)	PCOS	105.4±18.9	0.831
	nonPCOS	105.3±19.0	
Week 1 Weight (kg)	PCOS	102.2±18.4	0.884
	nonPCOS	102.0±18.4	
Week 2 Weight (kg)	PCOS	100.7±18.2	0.831
	nonPCOS	100.4±18.4	
Week 3 Weight (kg)	PCOS	99.6±18.4	0.783
	nonPCOS	99.3±18.4	
Week 4 Weight (kg)	PCOS	98.7±18.4	0.790
	nonPCOS	98.3±18.3	
Week 5 Weight (kg)	PCOS	97.7±18.3	0.808
	nonPCOS	97.4±18.3	
Week 6 Weight (kg)	PCOS	96.9±18.4	0.846
	nonPCOS	96.7±18.4	
Week 7 Weight (kg)	PCOS	96.2±18.5	0.832
	nonPCOS	96.0±18.7	
Week 8 Weight (kg)	PCOS	95.9±18.6	0.691
	nonPCOS	95.5±18.9	
Week 9 Weight (kg)	PCOS	95.5±18.7	0.699
	nonPCOS	95.0±19.1	
Week 10 Weight (kg)	PCOS	95.1±18.7	0.790
	nonPCOS	94.8±19.2	
Week 11 Weight (kg)	PCOS	95.1±18.8	0.660
	nonPCOS	94.6±19.4	
Week 12 Weight (kg)	PCOS	95.0±19.1	0.927
	nonPCOS	94.9±19.5	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at each time point, calculated using an independent t-test
***** marks the significant difference between the 2 groups, $p < 0.05$,

Table 28: Comparison of weekly BMI between PCOS (n=508) and matched non PCOS individuals (n=508)

Parameter	Category	Mean±SD	P†
Baseline BMI (kg/m^2)	PCOS	38.9±6.4	0.831
	nonPCOS	38.8±6.4	
Week 1 BMI (kg/m^2)	PCOS	37.7±6.3	0.816
	nonPCOS	37.6±6.2	
Week 2 BMI (kg/m^2)	PCOS	37.1±6.2	0.745
	nonPCOS	37.0±6.2	
Week 3 BMI (kg/m^2)	PCOS	36.7±6.3	0.714
	nonPCOS	36.6±6.2	
Week 4 BMI (kg/m^2)	PCOS	36.4±6.3	0.723
	nonPCOS	36.3±6.2	
Week 5 BMI (kg/m^2)	PCOS	36.0±6.3	0.751
	nonPCOS	35.9±6.2	
Week 6 BMI (kg/m^2)	PCOS	35.7±6.3	0.798
	nonPCOS	35.6±6.3	
Week 7 BMI (kg/m^2)	PCOS	35.5±6.4	0.774
	nonPCOS	35.4±6.4	
Week 8 BMI (kg/m^2)	PCOS	35.4±6.4	0.647
	nonPCOS	35.2±6.5	
Week 9 BMI (kg/m^2)	PCOS	35.2±6.4	0.651
	nonPCOS	35.0±6.6	
Week 10 BMI (kg/m^2)	PCOS	35.1±6.5	0.739
	nonPCOS	35.0±6.6	
Week 11 BMI (kg/m^2)	PCOS	35.1±6.5	0.614
	nonPCOS	34.9±6.7	
Week 12 BMI (kg/m^2)	PCOS	35.0±6.6	0.895
	nonPCOS	35.0±6.8	

Values are means ± standard deviation. Abbreviations: BMI, Body Mass Index
†Significance level of the difference between PCOS and non PCOS groups at each time point, calculated using an independent t-test
***** marks the significant difference between the 2 groups, $p < 0.05$

After 12 weeks of VLCD, there was a significant weight reduction for both groups when compared to baseline (PCOS: 105.4kg ±18.9 versus 95.0 kg ±19.1 p<0.001 and non-PCOS: 105.3kg ±19.0 versus 94.9kg ±19.5, p<0.001). There was also a significant change in BMI, as compared to baseline (PCOS: 38.9±6.4 kg/m ^{2} versus 35.0±6.6 kg/m ^{2}, p<0.001 and non-PCOS: 38.8±6.4 kg/m ^{2} versus 35.0±6.8 kg/m ^{2}, p<0.001). The total weight change did not differ significantly between the PCOS group and the non-PCOS group (-10.4kg ±10.6 versus -10.4 kg ± 10.4, p=0.938) and both of the groups achieved approximately 10% weight loss after the 12 week VLCD approach (PCOS: -9.7%±9.4 vs non PCOS: -9.7%±9.7, p=0.965. Moreover, no significant differences in the weekly weight change between the two groups were identified, as demonstrated at the following figure.

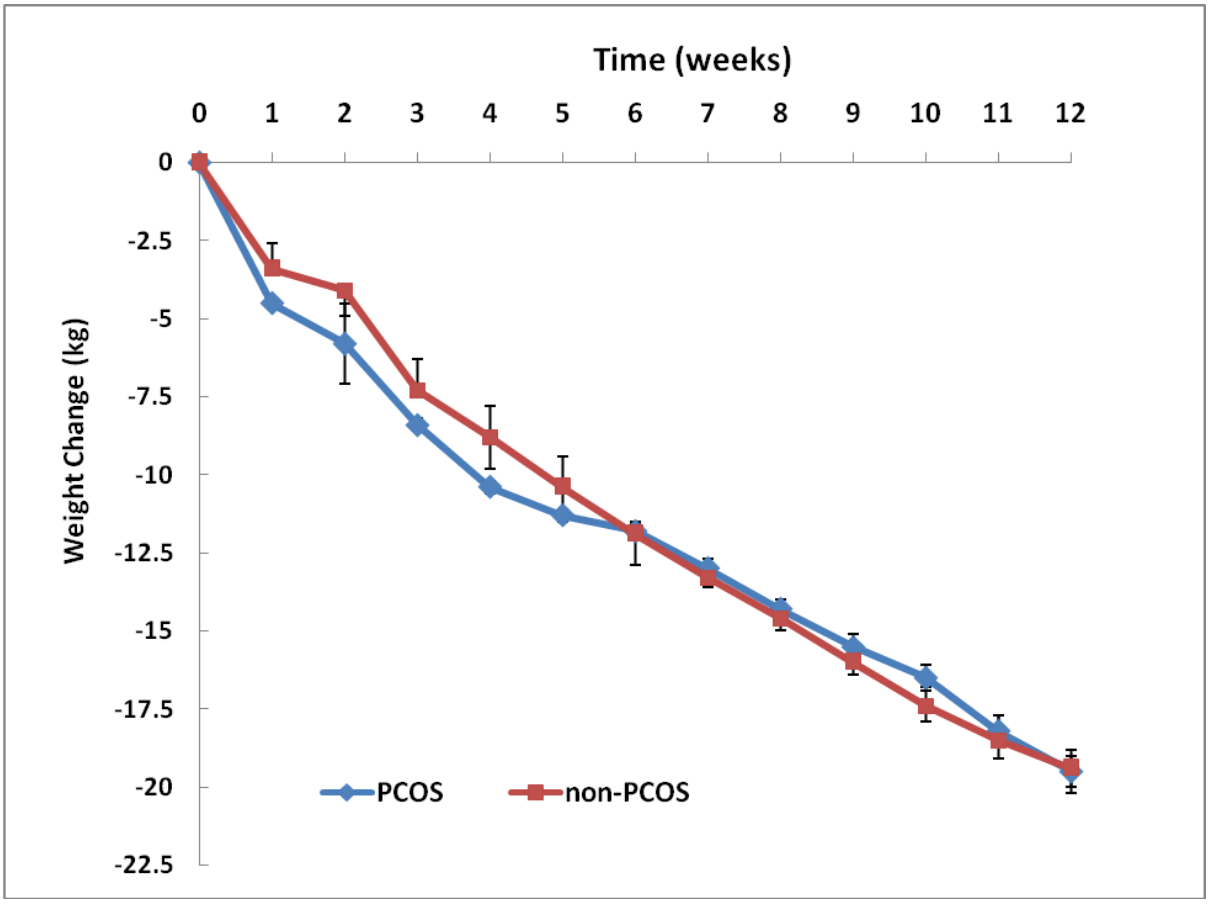

Figure 4: Weekly weight change for participants with and without PCOS (12 week BOCF, n=508 for each group), Error bars represent 1 SE

The tables below show the changes in systolic and diastolic blood pressure and pulse between the PCOS and non PCOS groups, after the 12 week period.

Table 29: Comparison of blood pressure and pulse between the PCOS and non PCOS groups at baseline and at 12 weeks

Parameter	Category	N	Mean±SD	P†
Baseline Systolic BP (mmHg)	PCOS	504	127.4±12.5	0.598
	nonPCOS	507	127.0±14.0	
Baseline Diastolic BP (mmHg)	PCOS	504	81.5±10.2	0.014*
	nonPCOS	508	79.9±9.7	
Baseline Pulse (bpm)	PCOS	504	76.5±9.0	0.694
	nonPCOS	506	76.3±9.2	
Week12 Systolic BP (mmHg)	PCOS	504	121.9±20.3	<0.001*
	nonPCOS	507	126.1±14.5	
Week12 Diastolic BP (mmHg)	PCOS	504	85.8±16.1	0.206
	nonPCOS	508	79.4±9.9	
Week12 Pulse (bpm)	PCOS	504	76.1±9.3	0.817
	nonPCOS	506	76.0±9.2	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups, calculated using an independent t-test
* marks the significant difference between the 2 groups, $p < 0.05$, calculated using an independent t-test
Week 12 Diastolic BP was adjusted for baseline difference using analysis of covariance (ANCOVA)

Table 30: Comparison of changes in blood pressure between the PCOS and non PCOS groups after 12 weeks of VLCD

Parameter	Category	N	Mean±SD	P†
Change in Syst BP (mmHg)	nonPCOS	507	-5.5±6.1	<0.001*
	PCOS	504	-0.9±6.1	
Change in Diast BP (mmHg)	nonPCOS	507	-0.4±5.1	0.517
	PCOS	504	-0.6±4.4	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups, calculated using an independent t-test
* marks the significant difference between the 2 groups, $p < 0.05$, calculated using an independent t-test

Finally, the distribution of the ethnic categories was also similar between the 2 groups of participants (figure 5 and 6), although the numbers of some minority groups differed. However, due to the small numbers in some of the ethnic groups, comparisons between the different ethnic categories could not be performed.

