Weight management in young women

A thesis submitted by

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Table of contents

Declaration of originality 4
Acknowledgements 6
List of figures 7
List of tables 9
Abbreviations 10
Abstract 12
Chapter 1 Introduction 14
1.1 Young women and weight gain 15
1.1.1 Prevalence of weight gain 15
1.1.2 Long term consequences of excess weight or weight gain in young women 16
1.1.3 Short term consequences of excess weight or weight gain in young women 20
1.1.4 Why do young women gain weight? 26
1.2 Young Women and Weight loss 40
1.2.1 Prevalence of weight loss attempts 40
1.2.2 Lifestyle interventions and weight loss in young women 42
1.2.3 Quantitative or qualitative lifestyle advice 51
1.2.4 Internet as a medium to provide long term weight management support 52
1.2.5 Metformin and weight loss in young women 53
1.3 Summary and gaps in knowledge 61
1.4 Objective 62
1.5 Aims 63
1.6 Hypotheses 64
Chapter 2 Hyperandrogenemia, psychosocial distress, and food cravings in overweight and obese young women 65
2.1 Abstract 68
2.2 Introduction 69
2.3 Methods 70
2.4 Results 74
2.5 Discussion 75
2.6 Figures and tables 80
Chapter 3 The effect of comprehensive lifestyle intervention or metformin on obesity in young women 82
3.1 Abstract 85
3.2 Introduction 86
3.3 Methods and procedure 87

3.4 Results 91
3.5 Discussion 95
3.6 Figures and tables 98
Chapter 4 The psychological effects of prescriptive vs general lifestyle advice for weight loss in young women 102
4.1 Abstract 105
4.2 Introduction 106
4.3 Methods 107
4.4 Results and discussion 110
4.5 Conclusions 114
4.6 Figures and tables 115
Chapter 5 Long term weight management through internet program in young women 117
5.1 Abstract 118
5.2 Introduction 120
5.3 Methods 121
5.4 Results 125
5.5 Discussion 127
5.6 Figures and tables 132
Chapter 6 Discussion and conclusion 136
6.1 Drug or diet 136
6.2 Restraint or freedom 137
6.3 Stress, hyperandrogenemia and food cravings 138
6.4 Internet-based weight management program 140
6.5 Young women and weight management 140
6.6 Limitations 142
6.7 Conclusion 143
Appendix 1. Questionnaires on socio-demographic characteristics, psychological distress (GHQ), self-esteem (RSE-B), food cravings inventory (FCI) and internet usage 146
Appendix 2. Post intervention questionnaire 156
Appendix 3. Exit interview (conducted by psychologist) 160
Bibliography 171

Declaration of originality

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List of figures

Figure 1.1 The 10-year incidence of major weight gain (≥5 kg/m^2) among men and women in US. The error bars indicate 95% confidence intervals. The numbers above the bars show relative risks for major weight gain in women compared to men, with 95% confidence intervals in parentheses. (Taken from Williamson et al, 1990, p669 [7])..... 14

Figure 1.2 Mean BMI by birth cohort for women in Australia in 1990 to 2000 with projections to 2010. (Taken from Allman-Farinelli et al, 2006, p6 [1])..... 16

Figure 1.3 The effect of adiposity signals such as leptin on the homeostatic (ie satiety) and non homeostatic (ie food reward) pathways in the regulation of food intake. ARC, arcuate nucleus (highlighted in blue); DMN, dorsomedial nucleus; FX, fornix; ME, median eminence; PFA, perifornical area; VMN, ventromedial nucleus. (Taken from Morton et al, 2006, p290 [81]).....27

Figure 1.4 Causes of weight gain in young women.....39

Figure 1.5 Mean expenditure on weight management strategies by young women (age 18 to 32, n=445) in Australia. (Taken from Ball et al, 2003, p586 [130])..... 40

Figure 1.6 Effect of metformin on BMI in non diabetic persons, percentage change. (Taken from Salpeter et al, 2008, p151 [75])..... 56

*Figure 2.1 Food cravings score (means ± SE, n=198) in young women with or without hyperandrogenemia (defined as Free Androgen Index > 4.97). * P<0.05 between groups after correcting for age, BMI and PCOS status. 80*

*Figure 2.2 Food cravings score (means + SE, n=198) in young women with or without menstrual disturbances (MD). * P<0.05 between groups after correcting for age, BMI and PCOS status. 80*

Figure 3.1. Flow diagram of participants' recruitment, randomization and completion of the interventions.....98

Figure 3.2 Estimated weight changes (± standard error) in participants randomised to comprehensive lifestyle program (circles, n=59), metformin plus general lifestyle advice (squares, n=65), or placebo plus general lifestyle advice (triangles, n=79). P<0.05 between changes in comprehensive lifestyle group compared to metformin and placebo groups. 99

Figure 3.3 Weight outcomes of participants after 12-weeks on comprehensive lifestyle program (n=59), metformin (n=65), or placebo (n=79). P<0.05 for chi-square analysis. 99

Figure 4.1 Flow diagram of participants' recruitment, participation and completion of the interventions..... 115

Figure 5.1 Flow diagram of participants' recruitment, randomization and completion of the interventions..... 132

Figure 5.2 Estimated weight changes (±SEM) of the groups receiving quantitative lifestyle advice (QT) or qualitative lifestyle advice (QL) from week 0 to 12 according to mixed model analyses. Both groups received online quantitative lifestyle intervention from week 12 to 48. Time, treatment and time-by-treatment were fixed factors in the linear mixed models. P<0.0005 for time-by-treatment effect..... 133

List of tables

Table 1.1 The long term consequences of excess weight or weight gain in early adulthood: a summary of results from prospective studies in women *20*

Table 1.2 The effect of insulin on androgen production *22*

Table 1.3 The short-term consequences of excess weight or weight gain in early adulthood: a summary of results in young women *25*

Table 1.4 Behavioural factors associated with weight gain in young women *32*

Table 1.5 Dietary trials conducted in young women (mean age: 18 to 40 years) *44*

Table 1.6 Exercise trials in young women *48*

Table 1.7 Randomised-controlled trials on the effect of metformin on body weight in non diabetic individuals *57*

Table 1.8 Randomised-controlled trials on the effect of metformin on body weight in PCOS women *59*

Table 2.1 Characteristics of study participants (n=198) *81*

Table 2.2 Regression coefficients for food cravings[a] in predicting psychological distress[b] (n=198)[c] *81*

Table 3.1 Estimated means and changes on clinical and metabolic outcomes[a] *100*

Table 4.1 Estimated means and changes for psychological measures for the prescription lifestyle advice (PLA) group (n=59) and the general lifestyle advice (GLA) group (n=144) *116*

Table 5.1 Treatment conditions in Phase I (week 0 to 12) and Phase II (week 13 to 48) . *134*

Table 5.2 Baseline characteristics of participants (n=203) *134*

Table 5.3 Body weight, energy intake and physical activity outcomes by treatment condition from baseline to Week 48[a] *135*

Table 5.4 Attrition by treatment condition over time[a] *135*

Abbreviations

AGRP	Agouti-related peptide
AMPK	AMP-activated protein kinase
ATP	Adult Treatment Panel
BMI	Body mass index
C	Carbohydrate
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	Coronary heart disease
DBS	Dieting Belief Scale
DPP	Diabetes Prevention Program
F	Fat
FAI	Free androgen index
FCI	Food Craving Inventory
GHQ	General Health Questionnaire
GLP-1	Glucagon-like peptide-1
HDL	High density lipoprotein
HOMA	Homeostasis model assessment
I	Internet support
IP	Internet plus in-person support
IRS-2	Insulin receptor substrate 2
LCD	Low calorie diet
LDL	Low density lipoprotein
LH	Luteinising hormone
M	Metformin
NA	Not available

NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NPY	Neuropeptide Y
NS	Not significant
OR	Odds ratio
P	Protein
P	Placebo
PCOS	Polycystic ovaries syndrome
PI-3	Phosphoinositide 3
PKC	Protein kinase C
QL	Qualitative lifestyle advice
QT	Quantitative lifestyle advice
RCT	Randomised controlled trial
RR	Relative risk
RSE-B	Bachman's revision of Rosenberg Self-esteem Scale
S	Structured, quantitative lifestyle advice
SEM	Standard error of the mean
SHBG	Sex hormone binding globulin
T	Testosterone
VLCD	Very low calorie diet

Abstract

Context

Young women are at high risk of weight gain but there has been limited knowledge on weight management in this group. Hyperandrogenemia and menstrual abnormalities are common co-morbidities of obesity in young women but their associations with food cravings are not known. Metformin has been shown to reduce body weight and improve metabolic outcomes in older adults but its effects on healthy overweight and obese young women have not been investigated. Quantitative lifestyle advice has been shown to be effective in inducing weight loss but its psychological effects on young women have not been extensively studied. The overall objective of this study was to investigate the effectiveness of metformin, quantitative lifestyle advice and internet-based intervention on weight management in young.