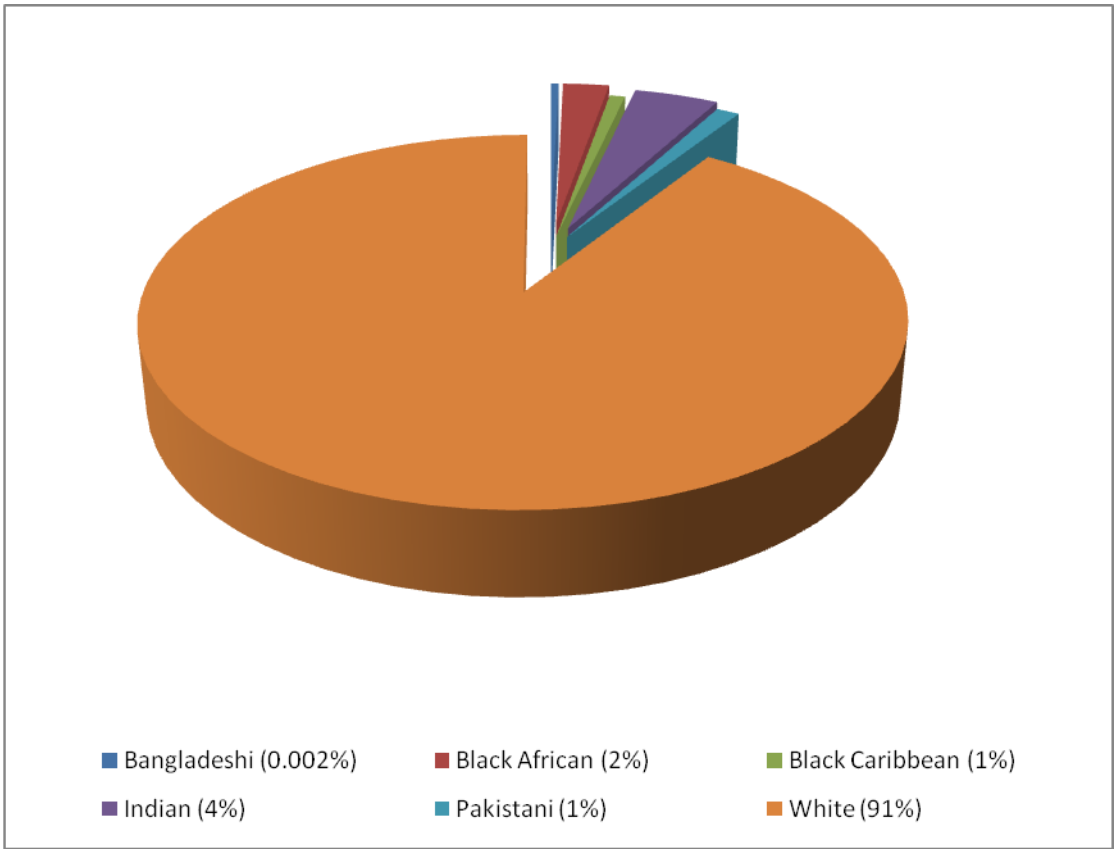

Figure 5: The different ethnic groups among the non PCOS (n=508) 12 week BOCF

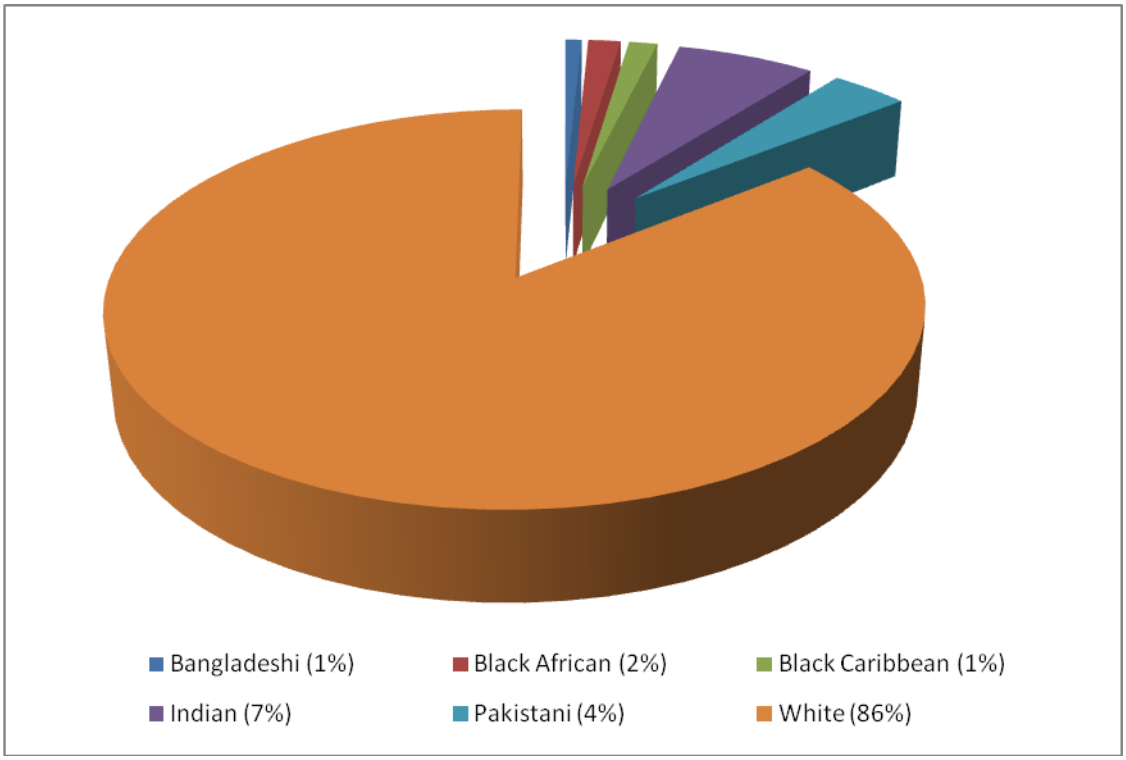

Figure 6: The different ethnic groups among the PCOS (n=508) 12 week BOCF

A combined analysis of the distribution of ethnic categories, showed greater proportion of Asians in the PCOS category (Table 31).

Table 31: Combined Ethnicities in the PCOS and non PCOS group

Combined Ethnicities	Non PCOS (%)	PCOS (%)	Total
Caucasian	459 (90.4%)	431 (84.8 %)	890
Asian	30 (5.9%)	57 (11.2 %)	87
African	19 (3.7%)	20 (3.9%)	39
Total	508	508	1016

(chi Square Value 0.010)

4.2.2 Completers analysis

As it can be seen from the following table, there were no differences between the PCOS and non PCOS women in age (yrs) (35.7±8.9 versus 35.8±8.9, p=0.946), height (m) (1.65±0.1 versus 1.64±0.1, p=0.212), weight (kg) (108.3±18.1 versus 107.4±19.8, p=0.713) and BMI (kg/m^2)(40.0±6.3 versus 40.0±6.3, p=0.955).

Table 32: Comparison of baseline characteristics between PCOS (n=137) and matched non PCOS (n=137)

Parameter	non PCOS (n=137)	PCOS (n=137)	P†
Age (yrs)	35.8±8.9	35.7±8.9	0.946
Height (m)	1.64±0.1	1.65±0.1	0.212
Weight (kg)	107.4±19.8	108.3±18.1	0.713
BMI (kg/m^2)	40.0±6.3	40.0±6.3	0.955

Values are means ± standard deviation. Abbreviations: BMI, Body Mass Index
†Significance level of the difference between PCOS and non PCOS groups at baseline, calculated using an independent t-test

The weekly weight loss as well as the weekly reduction in BMI, were similar for both groups, with no significant statistical differences (Table 33 and Table 34).

Table 33: Comparison of weekly weight (kg) between PCOS (n=137) and matched non PCOS (n=137) individuals

Parameter	Category	Mean±SD	P†
Baseline Weight (kg)	nonPCOS	107.4±19.8	0.713
	PCOS	108.3±18.1	
Week 1 Weight (kg)	nonPCOS	104.1±19.3	0.917
	PCOS	103.8±19.9	
Week 2 Weight (kg)	nonPCOS	103.4±26.3	0.724
	PCOS	102.4±17.4	
Week 3 Weight (kg)	nonPCOS	100.2±18.7	0.887
	PCOS	99.8±19.0	
Week 4 Weight (kg)	nonPCOS	98.6±18.5	0.748
	PCOS	97.9±19.7	
Week 5 Weight (kg)	nonPCOS	97.0±18.3	0.956
	PCOS	96.9±18.6	
Week 6 Weight (kg)	nonPCOS	95.4±18.3	0.619
	PCOS	96.5±16.7	
Week 7 Weight (kg)	nonPCOS	94.1±18.2	0.602
	PCOS	95.2±16.7	
Week 8 Weight (kg)	nonPCOS	92.7±17.9	0.515
	PCOS	94.1±16.7	
Week 9 Weight (kg)	nonPCOS	91.4±17.9	0.436
	PCOS	93.0±17.0	
Week 10 Weight (kg)	nonPCOS	90.2±17.8	0.600
	PCOS	91.4±17.4	
Week 11 Weight (kg)	nonPCOS	89.3±17.9	0.731
	PCOS	90.1±18.2	
Week 12 Weight (kg)	nonPCOS	88.0±17.6	0.381
	PCOS	89.8±16.7	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups at each time point, calculated using an independent t-test

Table 34: Comparison of weekly BMI (kg/m^2) between PCOS (n=137) and matched non PCOS (n=137) individuals

Parameter	Category	Mean±SD	P†
Baseline BMI (kg/m^2)	nonPCOS	40.0±6.3	0.955
	PCOS	40.0±6.3	
Week 1 BMI (kg/m^2)	nonPCOS	38.8±6.2	0.604
	PCOS	38.4±7.1	
Week 2 BMI (kg/m^2)	nonPCOS	38.5±9.2	0.461
	PCOS	37.8±6.1	
Week 3 BMI (kg/m^2)	nonPCOS	37.3±6.0	0.522
	PCOS	36.8±6.7	
Week 4 BMI (kg/m^2)	nonPCOS	36.7±6.0	0.407
	PCOS	36.1±7.0	
Week 5 BMI (kg/m^2)	nonPCOS	36.2±5.9	0.597
	PCOS	35.8±6.6	
Week 6 BMI (kg/m^2)	nonPCOS	35.5±5.9	0.900
	PCOS	35.6±5.9	
Week 7 BMI (kg/m^2)	nonPCOS	35.1±5.8	0.870
	PCOS	35.2±6.0	
Week 8 BMI (kg/m^2)	nonPCOS	34.5±5.7	0.756
	PCOS	34.7±6.0	
Week 9 BMI (kg/m^2)	nonPCOS	34.0±5.8	0.652
	PCOS	34.3±6.0	
Week 10 BMI (kg/m^2)	nonPCOS	33.6±5.7	0.859
	PCOS	33.7±6.2	
Week 11 BMI (kg/m^2)	nonPCOS	33.3±5.7	0.991
	PCOS	33.2±6.5	
Week 12 BMI (kg/m^2)	nonPCOS	32.8±5.7	0.568
	PCOS	33.2±6.0	

Values are means ± standard deviation. Abbreviations: BMI, Body Mass Index
†Significance level of the difference between PCOS and non PCOS groups at each time point, calculated using an independent t-test

After 12 weeks of VLCD, there was a significant weight reduction for both groups when compared to baseline (PCOS: 108.3 kg ±18.1 versus 89.8 kg ±16.7, p<0.001 and non-PCOS: 107.4 kg ±19.8 versus 88.0 kg ± 17.6, p<0.001). There was also a significant change in BMI, as compared to baseline (PCOS: 40.0±6.4 kg/m ^{2} versus 33.2±6.0 kg/m ^{2}, p<0.001 and non-PCOS: 40.0±6.3 kg/m ^{2} versus 32.8±5.7 kg/m ^{2}, p<0.001). The total weight change did not differ

significantly between the PCOS group and the non-PCOS group (-18.5 kg ±6.6 versus -19.4 kg± 5.7, p=0.190) and the percentage of weight loss achieved by PCOS women was 17.1% ±5.6 versus 18.2% ±4.4 by the non PCOS group (p=0.08). Moreover, no significant differences in the weekly weight change between the two groups were identified.

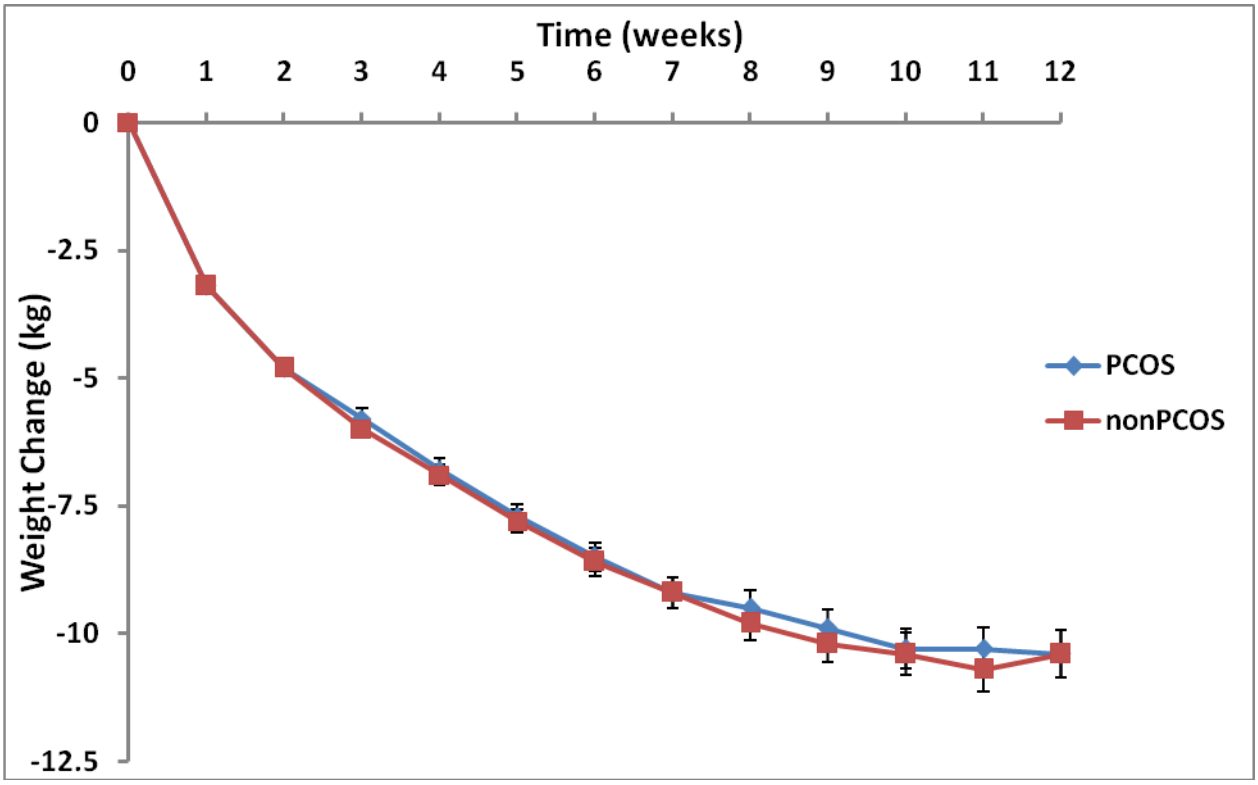

Figure 7: Weekly weight change for participants with and without PCOS (12 week completers, n=137 for each group), Error bars represent 1 SE

As there were not enough data to examine changes in waist, hip and bust, the next table shows the BP values at baseline and after 12 weeks of VLCD.

Table 35: Values on blood pressure and pulse between the PCOS and non PCOS groups at baseline and 12 weeks

Parameter	Category	N	Mean±SD	P†
Baseline Systolic (mmHg)	nonPCOS	137	130.5±13.9	0.014*
	PCOS	137	127.2±12.4	
Baseline Diastolic (mmHg)	nonPCOS	137	80.5±9.6	0.598
	PCOS	137	81.3±9.8	
Baseline Pulse (bpm)	nonPCOS	137	75.9±9.1	0.694
	PCOS	504	76.7±8.9	
Week 12 Systolic BP (mmHg)	nonPCOS	49	119.4±13.8	0.8
	PCOS	57	119.1±13.6	
Week 12 Diastolic BP (mmHg)	nonPCOS	49	74.9±10.2	0.237
	PCOS	57	77.5 ±11.6	
Week 12 Pulse BP (bpm)	nonPCOS	49	72.9±8.8	0.823
	PCOS	57	72.4±10.2	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Table 36: Comparison of changes in blood pressure between the PCOS and non PCOS groups after 12 weeks of VLCD

Parameter	Category	N	Mean±SD	P†
Change in Systolic BP	PCOS	57	-6.8±17.1	0.567
	non PCOS	49	-8.7±17.1	
Change in Diastolic BP	PCOS	57	-3.9±12.7	0.455
	non PCOS	49	-5.6±12.8	

Finally, the distribution of the ethnic categories was similar between the 2 groups of participants (figure 8 and 9), although the numbers of some minority groups differed. However, due to the small numbers in some of the ethnic groups, comparisons between the different ethnic categories could not be performed.