Methods

In the first 12-weeks, 203 overweight and obese young women (BMI 33.3$\pm$0.3 kg/m^2, age 28$\pm$0.3 years; age range:17-37) were randomized to one of three treatment arms to receive metformin (Diabex XR 1500mg a day) plus qualitative lifestyle advice (M-QL), placebo plus qualitative lifestyle advice (P-QL) or a structured lifestyle program (L-QT). L-QT consisted of an energy restricted diet with quantitative lifestyle advice (6000KJ; 40% protein, 40% carbohydrate, 30% fat), structured exercise program, and behavioural therapy. From weeks 13 to 48, all participants were placed on the structured lifestyle program conducted through a website. Outcome measures include body weight, fasting lipids, insulin, glucose, psychological distress, self-esteem, food cravings, energy intake and physical activity. Primary analyses were conducted using linear mixed models.

Results

At baseline, psychological distress and hyperandrogenemia were associated with increased food cravings (P<0.01). At 12-weeks, L-QT group had greater weight loss (-4.2±0.4 kg) compared to M-QL (-1.0±0.4 kg) and P-QL groups (-0.2±0.3 kg) (P<0.001). Attrition at week 12 was high particularly in L-QT group, ie 48% (28/59) for L-QT group, 34% (22/65) for M-QL group and 29% (23/79) for P-QL group (P=0.08). Baseline psychological distress and food cravings predicted attrition at week 12. At week 12, L-QT group had significantly greater improvements in psychological distress (-3.0±0.9 vs -0.84±0.52, P=0.013) and self-esteem (3.2±0.8 vs -0.04±0.4, P<0.001) compared to the M-QL and P-QL groups. At 48 weeks, both QT and QL groups maintained significant weight loss (-4.8±0.1 kg vs -1.3±0.4 kg respectively, P=0.0005). Weight changes from week 13 to 48 were similar between the groups (P>0.05). Attrition was similarly high in both groups by week 48 (78%; 159/203) (P=0.003). Being married or having children predicted attrition at week 48.

Conclusions

A structured lifestyle intervention program was more effective than metformin in achieving weight loss in young women. Quantitative lifestyle advice produced greater improvements in psychological outcomes compared to qualitative lifestyle advice. Internet-based weight loss program was effective in maintaining weight loss in young women independent of initial weight loss. High attrition rates were seen throughout the study, particularly among those who had greater psychological distress or food cravings, and those who were married or had children. Strategies on managing issues relating to psychological distress, food cravings and family responsibilities may allow better tailoring of weight management programs for this group.

Chapter 1 Introduction

A typical adult in the western world puts on weight until around 60 years old before stabilising and then losing weight [1, 2]. The greatest rate of weight gain occurs in early adulthood in Australia and US [1, 3, 4]. The National Longitudinal Survey of Youth in the United States reported that more than 80% of those who were obese by their mid-thirties had became obese in early adulthood [5]. Young women are particularly at risk of weight gain compared to men and older women [3, 6].

Figure 1.1 The 10-year incidence of major weight gain ($\geq$5 kg/m^2) among men and women in US. The error bars indicate 95% confidence intervals. The numbers above the bars show relative risks for major weight gain in women compared to men, with 95% confidence intervals in parentheses. (Taken from Williamson et al, 1990, p669 [7])

1.1 Young women and weight gain

1.1.1 Prevalence of weight gain

Women in Australia and US are more likely to develop obesity during adulthood compared to men [3, 5, 6]. Currently the average weight gain for US white women aged 25-35 years old is 0.39kg/year [2]. The average weight gain for younger women in Australia aged 18-23 years old is even higher, at about 0.67kg/year [8].

Not only are young women more likely to gain weight than young men, each generation of young women also supersedes the previous generation in weight gain. A study by Allman-Farinelli et al (2006) has shown that the average body weight of women in each age group increased with time [1]. In the US, women born in 1964 were gaining weight 28% more rapidly than women born in 1957 [5]. An Australian study in women similarly found that Generation X (born in 1966-1970) gained weight more rapidly than the baby boomers (born 1951-55), whose weight gain was in turn greater than the pre-war generations (born 1936-40) [1]. While data is not yet available for the Generation Y women (born 1976-1985), greater exposure to an obesogenic environment is likely to sustain if not worsen weight gain trends in this generation.

Figure 1.2 Mean BMI by birth cohort for women in Australia in 1990 to 2000 with projections to 2010. (Taken from Allman-Farinelli et al, 2006, p6 [1])

Weight gain affects a large proportion of young women in Australia, with 40% of them gaining more than 5% BMI in 4 years [9]. Those with a higher body weight at baseline are at greater risk of significant weight gain [5, 9]. Even moderately excess weight (eg 25-27 kg/m^2) at the age of 20-22 years old increases the risk of obesity in the mid-thirties by 60% [5]. Considering that more than 50% of young women are currently overweight or obese in the US, the weight trajectory of this group is of concern.

1.1.2 Long term consequences of excess weight or weight gain in young women

Being overweight or obese in young adulthood has been linked to a number of chronic diseases in mid-adulthood (Table 1.1), as reported in a number of large prospective cohort studies. The Nurses Health Study, which is one of the largest prospective cohort studies

conducted in women, found that those with higher body mass index (BMI) at 18 years (above 23.3 kg/m^2) had twice the risk of having coronary heart disease (CHD) by mid-age (RR=1.99) compared to women with BMI of less than 19.1 kg/m^2 at 18 years [10]. As all women in this study had BMI within the normal range, we can only speculate that those who were overweight or obese at 18 years may be at even higher risk of developing CHD in later life.

Being overweight or obese in young adulthood could also increase the risk of certain cancers and increases mortality in later life. Women who are overweight at 18 years old have a two-fold increased risk for premenopausal ovarian cancer after adjustment for smoking, age, and oral contraceptive use [11]. Other hormone-related cancers (of breast and uterus) are also associated with obesity in early adulthood [12]. Body weight in early adulthood also predicts overall mortality. Women who are overweight at 18 years of age are 1.66 times more likely to suffer premature death while those who are obese are nearly 3 times more likely to face premature death compared to the women with BMI between 18.5 kg/m^2 and 21.5 kg/m^2 [13]. These data suggest that overweight and obesity in young women could have debilitating and even fatal outcomes if left untreated.

Weight gain since early adulthood itself is also emerging to be a risk factor for a number of diseases (Table 1.1). Women who gain a significant amount of weight throughout adulthood (more than 20kg) are 2.7 times more likely to develop heart disease compared to those who maintain their weight (within 5 kg of body weight at age 18 years) [14]. However, even smaller weight gain is associated with increased risk. For example, those who gain 5 kg to 7.9 kg since age 18 have a 25% increased risk of CHD independent of other risk factors such as age, menopausal status, parental history of CHD, smoking and postmenopausal hormone use [10]. Similar relationships between weight gain and disease

risks are also reported for other cardiovascular-related risk factors and events such as the thickening of the carotid artery walls, high blood pressure, and ischemic stroke [15-17]. Thus, weight gain since adulthood could be a strong predictor of cardiovascular health in mid-age.

Adulthood weight gain is also associated with increased risks of other diseases such as diabetes, certain types of cancer, kidney stone formation, and adult-onset asthma [17-20]. Overweight young women who gain weight throughout adulthood are 20 times more likely to develop diabetes compared to normal weight, weight stable young women [17]. Significant weight gain (25 kg or more) since age 18 also increases the risk of breast cancer by 45% [20]. No relationship was observed between adulthood weight gain and colon cancer or premenopausal ovarian cancer [11, 14]. Finally, weight gain (more than 20kg) since age 18 increases the risk of all-cause mortality by 60% [21]. Thus, weight maintenance is a very worthwhile goal for young women.

The adverse effect of weight gain also applies to those whose weight changes are within the normal weight range. Previous weight gain increases the risk of CHD even among those with normal weight [10]. However, the effect of weight gain was far more detrimental for those who were already overweight or obese. Results from the Iowa Women's Health Study showed that normal weight young women who gained weight consistently till mid-age were 6.6 times as likely to develop diabetes as normal weight, weight stable women. In comparison, overweight young women with similar weight gain were 20 times as likely to develop diabetes compared to the same reference group [17]. Similar effects were also seen in shorter-term changes in the Coronary Artery Risk Development in Young Adults (CARDIA) study, in which overweight young adults who gained weight had more adverse changes in glucose, blood pressure, HDL-cholesterol and

triglycerides than normal weight young adults with similar weight gain [22]. The greater impact of weight gain in overweight and obese young adults is of concern, as those who were already overweight or obese were more likely to gain weight.

Several studies have found a stronger association between health outcomes with young adult body weights than with older adult body weights, even though the latter were measured closer to the actual diagnoses [12]. For example, a study in men found that BMI at age 22 years old is more strongly associated with cardiovascular disease than BMI at age 38 years old [23]. Cancer and mortality is also significantly related to early adulthood body weight, but not to later body weights [11, 12]. This observation is consistent with the known pathogenesis of these chronic diseases which involve a long and complicated process. It is possible that physiological stress caused by excess weight or weight gain in early adulthood initiated the processes of disease development which are detectable only in later years. If so, active prevention of chronic diseases may have to begin as early as young adulthood.

Table 1.1 The long term consequences of excess weight or weight gain in early adulthood: a summary of results from prospective studies in women

Study	*N*	Consequences of excess weight [RR, 95%CI]	Consequences of weight gain [RR unless specified, 95%CI]
Nurses Health Study [10, 11, 14, 16, 19-21]	121 700 women	• Coronary heart disease [1.99, 1.64-2.40] • Premenopausal ovarian cancer [2.05, 0.73-1.51]	• Coronary heart disease [2.65, 2.17-3.22] • Ischemic stroke [1.69, 1.26-2.29] • All cancers [1.5, 1.1-1.9] • Breast cancer [1.45, 1.27-1.66] • Kidney stone formation [1.70, 1.4-2.05] • Type 2 diabetes [2.4, 2.0-2.9] • All cause mortality [1.6, 1.3-1.9]
Nurses Health Study II [13, 18]	102 400 women	• Premature death [2.79, 2.04-3.81]	• Adult-onset asthma [2.5, 2.0-3.1]
Iowa Women's Health Study [17]	17252 women		• Diabetes [OR 19.14, 13.38-27.40] • Blood pressure [OR 7.63, 5.69-10.24] • Heart attack [OR 3.47, 1.94-6.20] • Other heart diseases [OR 2.94, 2.01-4.32]
Atherosclerosis Risk in Communities (ARIC) Study [15]	13282 men and women		• Increase in carotid artery wall thickness [change in white women: 0.013mm, 0.009-0.017]
United Kingdom's Royal College of General Practitioners Oral Contraception Study [12]	9918 women	• Cancer [1.48, 0.98-2.24]	

1.1.3 Short term consequences of excess weight or weight gain in young women

In addition to the increased long term risks of chronic diseases, overweight and obesity has immediate impact on young women's lives (Table 1.3). Obese young women have poorer health, as seen in greater rates of asthma, headaches, back pain, sleeping difficulties and more visits to their medical practitioners [24]. Weight gain also increases arterial stiffness

and worsens the metabolic profile of young women through adverse changes in LDL-cholesterol, HDL-cholesterol, triglycerides, fasting insulin, fasting glucose and blood pressure [25-27]. These changes in early adulthood may culminate in cardiovascular or other metabolically-related chronic diseases in mid-age. However, some of these classic 'mid-age lifestyle diseases' are starting to appear in young adulthood, as seen in a more recent and younger cohort study. This study found a 23% increased risk of metabolic syndrome in young adults with each 4.5 kg weight gain [28].

In the short term, overweight and obesity can affect the quality of life in young women by impairing their reproductive health. Obese young women are at greater risk of irregular periods, infertility, and polycystic ovaries syndrome (PCOS) [24, 29, 30]. PCOS is the most common cause of anovulatory infertility and is characterised by hyperandrogenemia, irregular menses and anovulation [31]. The prevalence of PCOS was estimated to be 5-8% of women of reproductive age using the previous NIH definition [32-35]. This number is estimated to increase by 65% using the revised Rotterdam criteria [31]. It is estimated that 30-60% of women with PCOS are overweight or obese in the Western world [33, 36-39]. Post-adolescence weight gain, especially in the abdominal area, is associated with greater self-reported symptoms of PCOS [40]. Obesity is likely to promote hyperandrogenemia and PCOS via hyperinsulinemia, a compensatory response in insulin resistance states. An increase in insulin level typically results in a concomitant increase in testosterone or androstenedione levels [41-43]. Conversely, a decrease in circulating insulin levels either by weight loss or insulin-sensitising treatment (eg through metformin) often leads to a reversal of hyperandrogenemia [44-46]. Several mechanisms have been identified to explain the observed relationship between hyperinsulinemia and hyperandrogenemia (Table 1.2).

Table 1.2 The effect of insulin on androgen production

Target organ	The effect of insulin
Pituitary	• Increases sensitivity to GnRH [47, 48]
Ovaries	• Increases the activity of 17,20 lyase [49]
	• Increases the activity of 3β-hydroxysteroid dehydrogenase and aromatase in the granulosa cells [50]
	• Increases LH receptors [47, 48]
	• Promotes ovarian growth and cyst formation [47, 51]
Liver	• Inhibits SHBG production [52]

Not only does obesity affect natural fertility, it may also decrease the efficacy of assisted reproductive technology. Women with higher BMI generally require higher doses of gonadotropin and longer periods of stimulation during *in vitro* fertilisation treatments [53-56]. When conception is successfully achieved, there are concerns about greater obstetric and neonatal risks associated maternal obesity. Higher maternal BMI is associated with increased risks of gestational diabetes, pregnancy-related hypertensive disorders, caesarean delivery, and prolonged hospital stay [57]. In addition, there are also greater risks of neonatal complications such as birth defects, hypoglycaemia, jaundice and prematurity associated with higher maternal BMI [57]. Weight gain is also a risk factor in this area. An increase of 5 to 10 kg from 18 years old to pregnancy is associated with a two-fold increase in the risk of gestational diabetes after adjusted for age, baseline BMI, ethnicity, parity and education [58]. Thus, obesity and weight gain in young women is not just a metabolic issue, but also has gynaecological consequences as well as consequences for their offspring as well.

The effect of obesity on mental health of young women also deserves attention. In Australia, anxiety and depression is the leading burden of disease and injury among young adults (aged 15-24 years), accounting for 32% of total burden in females and 17% in males

[59]. Women are 1.5 times more likely to report anxiety and affective disorders compared to men [60]. Overweight or obesity exacerbates the mental health of young women. The prevalence of mental disorders increases with body weight, with 57% of obese young women having had mental disorders at some point in their life, compared to 43% in overweight young women and 38% in normal weight young women [61]. Overweight women are also more vulnerable to depression or low self-esteem compared to overweight men [62, 63]. In view of the prevalence of mental disorders in young women especially among those who are overweight and obese, improving mental health should be one of the treatment goals of weight loss interventions in young women.

Struggling with overweight or obesity in early adulthood can have significant social implications for young women. Overweight or obese young women are less likely to report satisfaction with work or study, family relationships or social activities. They are also less likely to aspire to further education and more likely to have low perceived work ability [64, 65]. These may affect their vocational success and eventually, their socioeconomic status. The impact of obesity on career aspiration and satisfaction may be one of the causes for the observed relationship between obesity and socioeconomic status in the general population. In addition to jeopardising their own future, overweight and obese young women could also pass on their obesity-related problems to their offspring, not just through genetic predisposition, but also through physiological processes such as fetal programming and environmental processes such as modelling of lifestyle attitudes and patterns [66]. In this sense, addressing the issue of obesity in young women before they enter motherhood is a pivotal point in reversing the trends of obesity in future generations.

In summary, obesity and excess weight gain affects the metabolic, reproductive and mental health of young women. Further, it also increases the long term risk of chronic diseases.

The risk of obesity could also be passed on to their offspring, thus perpetuating the epidemic into future generations. There is an urgent need to promote healthy weight and prevent weight gain in young women.

Table 1.3 The short-term consequences of excess weight or weight gain in early adulthood: a summary of results in young women