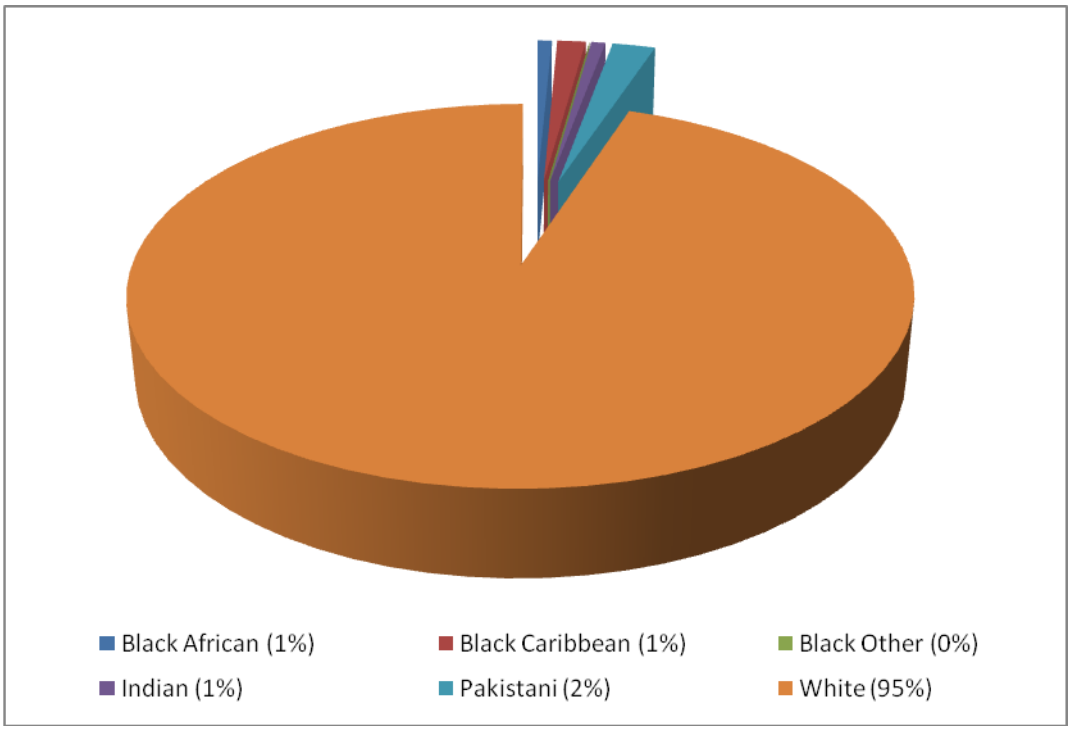

Figure 8: The different ethnic groups among the non PCOS (n=137) 12 week completers

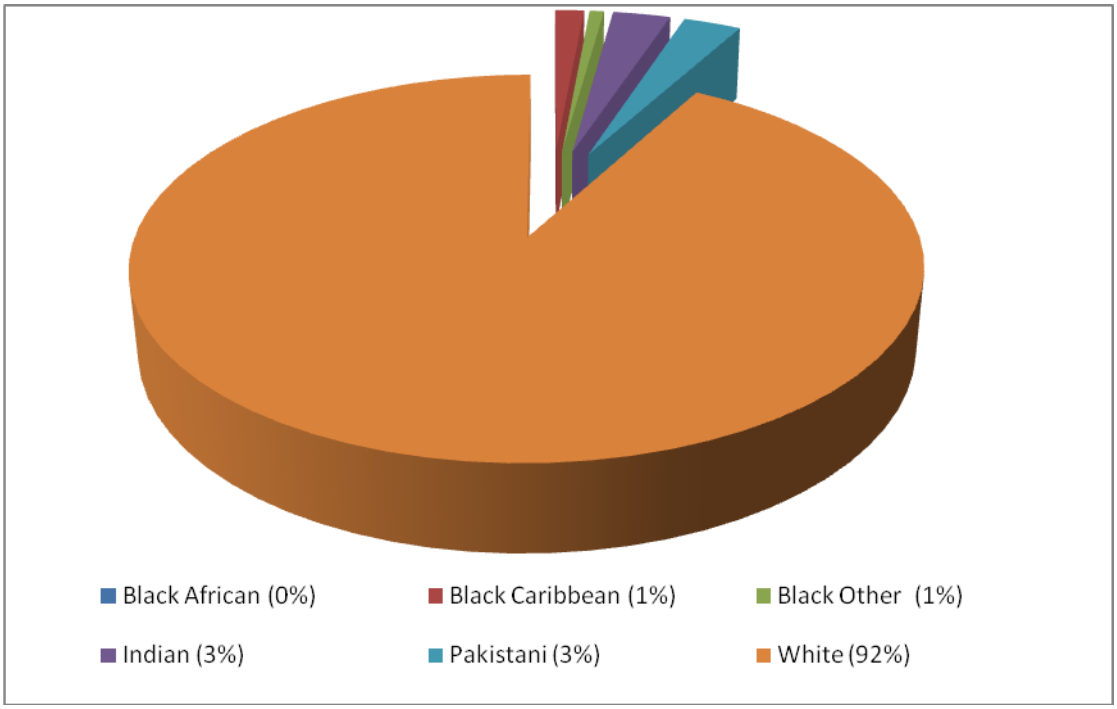

Figure 9: The different ethnic groups among the PCOS (n=137) 12 week completers

4.3 Part 3: Comparison of participants with and without PCOS 1 year after commencing the Lighter Life Total programme

4.3.1 1 year data from the participants who finished the 12 week programme

From the 274 participants who completed the 12 week programme, 1 year data were only available for 35 in the non PCOS category and 41 in the PCOS category. The following table shows that there were no differences between the PCOS and non PCOS women at baseline.

Table 37: Comparison of baseline and 1 year characteristics between PCOS (n=41) and non PCOS (n=35) individuals

Parameter	Category	N	Mean±SD	P†
Age (yrs)	nonPCOS	35	35.7±8.9	0.946
	PCOS	41	35.8±8.9	
Height (m)	nonPCOS	35	1.65±0.1	0.212
	PCOS	41	1.64±0.1	
Baseline Weight (kg)	nonPCOS	35	107.4±19.8	0.713
	PCOS	41	108.3±18.1	
Baseline BMI (kg/m^2)	nonPCOS	35	40.0±6.3	0.955
	PCOS	41	40.0±6.3	
Y1 Weight (kg)	nonPCOS	35	90.27±27.6	0.476
	PCOS	41	94.18±19.9	
Y1 BMI (kg/m^2)	nonPCOS	35	33.37±8.5	0.335
	PCOS	41	35.16±7.6	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups, calculated using an independent t-test
***** marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Even after a year, the weight was significant lower than baseline for both groups (PCOS: 108.3kg ±18.1 versus 94.2kg ±19.9, p<0.001 and non-PCOS: 107.4 kg ±19.8 versus 90.3±27.6, p<0.001). Similarly, BMI remained lower as compared to baseline (PCOS: 40.0±6.3 versus 35.2±7.6 kg/m^2, p<0.001 and non-PCOS: 40.06±6. kg/m ^{2} versus, 33.4±8.5kg/m^2, p<0.001). Moreover, the total weight

change did not differ significantly between the PCOS and the non-PCOS group (-18.9 kg ± 6.6 versus -20.4kg ±5.3, p=0.271) at 1 year, as it can be seen from the following figures. Moreover, the percentage of weight loss achieved by PCOS women at 1 year was similar with the one achieved by the non PCOS women (-15.6%±15.6 versus -12.4% ± 13.3, p=0.35).

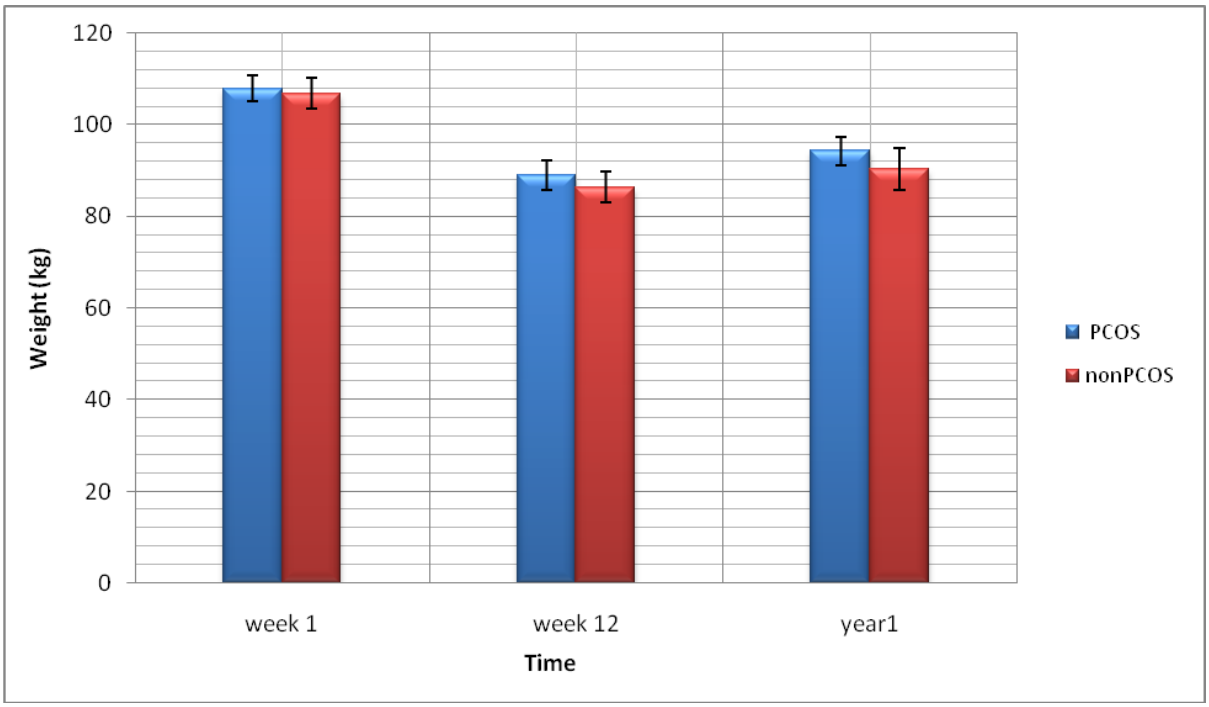

Figure 10: Comparison of weight at baseline, week 12 and 1 year between PCOS and PCOS (completers), Error bars 1represent 1 SE

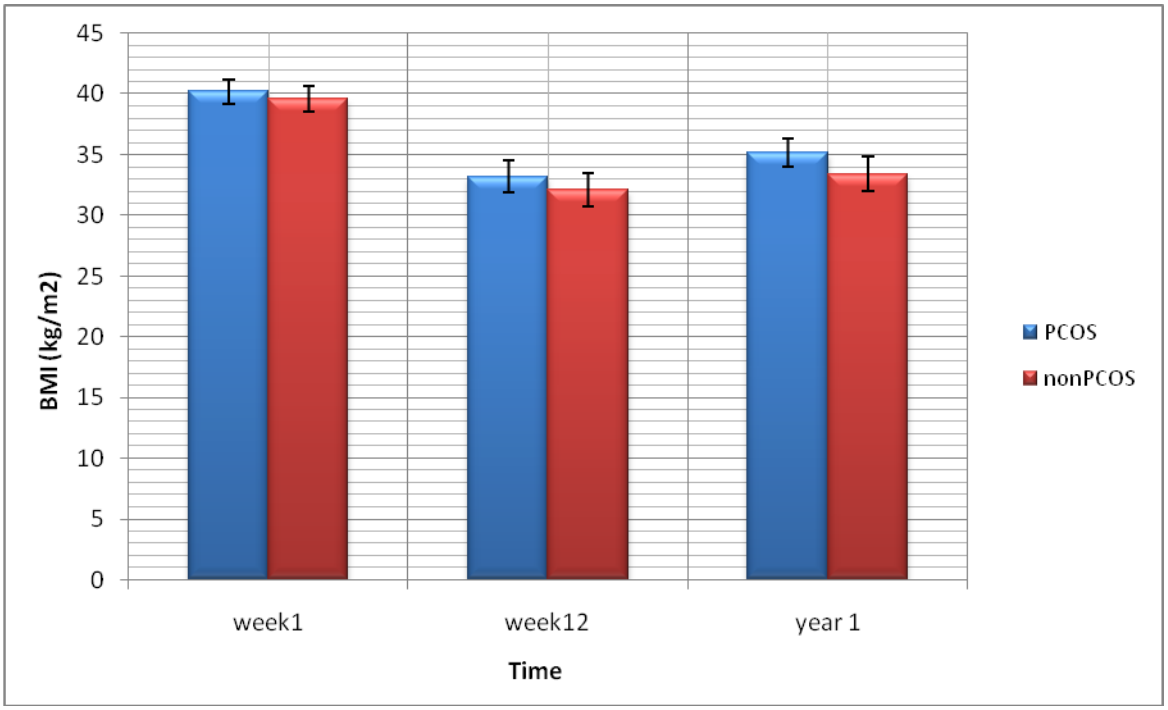

Figure 11: Comparison of BMI (kg/m^2) at baseline, week 12 and 1 year between PCOS and PCOS (completers), Error bars represent 1 SE

4.3.2 BOCF from the participants who finished the 12 week programme

The following table shows that there were no differences between the PCOS and non PCOS women both at baseline and at 1 year.

Table 38: Comparison of baseline and 1 year characteristics between PCOS (n=95) and non PCOS (n=103) individuals

Parameter	Category	N	Mean±SD	P†
Age (yrs)	nonPCOS	103	35.2±7.8	0.271
	PCOS	95	36.5±8.1	
Height (m)	nonPCOS	103	1.64±0.1	0.606
	PCOS	95	1.64±0.1	
Baseline Weight (kg)	nonPCOS	103	101.4±18.1	0.404
	PCOS	95	103.6±18.0	
Baseline BMI (kg/m^2)	nonPCOS	103	37.5±5.7	0.176
	PCOS	95	38.7±6.7	
Y1 Weight(kg)	nonPCOS	103	84.7±17.9	0.01*
	PCOS	95	91.4±18.9	
Y1 BMI (kg/m^2)	nonPCOS	103	31.3±5.8	0.002*
	PCOS	95	34.1±6.9	

Values are means ± standard deviation.
†Significance level of the difference between PCOS and non PCOS groups, calculated using an independent t-test
* marks the significant difference between the 2 groups at baseline, $p < 0.05$, calculated using an independent t-test

Even after a year, the weight was significant lower than baseline for both groups (PCOS: 91.5 kg ± 18.9 versus 103.6 kg ± 18.0, p<0.001 and non-PCOS: 84.7 kg ± 17.9 versus 101.4 kg ±18.1 , p<0.001). Similarly, BMI remained lower as compared to baseline (PCOS: 34.1±6.9 kg/m^2 versus 38.7± 6.7 kg/m^2, p<0.001 and non-PCOS: 31.3 ± 5.8 kg/m ^{2} versus, 37.5 ± 5.7 kg/m^2, p<0.001). Moreover, the total weight change differ significantly between the PCOS and the non-PCOS group (-12.3 ±14.7 kg versus -16.7±14.4, p=0.032) at 1 year, as did the percentage of weight loss: PCOS 11.3% ±13.6 versus non PCOS 15.9 %± 12.6, p=0.014.

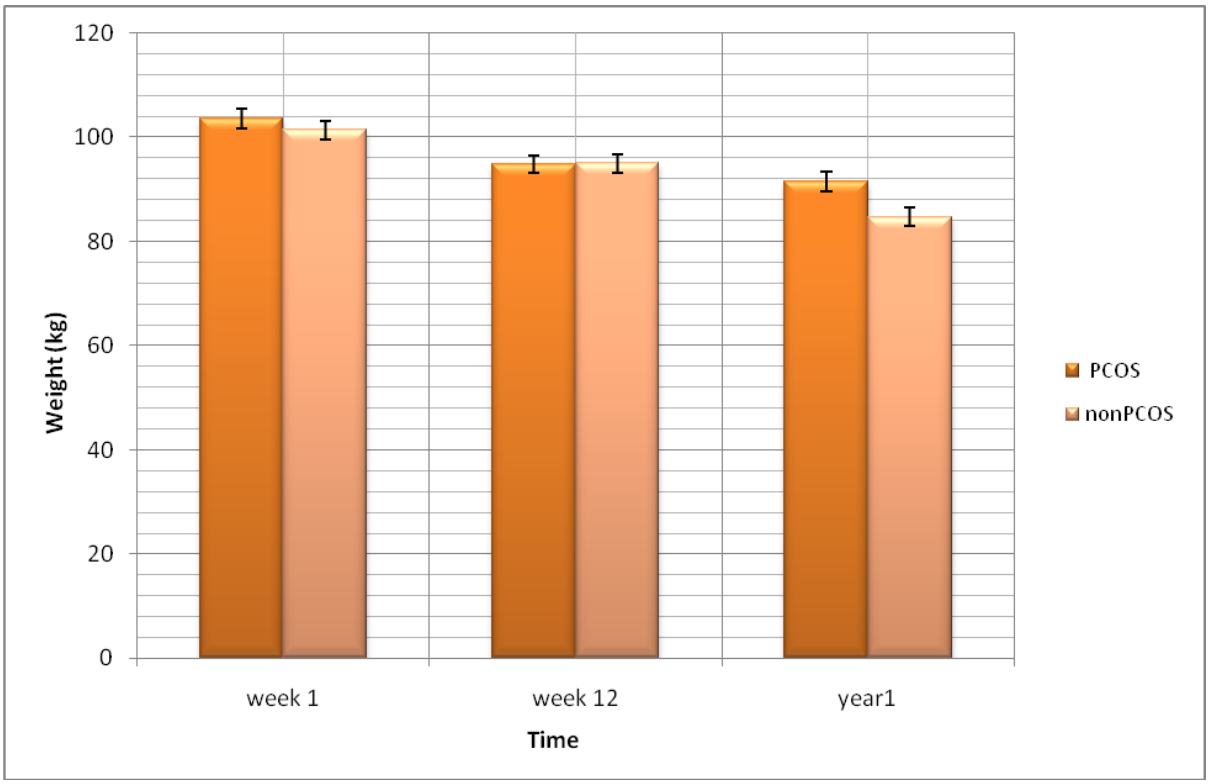

Figure 12: Comparison of weight at baseline, week 12 and 1 year between PCOS and PCOS at the BOCF analysis, Error bars represent 1 SE

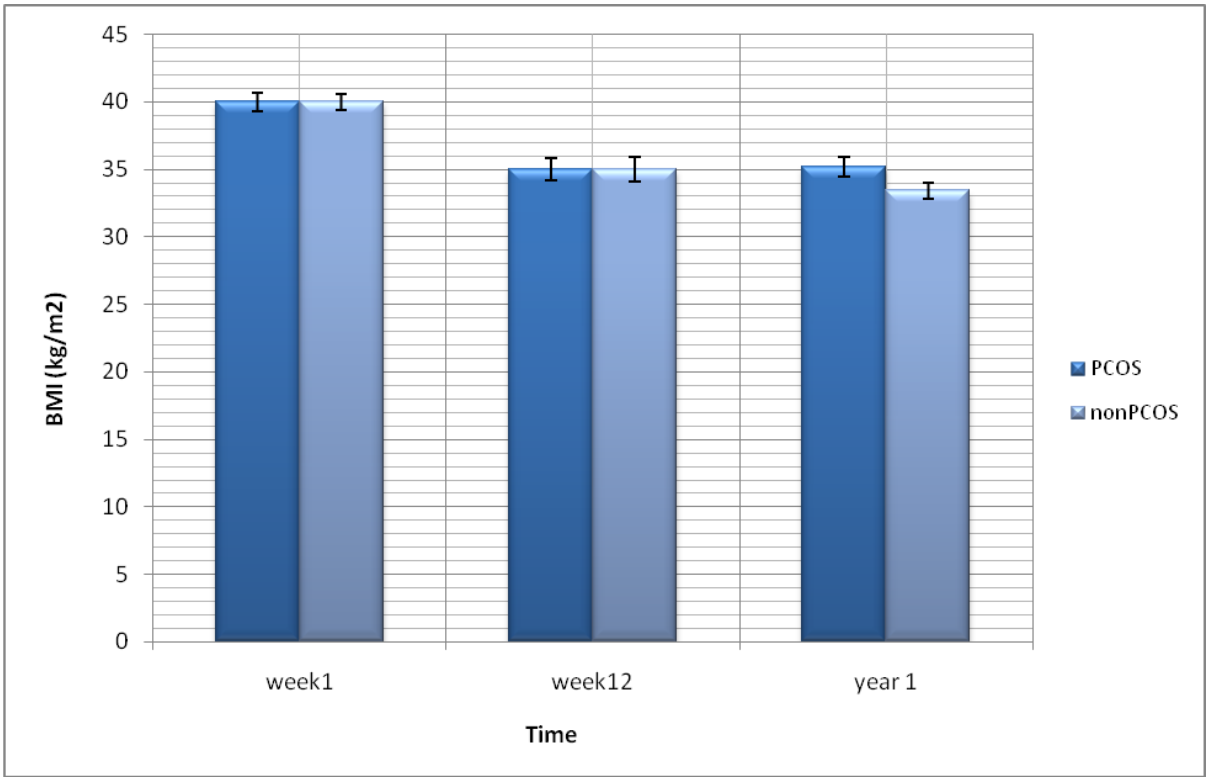

Figure 13: Comparison of weight at baseline, week 12 and 1 year between PCOS and PCOS at the BOCF analysis, Error bars represent 1 SE