Health domains	Consequences (Change, CI)	Notes
Metabolic [22, 25-28]	• Increase in LDL cholesterol (+0.17 mmol/L, 0.06-0.20) • Decrease in HDL-cholesterol (-0.09 mmol/L, -0.10- -0.08) • Increase in triglyceride (+1.13 mmol/L, 1.10-1.15) • Increase in fasting insulin (+1.23mU/L, 1.20-1.26) • Increase in blood pressure (+1.7 mmHg, 1.2-2.2) • Increased risk of metabolic syndrome (23%, 20-27%)	• Changes in LDL-C, HDL-C, triglycerides, fasting insulin, and blood pressure per 9.1kg (20lb) weight gain were adjusted for age, baseline weight, education, race, and cigarette smoking. • Metabolic syndrome risk per 4.54 kg (10 lb) weight gain was adjusted for age, race, sex, and physical activity.
Reproductive [30, 40, 57, 67]	• Increased risk of PCOS (RR 1.44, 1.10-1.89) • Reduced fecundity (OR 0.66, 0.49-0.89) • Increased risk of gestational diabetes (OR 2.95, 2.05-4.25) • Increased risk of pregnancy-related hypertensive disorders (OR 3.00, 2.40-3.74) • Increased risk of caesarean section (OR 2.02, 1.79-2.29) • Increased risk of neonates admission to intensive care (OR 1.25, 0.97-1.62)	• RR of PCOS stated were based on comparison between women with abdominal obesity and were overweight or obese at 31 years but were normal weight at adolescence, and women who were normal weight at 31 years. • OR for fecundity were based on obese primiparous women compared to normal weight women, adjusted for age, smoking, race, education, occupation and study center. • OR for gestational diabetes, hypertensive disorders of pregnancy, caesarean section, and neonates admission to intensive care were based on comparison between obese women and normal weight women, adjusted for maternal age, parity, educational status, smoking status, and ethnicity.
Psychological [62, 63, 68]	• Depression (OR 1.4, 1.06-3.68) • Lack of internal locus of control (OR 1.86, 1.24-2.78)	• OR for depression were based on comparison between women who were overweight or obese and normal weight women, based on depression cutoff score of 1.75, adjusted for father's social class, family type, smoking, use of alcohol and chronic somatic disease at 14 years • OR for internal locus of control were based on comparison between women with BMI $\geq$ 30 and normal weight women.
Social [64, 65]	• Low perceived work ability (χ^2=30.95) • Less satisfaction with work or studies (χ^2=37.5) • Less satisfaction with family relationships (χ^2=32.55) • Less satisfaction with social activities (χ^2=40.81) • Less likely to aspire for further education (χ^2=14.4)	• Perceived work ability was compared across BMI categories in women aged 31 years. • Satisfaction with work or studies, family relationships, social activities and aspiration for further education were compared across BMI categories in women aged 19 to 23 years.
General physical health [24]	• Back pain (OR 1.26, 1.08-1.48) • Sleeping difficulties (OR 1.35, 1.15-1.59) • Asthma (OR 1.30, 1.09-1.54) • Headaches (OR 1.47, 1.25-1.73) • More visits to medical practitioners (OR 1.28, 1.09-1.51)	• Comparison across BMI categories after adjusted for area of residence, age, education, smoking and exercise.

1.1.4 Why do young women gain weight?

Biological factors

Overweight and obesity in young women is associated with greater prevalence of reproductive disorders such as hyperandrogenemia or PCOS. Some evidence suggests that metabolic aberrations in these conditions may have perpetuated the obese state in the affected individuals. Altered satiety signalling is observed in women with PCOS [69, 70]. In addition, women with hirsutism, which is a physical sign of hyperandrogenemia, are also found to be at high risk of developing eating disorders including bulimia nervosa [71]. On the other hand, women with bulimia nervosa were also found to have increased levels of testosterone [72]. Treatment with antiandrogenic oral contraceptives reduces testosterone levels, hunger and binge-eating in women with bulimic eating disorder [73]. Metformin, an insulin sensitising agent which has been shown to inhibit androgen production in ovarian cells were also suggested to have a weight reduction effect [74, 75]. However, the effect of metformin on body weight in healthy young women has yet to be determined.

Aside from the hunger and satiety pathways, food intake is also regulated by the non homeostatic pathway, also known as the food reward pathway (Figure 1.3). Food reward may be mediated by neurotransmitters such as the endogenous opioid peptides, serotonin, and dopamine, which are also involved in the addiction of drugs of abuse [76-78]. This pathway may explain overeating behaviours which are inconsistent to the metabolic needs of the body. In human studies, food cravings are a subjective measure of the rewarding effect of a particular food. Food cravings reportedly occur in up to 97% of young women and 68% of young men [79]. Craved foods are usually higher in energy density and fat

content and lower in fiber compared to habitual diet [80]. Certain metabolic factors such as leptin have been shown to regulate food intake through both the homeostatic and non homeostatic pathways [81]. It is unclear if hyperandrogenemia, which affects the homeostatic pathway as described above, may also impact the food reward pathway in young women.

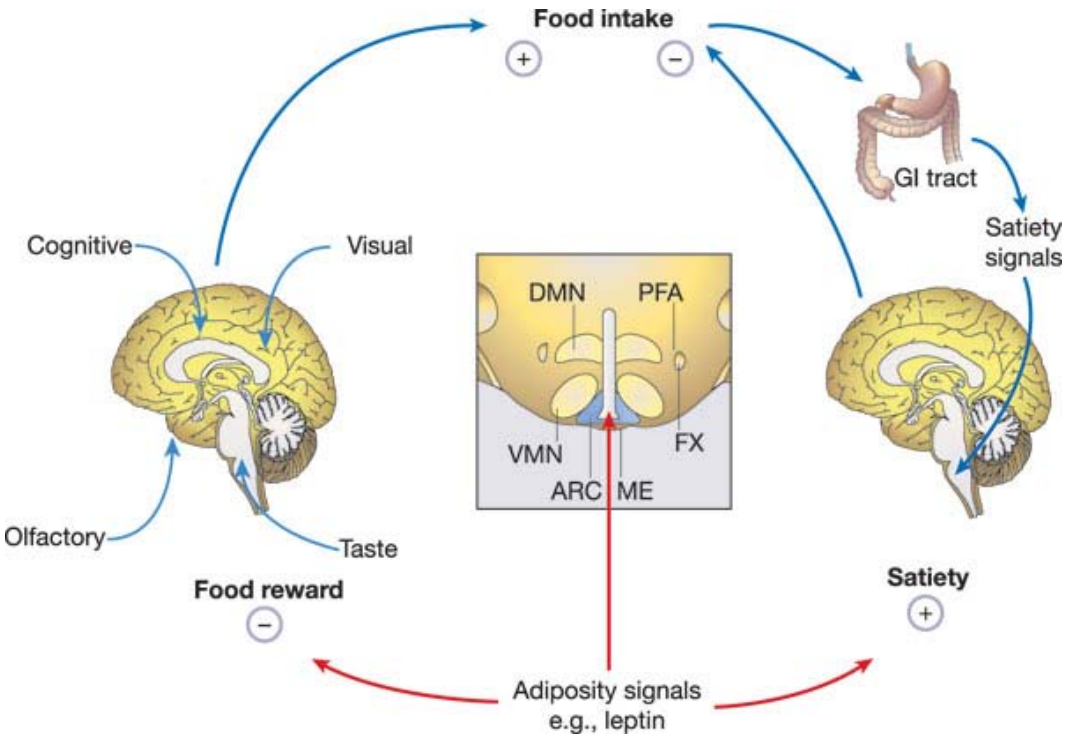


Figure 1.3 The effect of adiposity signals such as leptin on the homeostatic (ie satiety) and non homeostatic (ie food reward) pathways in the regulation of food intake. ARC, arcuate nucleus (highlighted in blue); DMN, dorsomedial nucleus; FX, fornix; ME, median eminence; PFA, perifornical area; VMN, ventromedial nucleus. (Taken from Morton et al, 2006, p290 [81]).

There is now strong evidence that genetic factors also play an important role in the etiology of obesity. The heritability of body mass index estimated from twin studies ranged from 50% to 90% [82, 83]. The effects of heredity on body mass index could be mediated through a number of factors in the regulation of body weight including eating behaviors. A twin study in Korea reported that the heritability estimates after correcting for sex and

gender were 0.31 +/- 0.036 for restraint, 0.25 +/- 0.098 for emotional eating, and 0.25 +/- 0.060 for external eating [83]. In this study, The Dutch Eating Behavior Questionnaire (DEBQ) was used to measure eating behaviour. In two other studies conducted in Sweden, UK and Finland which used the Three Factor Eating Questionnaire, heritability accounted for 26-63% of the variance in cognitive restraint, 9-60% in emotional eating, and 45-69% in uncontrolled eating [84, 85]. Aside from eating behaviours, meal patterns could also be explained by heredity. A study in the US by de Castro (1993) reported that 65% of the variance in energy intake, 44% in meal frequency and 65% in meal size were attributable to heredity [86]. Food preference, such as the liking and use-frequency of fatty foods were also found to be partly attributable to genetic factors, which accounted for 24-54% of the variance [84]. The impact of genetic factors on body mass index and the regulation of food intake may be stronger in adulthood than in childhood. While shared environment has been found to have a strong influence up to mid-childhood, this effect was no longer observed by adolescence [87]. Adult twin studies have generally shown that shared environment has little or no effect on body mass index, eating behaviours, or meal size and meal frequency when compared to genetic factors [83, 85, 86]. On the other hand, individual or non shared environmental factors continue to exert an important influence on BMI and eating behaviour in adulthood [82, 85, 88]. The strong influence of genetic factors on body weight regulation may explain the differences in body sizes among young women even when they were similarly exposed to lifestyle factors that increase the risk of obesity.