5. Discussion

One of the major health problems nowadays is the increasing prevalence of obesity. According to the National Infertility Group Report (2013), half of the women of reproductive age are either overweight or obese. Increased weight, and in particular central obesity, plays an important role in the development of PCOS, thus the majority of women with this syndrome are either overweight or obese (Gambineri et al. 2002). Although the exact pathophysiological interactions between excess weight and the clinical expression of PCOS have not been deciphered yet, it is generally acknowledged that obesity itself is an independent factor associated with disturbances in the sex steroid metabolism (Pasquali et al. 2006), insulin resistance (Reaven et al. 1983) as well as in menstrual irregularities (Svendsen et al. 2008). Obesity in PCOS however, exacerbates the reproductive, metabolic and psychological effects of excessive weight, thus optimal dietary guidelines in the area of PCOS are of crucial importance. Despite the fact that the first line treatment is weight loss through lifestyle interventions, the complexity and the heterogeneity of this syndrome in conjunction with the lack of robust large scale randomised clinical trials, lead to lack of optimal dietary guidelines. This study, attempted to investigate the effect of a commercial VLCD programme in conjunction with behavioural change meetings, on weight loss in overweight and obese women with PCOS as compared to women without this syndrome. Although further investigations are needed, the results suggest that women with PCOS lose the same weight at 12 weeks and maintain similar weight loss with the non PCOS group after 1 year. More details are discussed below.

5.1 Baseline Analysis

The prevalence of PCOS among the LL clients that followed the Total approach between 2006 and 2011, was only 0.5%, a percentage much lower than the current estimates, which vary from 5 to 26% (Hopkinson 1998). For example, 6.5% prevalence in unselected Caucasian population in Spain (Asuncion et al. 2000), 8.0% among Black and 4.8% among Caucasian in United States (Azziz et al. 2004) while Knochenhauer et al. (1998) found 4.7% of Caucasian and 3.4% of Black in United States. Volunteers were recruited from two universities and two general practice surgeries in Oxford. 230 women aged 18–25 years participated The prevalence of PCOS in this age group was as low as 8% or as high as 26% depending on which criteria were applied to define the syndrome. (Michelmore et al. 1999). However, as mentioned in the introduction, the studies that have estimated the prevalence of PCOS, not only were performed among different populations (e.g. Britain, Italy, Spain, USA) but also used different diagnostic criteria. Furthermore, due to the high costs of carrying out diagnostic tests in large populations, the results in the majority of the studies were based on convenience samples, usually less than 400 individuals (March et al. 2010). Consequently, the prevalence calculated in these studies could be biased as the population is comprised only by those who responded to the study advertisement. Regarding the database analysis included in this project, the sample gained was solely comprised of overweight and obese women, excluding any normal weight women with PCOS or overweight women with PCOS that followed any of the other approaches that LighterLife offers. Also, in the majority of the studies available in the literature, the age range of the sample is purposely limited to premenopausal women, whereas in this study the age range was wider (18-75 years), to represent all the age groups. Moreover, the prevalence of PCOS greatly depends on which criteria are used by the physicians to diagnose this syndrome. However, we are not aware of the criteria used for the diagnosis of the PCOS participants in the LL database. This can be attributed to the lack of notes regarding the diagnosis on the medical form and also to the fact that the medical practitioner who made the diagnosis could not be contacted. Another potential bias could be the financial status, as only women who can afford the weekly costs of this commercial programme (approximately

£80 per week) were included. Moreover, according to previous reports (Magnoti and Futterweit 2007, March et al. 2010) up to 69% of women with PCOS in the community may remain undiagnosed. Furthermore, anecdotal evidence from NHS Information Services Division supports that many cases of PCOS (PCOS population in Scotland, is 0.1% for 2010/11), are classified under endocrinological or fertility disorders, a fact that influences the actual prevalence of this syndrome.

During the database analysis, it was noted that the prevalence of PCOS was higher in Asians than in Caucasians (almost 3 times more), which is in accordance with a number of papers (Rodin et al.1998, Wijeyaratne et al. 2002, Eriksson et al. 2012). According to the literature, it has been observed that Asians are more predisposed to T2DM than Caucasians, which in connection with the strong link between decreased insulin sensitivity and PCOS, it could explain the higher prevalence of PCOS in Asians when compared to Caucasians (Wijeyaratne et al. 2011). Yet, some results are conflicting due to the limited research in this area (Crosignani and Nicolosi, 2001). In addition, the clinical presentation of PCOS may vary significantly between Caucasian and Asian populations due to the different genetic predispositions (Balen and Michelmore 2002). For example, is quite common for women of Asian origin to have increased body hair (or at least more noticeable).

The baseline analysis of the database revealed some significant differences in anthropometric and metabolic parameters between obese women with and without PCOS. Participants with PCOS were significantly younger than women without the syndrome, which could imply that many of them were prompted to search for a diagnosis after unsuccessful attempts to conceive, a fact that is in accordance with the literature. Another possible reason could be the influence of several socioeconomic factors, such as family environment and education received, which may have prompted them to ask for help at an earlier age.

Furthermore, PCOS participants had a higher weight and BMI than non PCOS. However, it is still debatable whether heavier women are predisposed to PCOS or are obese because they have PCOS or the differences between women with and

without PCOS are more likely due to environmental and lifestyle factors (Hoeger and Oberfield 2012)

Increased abdominal adiposity is another frequent characteristic among PCOS women (Barber et al. 2006, Kirchengast and Huber, 2001), even in cases of normal weight (Kirchengast and Huber 2001), although a small number of studies revealed no differences in body fat distribution between obese women with and without PCOS (Carmina *et* al. 2005). Moreover, in PCOS, central obesity per se, may play a crucial role in influencing the steroid metabolism as well as the insulin resistance. Initial results from the LL database showed that although the waist and hip circumference were higher in PCOS participants, the WHR did not differ significantly. However, the results may be biased, as measuring waist and hip girths in obese individuals, increases the risk for technical errors (Stewart et al. 2010*).* Also, larger bust circumference was observed in PCOS women, which could be attributed either to their higher BMI or to the frequent use of oral contraceptives, which is a common medication among women with PCOS, as it induces regular menstruation (Eriksson et al. 2012, Jernstrom and Olsson 1997).

Pulse and diastolic blood pressure did not differ between women with and without PCOS, however, PCOS women had lower levels of systolic blood pressure, despite the fact that they were heavier and literature has shown that PCOS may predispose towards hypertension (Chen et al. 2007). The lower values observed, could be attributed to the fact that PCOS women were younger or depict that they receive regular medication to control their pressure (52 women with PCOS receive antihypertensive medication versus 16 non PCOS).

5.2 12 weeks and 1 year analysis

It is generally proposed that as little as 5% weight loss can improve fertility outcomes. In this study, PCOS (completers) achieved similar weight reduction with the non PCOS (completers) group: was 17.1% ±5.6 (PCOS completers) versus 18.2% ±4.4 by the non PCOS group (p=0.08). after 12 weeks of VLCD in

conjunction with group counselling. The ITT analysis (for the participants that started the 12 week programme but did not complete it), showed more conservative results, due to fact that the BOCF method was used (10% weight loss for both PCOS and non PCOS participants), however both of the groups achieved approximately 10% weight loss after the 12 week VLCD approach (PCOS: -9.7%±9.4 vs non PCOS: -9.7%±9.7, p=0.965. Interestingly, at 1 year, a weight loss of 12.4% was still maintained for the PCOS individuals versus 15.6% for the non PCOS group, p=0.35.

These results are intriguing because a number of papers have mentioned that women with PCOS may face difficulties in achieving weight loss due to some metabolic issues, however none of them tested the response of women with PCOS to a VLCD with an incorporated behavioural component. More specifically, PCOS patients may have reduced postprandial thermogenesis associated with reduced insulin sensitivity (Robinson et al. 1992). Moreover, adjusted basal metabolic rate (BMR) appears to be statistically significantly lower in women with PCOS, and is more evident in women with both PCOS and insulin resistance (Georgopoulos et al. 2009).

Furthermore, after diet-induced weight loss, due to a number of compensatory changes, weight regain may be stimulated. For example, the postprandial excretion of cholecystokinin (CCK), a hormone which increases satiety, appears to be significantly reduced after weight reduction in previously obese patients. Moreover, PCOS patients very often have deranged appetite regulation due to reduced postprandial CCK secretion, when compared to control age and BMI matched individuals without PCOS (Hirschberg et al. 2004). However, in cases where the weight reduction was achieved via a ketogenic diet –a high protein, high fat, low carbohydrate plan-, the levels of CCK maintained at similar concentrations with the ones before the weight loss (Chearskul et al. 2008). This could suggest that due to the anorexogenic effect of ketosis, the levels of CCK were normalised among the PCOS patients and similar weight loss was achieved when compared to the non PCOS group.