Behavioural factors

When asked about the reasons for their weight gain, more Australian women cited changes in physical activity and changes in the amount of food and drink consumed than for any other reasons [89]. This is supported by objective data obtained from research studies and national surveys. The last National Nutrition Survey in Australia conducted in 1995 found

that the proportion of purchased food and beverages peak in the age group of 19 to 24 years old among females [90]. Greater consumption of fast food and take-away foods is associated with weight gain in young women when adjusted for occupation, marital status, parity, baseline weight, or education [9, 91, 92]. National data in Australia has also shown that about half of all young women have inadequate fruit consumption while nearly 90% of them have inadequate vegetable consumption [60]. In Australia, young women (age 19 to 24) also had lower median intakes of most micronutrients compared to older women (age 44 to 65), including in folate and iron intakes [93]. The picture emerging from these data suggest that young women are having poor quality diets dominated by convenience food while lacking in foods from the main food groups. This dietary pattern is high in energy but low in nutrients. Dietary patterns which are high in refined foods and low in fruits and vegetables have been associated with weight gain in women [94]. On the other hand, higher intakes of fruits, vegetables and wholegrains are associated with greater weight loss in women, with a greater effect in obese women [95].

Alcohol

Excessive alcohol consumption is also a growing issue in young women. Australian young women who drink alcohol at levels associated with increased long term risk (15 standard drinks or more per week) and increased short term risk (5 standard drinks or more per occasion) peak in the age group of 18 to 24 years old, with 20% at long term risk and 45% at short term risk [96]. Women of all ages are also drinking more. The proportion of women drinking at excessive levels has nearly doubled from 1995 to 2004-2005 [60]. High alcohol consumption could contribute to excessive energy intake. In addition to the significant health and social risks, high alcohol intakes could also be one of the contributors to overweight and obesity in young women.

Physical activity

Low levels of physical activity could be another possible cause of weight gain in young women. About one-third of young women in Australia between the ages of 18 and 44 are physically inactive [60]. The CARDIA study, which involved young adults from 18 to 30 years old at baseline, found a significant decrease in self-reported physical activity among young women during the 7-years follow-up period [97]. Those in the study who increased their physical activity had an attenuated age-related weight gain, with a more pronounced effect among overweight and obese women [98]. Thus a decrease in physical activity may contribute to weight gain in young women, especially in overweight and obese young women.

Sedentary behaviours

Besides low levels of physical activity, high levels of sedentary behaviours could also lead to weight gain. Heavy television viewing (more than 4 hours per day) is associated with greater BMI in American young women [99]. Similarly, an Australian study found that those who watched television for more than 4 hours per day were four times more likely to be overweight [100]. About 10% of young adults in Australia aged 18 to 44 years old watch at least 4 hours of television in a day [100]. Lower levels of television viewing also increase the risks of obesity. About 1 to 2.5 hour of television viewing per day could increase the risk of overweight to nearly 2 fold [100]. This is possibly due to the compensatory decrease in incidental physical activities during television viewing. It is probably for the same reason that young women who spent more time sitting are also more likely to gain weight [9]. According to the CARDIA study, the average television viewing time for American young women aged 23 to 29 years old is 2hr/day for white women and 3 hr/day for black women [99], which is sufficient to increase their risk of becoming

overweight. Interestingly, high levels of physical activity do not eliminate the obesogenic effects of television viewing. The relationship between television viewing time and obesity existed even among those who were physically active [100].

Sleep duration

One of the lifestyle changes that occur during young adulthood is the decrease in sleep duration. The Zurich Cohort Study started in 1978 with 4547 men and women aged 19 found that sleep duration decreases with age [101]. A significant association between short sleep duration and obesity is found in younger adults (at age 27, 29, and 34) but not in older adults (age 40) [101]. This remains significant after adjusted for sex, education level, physical activity level, smoking, binge eating, childhood depression and family history of obesity [101]. Dietary intake was not adjusted for in the analyses, and thus could account for the relationship between sleep duration and obesity. Recent opinion on this topic suggests that short sleep duration could lead to increases in appetite, alterations in glucose metabolism and decreases in energy expenditure [102], all of which are potential mechanisms linking short sleep duration to obesity. Further research should be conducted to explore this relationship in young adults.

All the causes discussed up to this point suggest that weight gain in young women is likely to be due to a range of ‘modifiable’ health behaviours such as dietary intake, physical activity, alcohol consumption, sedentary behaviours and sleep deprivation (Table 1.4). However, decades of research in lifestyle modification alongside with the ever growing problem of obesity suggests that these factors are more difficult to modify than it seems. To change the health behaviour of young women, it may be helpful to understand the underlying factors driving these behaviours.

Table 1.4 Behavioural factors associated with weight gain in young women

Factors	
Diet [60, 94, 95]	• About half of all young Australian women have inadequate fruit consumption while nearly 90% of them have inadequate vegetable consumption • High intakes of refined foods and low intakes in fruits and vegetables have been associated with weight gain in women
Alcohol intake [60, 96]	• 20% of Australian young women drink alcohol at levels associated with increased long term risk (15 standard drinks or more per week) and 45% at increased short term risk (5 standard drinks or more per occasion) • The proportion of Australian women drinking at excessive levels has nearly doubled from 1995 to 2004-2005
Physical activity [60, 97, 98]	• About one-third of young women in Australia between the ages of 18 and 44 are physically inactive [60] • Physical activity decreases in young adulthood (-58$\pm$204 Exercise Unit in US black women and -102$\pm$264 Exercise Unit in US white women)
Sedentary activity [99, 100]	• Heavy television viewing (more than 4 hours per day) is associated with greater BMI (OR 1.5, 1.1-2.2 in US black women; OR 2.3, 1.4-3.9 in US white women, OR 4.14, 2.0-8.4 in Australian adults) • 10% of young adults in Australia aged 18 to 44 years old watch at least 4 hours of television in a day
Sleep duration [101]	• Sleep duration decreases with age • Short sleep duration among young adults predicted obesity (OR 8.2, 1.9-36.3)

Psychosocial factors and life events

Young adulthood is a life-stage characterised by substantial change. Many of these changes occur as part of the process of taking up adult responsibilities, such as being financially independent, caring for significant others, nurturing the next generation, or finding one's niche in society. This section will explore the effect of these events on the body weight and lifestyles of young women.

Marriage

Marriage predicts weight gain in women but not in men [103]. The NHANES cohort in the US found that those who married had a 50% increase in risk for major weight gain (ie more than 13 kg weight gain during 10 years of follow-up) [104]. Similar trends were noted in young women in other countries such as Finland and Australia [9, 105]. This is probably a consequence of lifestyle changes after marriage in young women. Being married was associated with decreased physical activity in young women while living with a partner has been shown to increase energy intake [106, 107]. A study on cohabitation found that couples living together had greater motivation to prepare meals and were more likely to have alcohol during meals [107]. There were also feelings of shared guilt over temptations and shared motivation over dietary restriction which may affect eating patterns [107]. Together, evidence suggests that marriage is a predictor of weight gain in young women.

Pregnancy and child-rearing

Women who have had children were more likely to have gained excess weight [9, 108]. Pregnancy could also change body shape by increasing waist-to-hip ratio independent of weight gain at 12 months postpartum [108]. On average women retain 0.5 to 3kg from

pregnancy, although this can vary greatly between individuals [109]. Gestational weight gain has increased in the last four decades across all BMI categories [110]. While some women are able to return to their pre-pregnancy weight at 6-12 months postpartum, the majority (~73%) remained at a higher BMI [109]. Normal weight women who became overweight after pregnancy had slightly higher pre-pregnancy BMI, greater weight gain during pregnancy, and less weight loss after pregnancy compared to those who returned to their normal weight after pregnancy [111]. Those who did not return to normal weight at 1 year after delivery had a steeper weight trajectory over the following 14 years, so that they ended up with greater weight gain in the long term compared to their counterparts [111]. Women who retained more weight after pregnancy tended to have higher energy intake, more frequent snacking, less regular lunch and less physical activity during or after pregnancy [112]. These studies suggest that pregnancy is a vulnerable period during which some young women could experience significant permanent weight gain. In some cases, pregnancy could trigger a new pattern of body weight characterised by greater long term weight gain.

As having children involves more than the biological process of pregnancy and childbirth, the child-rearing responsibilities that follow could also affect the lifestyles of young women. Women with children were more than twice as likely to be physically inactive compared to those who did not have any children after controlling for age, BMI and baseline physical activity level [106]. Women with children also perceived leisure time physical activity, incidental physical activity and transport physical activity as less feasible, but perceived work or domestic physical activity as more feasible [113]. Anecdotally, certain tasks associated with childcare such as ‘running after the kids the whole day’ seem to imply a high level of domestic physical activity. However, its contribution to energy expenditure has not been investigated. Caring for children may also

affect dietary intake of young women but the effect of childcare on energy intake has also not been investigated. A greater understanding on the impact of child-rearing on young women's lifestyle pattern may help to determine appropriate strategies to improve the lifestyle of young women with children.

Employment

Employment could be yet another risk factor for weight gain in young women. Young women who were still studying were less likely to gain weight [9]. This too could be due to changes in lifestyle associated with beginning employment. Starting paid work is associated with increased risk of physical inactivity while returning to study is associated with decreased risk of inactivity in young women [106]. Employment may also change dietary habits of young women. One study suggested that working women expressed greater dislike for food shopping, greater time concerns with cooking, and had less tendency to value family's health and preference in food preparation compared to housewives [114]. Less time availability coupled with greater financial ability provided the option for women to pay for services that were traditionally women's responsibilities, such as child-caring, cleaning and cooking [115]. This suggests that working women may purchase meals more frequently compared to housewives but this has not been investigated. Further research is required to explore the effect of employment on the health of young women.

Social environment

Previous studies in twins have found that aside from genetic factors, individual or non shared environmental factors were important determinants of BMI and eating behaviour in adults [83, 85, 86]. One of these factors could be social influences outside the parental family. Social influence seems to be an important determinant of young women's health

behaviour, to a greater extent than it is for young men. Young women were more likely to perceive social situations as barriers to healthy eating or being physically active [116]. Women with children perceived the lack of support from partner, children or friends as barriers to physical activity and healthy eating [117]. Dietary habits such as fruits, vegetables and wholegrain intakes were also predicted by perceived social norms (eg how important healthy eating was to their friends) and subjective norm (eg whether their friends think they should eat healthier) [118]. The social influences on young women's health behaviour could ultimately affect her body weight. Support or sabotage by friends and family predicted the success of weight maintenance in young women [119]. A recent study also found that social relationships could be responsible for the spread of obesity between friends or family members [120]. In the study, Christakis et al (2006) reported that a person's chance of becoming obese increased by 57% if she had an obese friend or by 37% if she had an obese spouse [120]. All of these suggest that the social environment of young women could be an important determinant of their body weight.

Perceived social roles

An interesting point to note is that even though young men also go through these life events (excluding pregnancy and childbirth), their body weight was somewhat less affected by these events [103]. Perhaps the reason young women gained weight at these time points were not just due to a change in the physical circumstance, which equally affects young men, but also due to changes in social circumstances. At each of these life events mentioned above, young women gained a new social role, such as mother, partner, or family caregiver, in addition to their existing social roles as employee or student, daughter, and friend. Being involved in more than one of these social roles was associated with worse overall health in young women, while the reverse is true in older women [121]. It is possible that pressing responsibilities accompanying these roles compete for priorities in

young women's lives such that health was not a main focus. This may explain why nutrition and physical education alone, even if delivered with behavioural therapy, may have short-lived effects in this group.

As social role is a construct of ideologies and beliefs held by the individual and her society, some of these beliefs may have generated additional challenges related to these roles. For example, some young women with children felt guilty for taking time out for themselves and leaving their children in other's care because to them this constitutes failure in fulfilling their role as a 'good mother'[122]. On the other hand, those who believed that being good mother does not involve only caring for their children but also include being a good role model in health for their children found that motherhood *enabled* them to focus on their own health [122]. In the same way, certain beliefs and ideologies defining the roles of a 'good wife', 'good employee', 'good mother' and 'good friend' may affect the choices of young women either positively or negatively. Perhaps some of these ideologies need to be challenged. For example, despite a greater proportion of women engaged in paid occupations, gender inequalities still exist in childcare and household responsibilities within the household [122]. Inequalities also exist in the entitlement for personal leisure time within the household, whereby men were more likely to prioritise personal leisure time over household chores while the opposite is probably true for women [122]. This may explain why women in general are more time-pressured than men [123]. With the changing roles of women in our society in recent decades, re-definition of these social roles may be necessary to improve the lifestyles of young women.

Time pressure and stress

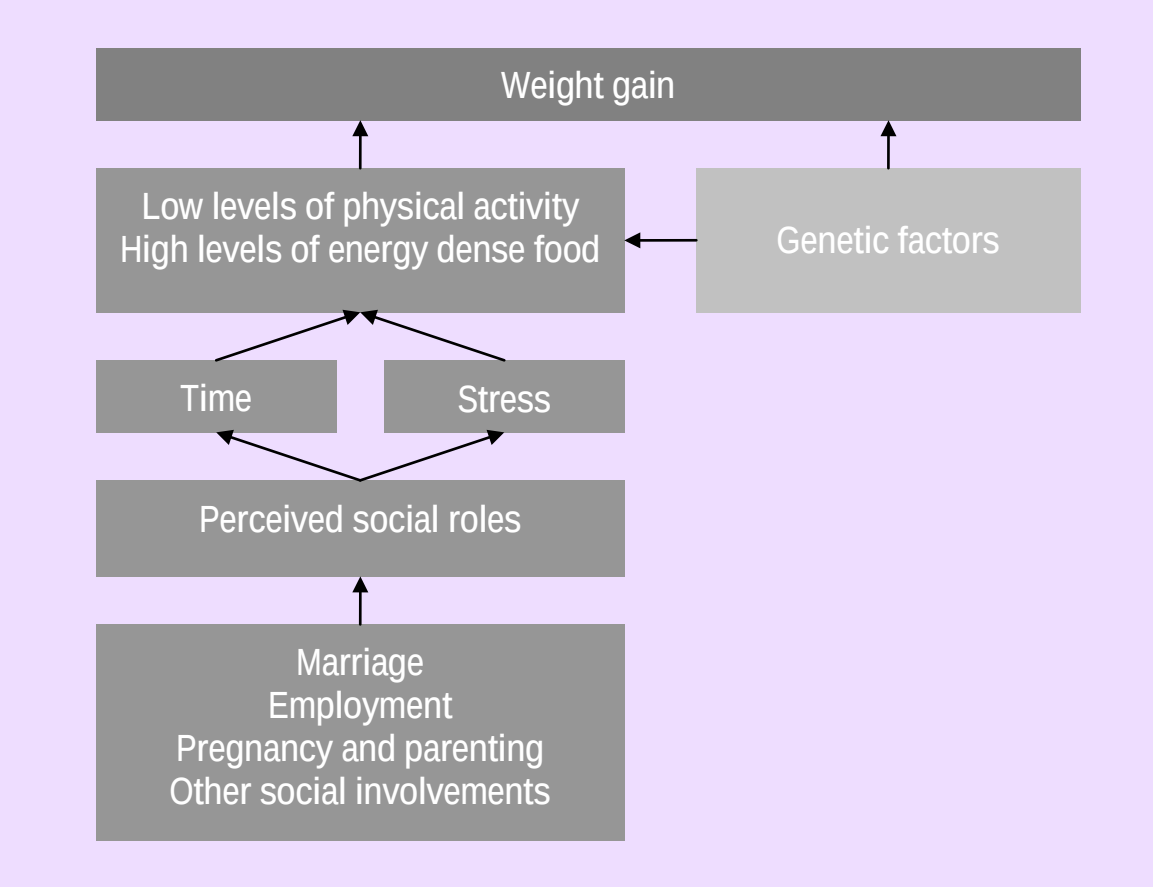
Social roles may affect young women's lifestyle choices through their time availability. Fulfilment of these roles places a high demand on young women's time. 'Time poverty'

may be an important cause of poor lifestyle habits and poor health in this group. Young women cited lack of time and lack of motivation as the most important barriers to physical activity and healthy eating [117]. Lack of motivation for healthy eating and exercise could be a reflection of lower priority for these agenda compared to other life responsibilities. Data from the Australian Bureau of Statistics revealed that the percentage of individuals who were chronically time pressured increases with age (measured from 15 years old) and peak in age 35 to 39 years old before decreasing. More women than men felt that they were chronically time pressured [123]. In support of our discussion on social roles, marital status and the number of children were also positively associated with time pressure [123].

Time pressure may also contribute to weight gain by increasing stress in young women's lives. Stress has been associated with greater preference for foods high in fat and sugar [124-126]. Women are more likely to eat in response to mood compared to men [63]. One study in the US on low-income overweight and obese mothers (age 18 to 35 years) found that participants reported taking large portions of energy-dense comfort food such as chocolate and ice-cream to cope with daily stress [127]. Stress-driven eating is significantly associated with obesity in women (OR 3.24 95%CI 2.19-4.79) but not in men [126].

In summary, lifestyle behaviours are shaped by powerful influences in young women's lives such as the perceived obligations associated with being a wife, mother, daughter, colleague, or friend. These responsibilities could become barriers to healthy lifestyles in young women through its time and emotional costs. Although perceived attractiveness and weight concerns are important predictors of personal happiness and self-esteem in women [128, 129], it appeared that these personal motivators were not sufficient to overcome barriers to healthy lifestyles in some young women.

Figure 1.4 Causes of weight gain in young women



1.2 Young Women and Weight loss

1.2.1 Prevalence of weight loss attempts

At first glance, targeting young women for weight loss may seem unnecessary as it is generally assumed that young women were probably one of the most motivated demographic groups for weight loss. On average, 30-50% of young women across all BMI groups have attempted to lose weight [130]. The prevalence of young women who attempted weight loss increases with BMI [130]. A study in female college students (age 18 to 24 years) in the United States reported that as many as 91% of overweight young women and 86% of obese young women tried to lose weight [131]. Primary sources of pressure to lose weight were self (54%), followed by media (37%) and friends (32%) [131]. The most common methods of losing weight were restricting the amount of food eaten, eating low fat versions of food and drinks, and exercising [131]. Young women were also willing to spend money on losing weight. In 2001, Australian young women spent $414 million on weight control which included commercial weight loss programs, gym memberships, or exercise equipment [132].