5.3 Strengths and Limitations

Although the gold standard in evaluating healthcare interventions are carefully designed, conducted and reported randomised controlled trials, due to time limitations and financial restraints, the utilisation of the extensive LighterLife database was the most appropriate method for this project. These population-based retrospective analyses, assessed the effectiveness of a commercial VLCD in conjunction with weekly counselling group sessions, as it runs for real clients who joined the programme to achieve weight reduction. This can be seen as a strength, because the results depict a snapshot of the PCOS community. Also, due to the fact that the population of the database was drawn from several geographic areas around the UK, any socioeconomical biases associated with sample selection were minimised. However, deprived areas may have not been represented in this analysis, as participation on this commercial programme requires a good financial status.

The main strength of the current study is that this is the largest investigation to date, of the effect of a commercial VLCD in conjunction with a behavioural component, on obese women with PCOS as compared to obese women without this syndrome. Its findings suggest that women with PCOS lose the same amount of weight and at the same rate as non-PCOS women, after following a commercial VLCD programme for 12 weeks, and that at least 13% weight loss is maintained at 1 year follow up. Although mainly based on anecdotal evidence, there is the wide perception that overweight and obese women with PCOS find it harder to lose weight when compared to women without this condition, either due to underlying physiological mechanisms that could influence the energy expenditure e .g reduced postprandial thermogenesis in PCOS (Robinson et al. 1992) or due to the emotional distress that accompanies this disorder, and predisposes towards increased energy consumption.

While improvements in weight and BMI have been reported by other studies using variable dietary approaches, these studies lacked a control group (Moran et al. 2003; Moran et al. 2006; Stamets et al. 2004) whereas in the present study, women without PCOS acted as the control group and were also matched

for age and BMI for further analysis. Moreover, this is the only study in the area of PCOS and VLCDs that incorporates the counselling component, although the effect of counselling per se was not assessed. However, it is known that the element of the behavioural change, not only can enhance weight loss but may also improve the completion rates of weight loss programmes (Brown et al. 2004). This support is of extreme importance among PCOS patients, where higher incidences of depressive and anxiety disorders may predispose them towards unhealthy eating behaviours.

However, a number of limitations were encountered throughout the analysis, mainly associated with either the retrospective design of this research or with the lack of data in some cases.

Firstly, there is no information on the criteria used for diagnosis of the PCOS status and it is highly possible that each of the PCOS women have been diagnosed by a different doctor. It is also probable that some women in the non PCOS group may have remained undiagnosed. This could impact not only in underestimating the prevalence of PCOS in this sample but could also influence the differences between the PCOS and non PCOS group (they could be less prominent). Moreover, due to the small numbers encountered in some of the ethnic groups, comparisons between the different ethnic categories encountered, could not be performed. However, wherever appropriate, some smaller groups were combined into larger groups e.g. Indians, Bangladeshis and Pakistanis were combined under the category of Asians.

In addition, it was initially planned that the medications would be categorised into Defined Daily Doses as this is the "assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO 2009). However, information on the dosage was not always available and in some cases instead of the name of the medication or the active compound, the description of the health issue was provided. Moreover, the medication list was not updated after the 28day checkups, and a history of the medication consumption by the participants throughout the VLCD was provided instead. Thus, changing the prescription as a result of weight loss (e.g. Metformin) could not be assessed.

Furthermore, a number of measurements regarding waist, hip and bust circumferences as well as systolic and diastolic blood pressure and pulse were missing, a fact that may have influenced the findings of this project. Although for the 12 week data the analyses were performed for all the available values, for the 12 month data only weight and attendance rates were available.

Moreover, the attendance rates were not always provided and in some cases the numbers given could imply either the attendance of the counselling session or just the visit of the individual in order to get the weekly supply of foodpacks or both. Also, the total numbers of weeks on weight loss or management (food re-introduction programme after the VLCD) were not always mentioned in the database.

In addition, although the LighterLife Counsellors are trained to perform the anthropometric measurements via standardised techniques, it is possible that a number of interobserver and intraobserver errors may have occurred, which may have lead to overestimation or underestimation of some measurements. Furthermore, although the facilitators have been trained to run the counselling sessions according to protocols based on CBT and TA, the individual approach and experience of each counsellor may influence the attendance and the long term efficacy of the program.

5.4 Conclusion

PCOS is a complex condition, with diverse implications which include reproductive, metabolic and psychological comorbidities. Its clinical management should focus on lifestyle changes with medical therapy when required, as well as providing patients with support and education. Moreover, a VLCD in conjunction with behavioural changing sessions and nutritional counselling for food reintroduction, can comprise an effective way of weight loss among women with PCOS. However, evidence-based guidelines are still needed to guide clinicians and patients in optimummanagement of this syndrome.

The present retrospective analysis suggests that women with PCOS lose the same amount of weight and at the same rate as non-PCOS women, after following a commercial VLCD programme for 12 weeks, in conjunction with group counselling sessions. Moreover, the weight maintenance at 12 months is similar for both the PCOS and non PCOS participants. Consequently, this approach could be used as an effective alternative to standard low calorie diets, especially in cases where difficulties in achieving weight loss are encountered.

5.5 Future Research Implications

There are several suggestions for further research in the area of PCOS. Firstly, the aetiology of PCOS as well as the interaction between genes, obesity, androgens and insulin resistance into the development of PCOS requires further research, including both laboratory studies and human trials.
Secondly, the prevalence of PCOS in the UK should be estimated via the use of the same criteria. Moreover, a consensus over a global definition of PCOS should be reached, to assist future studies. It would also be useful to compare the prevalence and presentation of the syndrome among different ethnicities. For example, Asian women would be an interesting group to be targeted due to the greater prevalence of PCOS.

Thirdly, well planned long-term randomised controlled clinical trials with at least 1 year follow up -and if possible to follow up until live births are achieved- are required. Also, comparison of the efficacy of the VLCD in conjunction with and without counselling -and other forms of behavioural therapy - in PCOS versus non PCOS, in age and BMI matched sample would be very interesting to be performed.

Fourthly, further investigations are needed to investigate the metabolic rate and the postprandial thermogenesis in well designed studies comparing PCOS patients with age and BMI matched non-PCOS participants.

Fifthly, data on the aetiology of PCOS as well as the hormone regulation of appetite and satiety in PCOS overweight/obese patients, require further investigation, so studies with greater sample size are needed.

Sixthly, qualitative analysis investigating the personal experiences of weight loss among women with PCOS has not been conducted yet. Interviews or focus groups could be used to identify the spectrum of barriers that women with PCOS face while trying to lose weight.

Last, the concept of triangulation could be used to add more insight into the subject of weight loss in overweight/obese women with PCOS. According to this concept, quantitative and qualitative methods can be combined to supplement and complement each other and offer a pluralistic methodological approach (Bryman, 2001). This method will provide a more complete way of fulfilling the research aim, by generating meaningful information that may have not been discovered with the sole use of one approach. For example, the quantitative data can prove whether one dietary approach was successful or not (objective reality) whereas the qualitative approach will explain in depth this success or failure from an individual's/group's point of view (intersubjective reality). Moreover, this could lead to the generation of new hypotheses which could be tested through carefully designed clinical trials.

5.6 Recommendations for LighterLife Database Practice

Due to the retrospective nature of this project and the problems encountered, the following recommendations could be implemented for a better practice in the future:

Firstly, it would be useful for the counsellors to document for all their clients, who is attending each of the weekly behavioural sessions offered, as the behavioural therapy could possible enhance the weight loss and contribute to longer term weight maintenance.

Secondly, synoptic tables with clear distinction between weeks of weight loss and management phase for each of the participants would be helpful.

Moreover, changes in medication prescription and dosages should be recorded, to assess the effect of weight loss on medication.

Last, the LL counsellors could improve their record keeping strategies e.g. electronic files instead of handwriting practice, to minimise loss of data.

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7. Appendix

7.1 Client Information Form

LighterLife® Total

Client Information Form

Counsellor Cohort ID _____ **Client CIF number** _____ **Today's date** _____

Forename _____ **Surname** _____ **Date of birth** _____ **Age** _____ **M** ☐ **F** ☐

Address _____

_____ **Postcode** _____

Daytime tel (inc. area code) _____ **Evening tel (inc. area code)** _____

Mobile tel _____ **Email address** _____

Ethnic origin _____ **Where did you hear about LighterLife Total?** _____

LIFESTYLE

Smoking:	**Yes**	**No**
Do you smoke?	☐	☐

If **yes**, how many do you smoke a day?
Less than 10 ☐ 10-20 ☐ More than 20 ☐

If you used to smoke, when did you quit? ☐ Years ago
How many did you smoke a day?
Less than 10 ☐ 10-20 ☐ More than 20 ☐

Have you ever had / do you have:	**Yes**	**No**
Epilepsy, seizures, convulsions	☐	☐
Type 1 diabetes	☐	☐
Porphyria	☐	☐
Total lactose intolerance	☐	☐
Heart failure, arrhythmia, valve disease requiring treatment	☐	☐
Schizophrenia and delusional disorder, psychotic episode, bi-polar disorder	☐	☐
Major depressive disorder	☐	☐
Severe renal / liver disease	☐	☐
Current active anorexia, bulimia or currently undergoing treatment for any other eating disorder	☐	☐

Have you had / do you have:	**Yes**	**No**	**If yes, please give details**	**Date**
Thrombosis or treatment for thrombosis in the last six months	☐	☐	_____	dd mm yy
Stroke / TIA	☐	☐	_____	dd mm yy
Heart problems, including heart attack and angina	☐	☐	_____	dd mm yy
Any serious illness, injury, trauma and / or surgery in the last three months	☐	☐	_____	dd mm yy

Are you:	**Yes**	**No**	**If yes, please give details**	**Date**
Undergoing or due to undergo any course of treatment (see over for medication) / surgery / investigation / referral	☐	☐	_____	dd mm yy

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Are you taking any medication prescribed by your doctor (other than HRT and contraception)? Yes ☐ No ☐
If yes, please list:

Name of medication	What is it for?