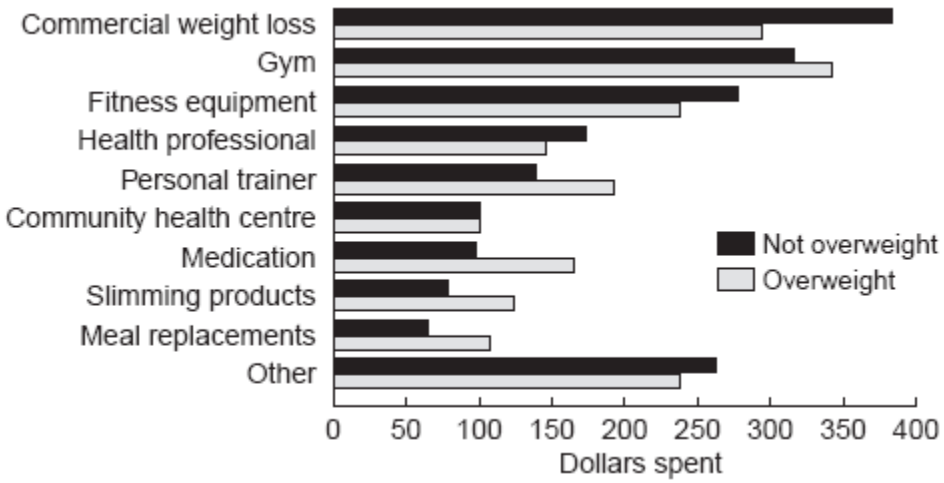


Figure 1.5 Mean expenditure on weight management strategies by young women (age 18 to 32, n=445) in Australia. (Taken from Ball et al, 2003, p586 [132])

Weight loss attempts do not often equate to weight loss success. Women were more than twice as likely (OR 2.4, CI 2.2-2.7) than men to attempt weight loss, but men were 40% more likely to succeed in these attempts (OR 1.4, CI 1.0-2.1) [133]. In a large clinic-based weight loss program involving meal replacements and group sessions (n=866), females were found to be 30% more likely to drop out of the study, while those who were under the age of 40 were 66% more likely to drop out of the study [134], making age and gender the most important predictors of attrition. Findings from other large-scale weight loss studies similarly found that young, female participants tended to drop out of weight loss interventions [135, 136].

The reasons for young women's inability to lose weight despite strong motivation are not well understood. Biological factors such as genetic predisposition to obesity, as previously discussed in Section 1.1.4, may undermine their efforts in weight loss. Altered appetite regulation including impaired ghrelin and cholecystokinin secretion has also been reported in women with PCOS [69, 137], suggesting that metabolic aberrations may contribute to obesity in some women. Stress could also contribute to obesity through chronic stimulation of the hypothalamic-pituitary-adrenal (HPA) axis by excess cortisol [138]. Both stress and highly palatable foods stimulate the brain reward systems such as the dopamine and opioid systems [139]. Repeated stimulation of the reward pathway could promote dependency. Stress have been shown to be involved in the acquisition and maintenance of drug addiction [138, 139]. Similarly, higher stress levels have been shown to be associated with greater intake of high fat foods [140]. The positive association between stress and food intake was especially prominent in individuals with high cortisol reactivity [141], suggesting an epigenetic effect on obesity. In addition to these biological factors, other factors relating specifically to young women including the psycho-social and behavioural

changes resulting from marriage, childbirth and commencing paid work, as discussed in Section 1.1.4, may also explain the preferential drop out among young women when compared to older men and women.

1.2.2 Lifestyle interventions and weight loss in young women

A small number of studies have looked at the effect of lifestyle modification on young women's health, mainly in young women with PCOS. One study investigated a weight gain prevention program in healthy young women with normal or excess weight in Sweden [142]. To our knowledge, there has not been any weight loss study focussing on healthy overweight or obese women. This section will review the efficacy of various components of lifestyle modification on body weight and metabolic health. Due to limited studies in healthy overweight or obese young women, trials involving women with PCOS or mixed population will also be discussed.

Dietary interventions for weight loss

In the general population, lifestyle intervention typically encourages participants to reduce their energy intake by 500-1000 kcal/day to achieve a gradual weight loss of 0.5kg/week [143]. Traditionally, energy restriction is achieved by having a low-fat, high carbohydrate diet. However, increasingly studies suggest that diets with reduced glycemic loads such as high protein diets, low glycemic index diets or even very low carbohydrate diets were associated with greater metabolic benefit compared to the conventional low-fat high (mostly refined) carbohydrate diet [144-148]. In particular, diets with higher protein recommendations were beneficial in preserving muscle mass during weight loss [149]. *Ad libitum* studies reported a spontaneously lower energy intake with higher protein diet

compared to high carbohydrate diet [150, 151] possibly due to the satiating properties of protein [152].

In young women with PCOS, energy restricted high carbohydrate or high protein diets were found to be equally effective in producing weight loss of around 8kg in 16 weeks [153]. Other energy restricted dietary strategies such as very low calorie diet (4200KJ per day), very low carbohydrate diet (<20g carbohydrate per day) and meal replacements for 16 to 24 weeks have also been shown to be effective in weight loss in young women (Table 1.5) [154-156]. Weight loss from lifestyle interventions improved metabolic parameters in young women with PCOS, such as fasting insulin, LDL cholesterol and triglyceride levels [153-155]. Reproductive outcomes such as ovulation rates, menstrual cyclicity, testosterone and sex-hormone binding globulin levels, hirsutism, and pregnancy rates were also improved following weight loss through lifestyle modification [153, 157, 158]. These findings suggest that energy restriction is efficacious in producing weight loss and its associated benefits in metabolic and reproductive health but insufficient studies were conducted in young women to determine if certain dietary strategies were associated with greater metabolic or reproductive benefit beyond weight loss.

Table 1.5 Dietary trials conducted in young women (mean age: 18 to 40 years)

Study	n	Duration	Intervention	Weight loss	Metabolic	Reproductive
Kiddy et al (1989) [159]	5	4 wks	**Diet (non RCT)** 1386 KJ/day for 4 wks 42.7%C 33%P 29%F	-7.1kg	Decreased fasting insulin	Increased SHBG, decreased free T
Pasquali et al (1989) [160]	20	6-12mo	**Diet (non RCT)** 4200-6300 KJ/day 50%C 20%P 30%F	85.9→76.1kg	Decreased fasting insulin	Improved ovulation and pregnancy, decreased T, progesterone and LH
Kiddy et al (1992) [157]	24	7 mo	**Diet (non RCT)** low fat low cal BMI>30: 1386 KJ/day for 4 wks, then 4200 KJ/day low fat for 6 months BMI<30: 4200 KJ/day for 7 months	91.9→85kg	Decreased fasting insulin	Decreased free T Among those who lost >5% weight: increase SHBG, decreased hirsutism, improved ovulation and menstrual cyclicity.
Holte et al (1995) [161]	13	14.9 mo (mean)	**Diet (non RCT)** 5000 KJ/day—continued until no further wt loss, and wt stable for 1 mo	-14%	Decreased fasting insulin	7/13 had improved menstrual cyclicity. Decreased T and FAI, increased SHBG
Andersen et al (1995) [154]	9	24 wk	**Diet (non RCT)** 4 wks 1800 KJ/day; 25g C 51g P 5g F /100g 20wks 4200-6300 KJ/day 59%C 22%P 20%F **Exercise:** Advised to take walks	-9% fat mass	Decreased fasting insulin, PAI-1, fibrinolysis	2 had normal menstrual cyclicity and became pregnant
Jakubowicz and Nestler (1997) [162]	12	8 wks	**Diet (non RCT)** 4200-5000 KJ/day, 43% C 23%P 35%F	32→29.6 kg/m^2	Decreased fasting insulin	Decreased T, increased SHBG, decreased basal and stimulated 17alpha hydroxyprogesterone
Van Dam et al (2002) [163]	15	7 days	**Diet (non RCT)** 4200 KJ/day replacement drinks (Modifast and Nutridrink) Modifast: 42%C 43%P 15%F Nutridrink: 48%C 13%P 39%F	115→112kg	Decreased fasting insulin, fasting blood glucose	Decreased T
Van Dam et al (2004) [164]	15	7days, then followup for 29 wks	**Diet (non RCT)** 4200 KJ/day replacement drinks (Modifast and Nutridrink) Modifast: 42%C 43%P 15%F Nutridrink: 48%C 13%P 39%F	37.5→33.4 kg/m^2 in responders and 41.9→37.2 kg/m^2 in non responders	Decreased fasting blood glucose in responders	Increased SHBG. Decreased FAI and FSH in responders