WOMEN ONLY

Please answer EVEN if the questions below seem irrelevant to you (eg post-menopausal)

	Yes	No	If yes	Date
Are you pregnant?	☐	☐		
Have you given birth in the last three months?	☐	☐	When was the baby born?	dd mm yy
Are you breastfeeding as the baby's main form of nutrition?	☐	☐		
Have you miscarried at more than 20 weeks gestation?	☐	☐	When was the miscarriage?	dd mm yy

I agree to the release of the contents of this form to my LighterLife Counsellor and LighterLife UK Limited. I agree to notify my LighterLife Counsellor if there are any changes to the information provided in this form.

If I require copies of any personal data held by either my LighterLife Counsellor or LighterLife UK Limited, I will write to my Counsellor or to LighterLife UK Limited at Cavendish House, Parkway, Harlow Business Park, Harlow, Essex CM19 5QF. A small fee may be charged.

LighterLife UK Limited will pass on my contact details to third-party survey agencies who may contact me from time to time to ask for telephone feedback on LighterLife's programmes. Unless I write to LighterLife to advise otherwise, I agree to be contacted by such third-party survey agencies. Both my LighterLife Counsellor and LighterLife UK Limited will comply with the Data Protection Act 1998 in processing my personal data.

LighterLife UK Limited would like to contact me with news, promotions, and other relevant information which may be of interest to me. The information I provide is for the sole use of LighterLife UK Limited and will not be passed on to third parties. I wish to be contacted (please tick this box). ☐

SIDE EFFECTS

Some clients may experience side effects while on the LighterLife Total very-low calorie diet. The most commonly reported side effects of a restricted carbohydrate, very-low-calorie diet are: headaches, dizziness, feeling cold, hunger and gastrointestinal disturbance (nausea, diarrhoea, constipation). More uncommon side effects of losing weight may include cramps, fatigue, dry mouth, halitosis, hair shedding, gout, excess skin, changes in menstrual cycle and fertility, and rarely on occasions an increased risk of gallstone formation.

CLIENT SIGNATURE

I declare the answers I have given are correct and accurate to the best of my knowledge, and I confirm that I have read and understood the potential side effects. I authorise the release of this form to my LighterLife Counsellor and to LighterLife UK Limited Central Office.

Signature _____ Date _____

COUNSELLOR TO COMPLETE

Height in metres ☐ Weight in kg ☐ Height² ☐ BMI ☐ Waist circumference in cm ☐

Medically eligible: **Yes** ☐ **No** ☐ **Not yet** ☐

Comments _____

_____

COUNSELLOR NOTES

7.2 Health Questionnaire

Health Questionnaire

LighterLife® Total

Your patient would like to join the LighterLife Total weight-management programme. This offers the obese or those with a raised waist circumference a nutritionally complete very-low-calorie diet (VLCD), providing 500-600 kcal and a minimum of 50g carbohydrate per day. Patients attend weekly group meetings which use techniques from cognitive behavioural therapy and transactional analysis to support behaviour modification for sustainable weight management. LighterLife Total is compliant with NICE guideline 43 on the treatment of obesity.

tel: 01279 636998 **email: medicalcare@lighterlife.com** **web: www.lighterlife.com/clinical**

Your patient _____ Date of birth _____

Address _____

_____ Postcode _____

Height _____ Weight _____ Waist circumference _____cm

Email _____ BMI _____

Counsellor cohort ID _____ Client CIF number _____

1. The 'yes' boxes in this section are exclusion criteria for LighterLife Total.

Has your patient experienced:	**Yes**	**No**
Epilepsy, seizures, convulsions	☐	☐
Type 1 diabetes	☐	☐
Porphyria	☐	☐
Total lactose intolerance	☐	☐
Heart failure, arrhythmia, valve disease requiring treatment	☐	☐
Schizophrenia and delusional disorder, psychotic episode, bi-polar disorder	☐	☐
Major depressive disorder	☐	☐
Severe renal / liver disease	☐	☐
Current active anorexia, bulimia or currently undergoing treatment for any other eating disorder	☐	☐

2. The 'yes' boxes in this section may exclude your patient from participating in LighterLife Total.

Has your patient had:	**Yes**	**No**	**Date**		**Yes**	**No**		**Yes**	**No**
Thrombosis or treatment for thrombosis in the last six months	☐	☐	dd mm yy	Is the condition stable?	☐	☐	I agree to monitor my patient during the VLCD	☐	☐
Cerebrovascular disease	☐	☐	dd mm yy	Is the condition stable?	☐	☐	I agree to monitor my patient during the VLCD	☐	☐
Cardiac disease, including angina and MI	☐	☐	dd mm yy	Is the condition stable?	☐	☐	I agree to monitor my patient during the VLCD	☐	☐

3. Has your patient had:	**Yes**	**No**	**Details**	**Date**
Any serious illness, injury, trauma and / or surgery in the last three months	☐	☐	_____	dd mm yy
Is your patient:	**Yes**	**No**		
Undergoing or due to undergo any course of treatment (see over for medication) / surgery / investigation / referral	☐	☐	_____	dd mm yy

4. Please indicate any other significant medical history

_____

_____

_____

Blood pressure and pulse rate: BP _____ Pulse rate _____

Is the pulse rate regular? Yes ☐ No ☐ If irregular, does the patient require treatment / investigation? Yes ☐ No ☐

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WOMEN ONLY

Please answer EVEN if the questions below seem irrelevant to your patient (eg post-menopausal)

	Yes	No	If yes	Date
Is the patient pregnant?	☐	☐		
Has the patient given birth in the last three months?	☐	☐	When was the baby born?	dd mm yy
Is the patient breastfeeding as the baby's main form of nutrition?	☐	☐		
Has the patient miscarried at more than 20 weeks' gestation?	☐	☐	When was the miscarriage?	dd mm yy

MEDICATIONS

Oral hypoglycaemic/insulin medication

The LighterLife Total VLCD provides 500-600 kcal and a minimum of 50g CHO per day, which will reduce plasma glucose levels. Type 2 diabetics will require planned review of hypoglycaemic agents and insulin, which are usually reduced or stopped at the commencement of the LighterLife Total VLCD.

Name _____ Dose _____ Date started _____

Name _____ Dose _____ Date started _____

Anti-hypertensive medication

Blood pressure can reduce with weight loss and medication will require review and titration.

Name _____ Dose _____ Date started _____

Name _____ Dose _____ Date started _____

Diuretic medication

This restricted-carbohydrate VLCD initiates an increased natural diuresis. It is likely your patient will also consume additional fluids to replace those found in conventional food. In combination with diuretic medication, this can potentially disturb electrolyte equilibrium. Diuretic medication will require review.

Name _____ Dose _____ Date started _____

Other prescribed medication

Name	Dose	Indication	Date started
			dd mm yy
			dd mm yy
			dd mm yy
			dd mm yy
			dd mm yy
			dd mm yy

This questionnaire allows LighterLife to ascertain your patient's medical status and operate exclusion criteria. In signing this form you confirm that the information provided is true to the best of your knowledge. It does not transfer medical responsibility for LighterLife Total to you, your practice or your employer. Your patient is aware that you may levy a charge for this service and, where a fee is charged, your patient will pay you directly.

DOCTOR / PRACTICE NURSE SIGNATURE

Please confirm by signing this form that you are aware medication monitoring / adjustment may be required and that, where appropriate, you will arrange this with your patient during the LighterLife Total VLCD.

Doctor's / practice nurse's signature _____
(Delete where appropriate)

Please print name _____

Date _____

Please confirm whether this is the patient's registered surgery

Yes ☐ No ☐

Surgery stamp

All medical information on this form is for LighterLife UK Limited use only. LighterLife UK Limited complies with the Data Protection Act.

PATIENT SIGNATURE

I confirm that the information on this form is correct and accurate and no material information has been omitted. If I become aware that any of the information in this form is incorrect or out of date, I will inform my LighterLife Counsellor immediately. I authorise the release of this form to my LighterLife Counsellor and to LighterLife Central Office.

Patient signature _____ Date _____

7.3 Ongoing Check-Up

LighterLife® Total

Ongoing Check-Up

In accordance with COMA recommendations, this patient is required to have a brief check-up every four weeks while using the LighterLife Total very-low-calorie diet (VLCD). Patients have been informed and agree to pay any fee directly to you themselves.

Completing and signing this form does not place medical responsibility for the LighterLife Total VLCD on you or your practice.

Name: _____ Date of birth: _____

Address: _____

_____

Postcode: _____ CIF number: _____

Please detail any prescribed medication.

Prescribed medication	Purpose of medication	Dose

Has there been a significant change in medical status? Y / N Please comment:

_____

_____

_____

Blood pressure / pulse

Systolic	Diastolic	Pulse

GP / nurse / pharmacist signature (delete where appropriate)

I declare the answers I have given are a true statement to the best of my knowledge.

GP / nurse / pharmacist signature: _____

Date: _____

Please authenticate with surgery stamp

For more information on the LighterLife Total VLCD, to request a clinical information brochure or to speak to a member of our clinical team, please contact us using the details below.

Patient signature

I declare the answers are a true statement and I authorise the release of this form to my LighterLife Counsellor and LighterLife Central Office.

Patient's signature: _____

Date: _____

LighterLife UK Limited, Cavendish House, Parkway, Harlow Business Park, Harlow, Essex CM19 5QF. 01279 636998. www.lighterlife.com/clinical

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