Study	n	Duration	Intervention	Weight loss	Metabolic	Reproductive
Moran et al (2003) [153]	28	16 wk	**Diet (RCT)** 6000 KJ/day HP 40%C 30% P 30%F LP 55%C 15% P 30%F	-7.7 kg	Decreased fasting insulin, LDL cholesterol, triglyceride.	44% had improvement in ovulation
Crosignani et al (2003) [165]	33	6 mo	**Diet (non RCT)** 5000 KJ/day 55%C 20%P 25%F **Exercise**: Advised to do some swimming or aerobics at least 2/wk	76% lost >5%wt, 33% lost >10% wt .	Not reported	Among those who lost >5% weight: 7% had resumed normal menstrual cyclicity, 10 were pregnant. 8 live births.
Moran et al (2004) [69]	10	16 wk	**Diet (RCT)** 6000 KJ each HP 40%C 30% P 30%F LP 55%C 15% P 30%F	94.8→87.7	Not reported	Not reported
Stamets et al (2004) [166]	26	1 mo	**Diet (RCT)** 4200KJ deficit per day HP 40%C 30%P 30%F LP 55%C 15%P 30%F	-4kg	Decreased fasting insulin	Decreased T
Mavropoulos et al (2005) [155]	11	24 wk	**Diet (non RCT)** Very low carbohydrate diet (< 20g CHO/d) **Exercise:** encouraged to exercise 3/wk	-12.1%	Decreased fasting insulin	Decreased free T and LH:FSH ratio
Tolino et al (2005) [158]	14 4	7 mo	**Diet (non RCT)** BMI>30: 1400 KJ for 4 wks, then 1000cal low fat for 6 months BMI<30: 4200 KJ for 7 months	92→86 kg	Decreased fasting insulin	Among those who lost >5% weight: Decreased free T, increase SHBG, decreased hirsutism, 25% conceived. Improved ovulation and menstrual cyclicity
Bruner et al (2006) [167]	12	12 weeks	**Diet (RCT)** Canadian Food Guide to Healthy Eating **Exercise:** A combination of endurance and resistance activities 3 d/week	NS	Decreased fasting insulin	Not significant
Moran et al (2006) [156]	23	8 wk + 6 mo	**Diet (RCT)** <u>8 weeks (5000KJ/day)</u> 2 meal replacements plus low-fat dinner and snacks for 8 weeks <u>6 month</u> fat counting (<50g/day) or carbohydrate counting (<120g/day) **Exercise**: 8000 steps/day	-4.7kg	Decreased fasting insulin and blood glucose, decreased systolic blood pressure	Decreased T. 57% had improved menstrual cyclicity

Physical activity interventions for weight loss

It is commonly assumed that physical activity assists in weight management by contributing to the increase in energy expenditure. The International Association for the Study of Obesity consensus statement stated that 60 to 90 minutes of moderate intensity activity per day is required for the secondary prevention of obesity for the general population [168]. This statement was based mainly on prospective studies conducted at the population level [168]. The National Weight Control Registry similarly found an important role for physical activity on long term weight loss maintenance [169]. Although these observational studies support the role of physical activity in weight management, their results have not been consistently reproduced in randomised controlled trials (RCT). In a recent review on physical activity and weight management, only 2 out of 17 RCT reported a significant benefit of adding physical activity to dietary intervention for weight loss [170]. Physical activities ranging from 60 to 240 minutes per week resulted in a 1.5kg weight loss advantage compared to diet-only interventions, but this do not always reach statistical significance [170]. Similarly disappointing results were seen in weight maintenance. Although physical activity has been suggested to play an important role in long term weight maintenance, only 3 out of 8 RCT confirmed the additional benefit of physical activity to diet-only interventions in weight maintenance [170]. Despite its limited effect on weight loss, evidence suggest that physical activity independent of weight loss could reduce abdominal fat and improve insulin sensitivity in overweight and obese individuals with cardiometabolic risks [171].

A prospective cohort study in older women found that those who had more than 5 hours of vigorous activity per week gained 0.5 kg less than their inactive peers in 6 years, suggesting a small effect for the effort involved [172]. Intervention studies in mixed population similarly reported negligible effects of exercise alone in weight loss in young

women. An exercise-only intervention in overweight young women consisting of aerobic exercise (mainly treadmill, target intensity of 55%-70% of maximum oxygen capacity, 45 minutes per session, 5 sessions per week for 16 months) did not result in significant weight or fat loss [173]. In the absence of weight or fat loss, aerobic exercise produced improvement in insulin sensitivity in normal weight young women but not in overweight young women [174, 175]. In overweight and obese young women with PCOS, exercise decreased waist-hip-ratio, body mass index and homocysteine levels [176, 177]. It is unclear if the positive effect of exercise on body weight could be related to hyperandrogenemia in PCOS women, as physical activity was also found to be beneficial in producing weight loss in men [173, 178]. In a recent study in women with PCOS, the addition of exercise training to dietary intervention did not result in greater weight loss, but it caused greater decreases in fat mass and smaller decreases in lean mass compared to the diet-only intervention [179]. Similar benefits in body composition were also seen in women without PCOS [180]. The benefits of exercise on body composition suggest that exercise is an important component of weight management in young women.

Table 1.6 ***Exercise trials in young women***

Study	n	Duration	Intervention	Weight and body composition	Metabolic effects
Donnelly et al (2003) [173]	33F	16 mo	**Exercise (RCT)** 5 sessions/week, up to 45 mins at 55-60% maximum oxygen capacity Control: maintain usual lifestyle	No significant change in BMI and fat mass, compared to significant increase in BMI and fat mass in control.	Not reported
Potteiger et al (2003) [174]	20F	16 mo	**Exercise (RCT)** 3-5 sessions/week, 20-45 mins, 60-75% of heart rate reserve Control: no intervention	No significant change in BMI and fat mass, compared to significant increase in BMI and fat mass in control.	Lower fasting and 2-hour glucose compared to control at certain time points, but no significant change from baseline.
Poehlman et al (2000) [175]	51	6 mo	**Exercise (RCT)** Endurance training: 3 sessions/week, up to 40 mins, 90% HR max. Resistance training: 3 days/week. Control: not mentioned	Weight and BMI increased with resistance training. No significant change in fat mass in all groups.	Improved insulin sensitivity in endurance and resistance exercise groups.
Vigorito et al (2007) [176]	90	3 mo	**Exercise (RCT)** 3 sessions/week, 30 mins at 60-70% maximal oxygen consumption Control: no intervention	Significant reduction in BMI	Significant improvement in insulin sensitivity
Randeva et al (2002) [177]	21	6 mo	**Exercise (non RCT)** Brisk walking for 20-60 mins at least 3 times a week.	No significant change in BMI	Significant improvement in homocysteine

F=female, trial included both males and females

Comprehensive lifestyle programs for weight loss

Expert panels such as the National Health Institutes recommended a combination of diet, exercise and behavioural therapy for long term obesity treatment in the general population [181]. Self-monitoring, which is an important aspect of behavioural modification, was found to be an important correlate of long term weight maintenance in the US National Weight Control Registry [169]. Findings from the Registry reported that those who frequently monitored their food intake lost significantly more weight than those who monitor their intake less frequently (18 kg vs 5 kg) [169]. Self-monitoring of body weight by frequent weighing was also associated with better weight maintenance [182]. In support

of this observational evidence, intervention studies found that the addition of behavioural therapy which included self-monitoring and other self-regulatory aspects improved the efficacy of diet and exercise interventions on weight loss [183-186].

Very few combined interventions (ie including diet, exercise and behavioural therapy) were conducted in young women. The Health Hunters program from Sweden is the only weight management lifestyle program developed specifically for this group [142]. This one-year program was developed to prevent weight gain in normal and overweight young women between the ages of 18 to 28 years with at least one obese parent. The program provided information and self-help materials in three main areas: diet, physical activity and weight control. All participants in the intervention group received some core materials from all three areas, but they could choose when and which area they wish to focus on at any time. The program consisted of one face-to-face visit at baseline followed by regular contact through telephone, email, occasional group sessions and visits with dietitians. Thirty out of the 40 young women completed the program. Intention-to-treat analysis found that the intervention group lost a modest 1.9 kg while control group gained 2.6 kg ($P<0.05$). Completers' analysis found that the intervention group had significantly greater improvement in BMI, waist circumference and waist-hip-ratio compared to the control group. However, the small magnitude of weight reduction achieved (<5%) may be of limited clinical significance. Further research on more effective strategies is needed to induce and maintain clinically significant weight loss in overweight and obese young women.

The Fertility Fitness program in South Australia was a lifestyle program developed for obese infertile women with the aim of improving reproductive health. Most of their participants were young women with an average age of around 30 years old [187, 188].

The program consisted of 2-hour sessions per week for 24 weeks. Each session consisted of an hour of exercise led by a coach, followed by an hour information session led by various health professionals such as psychiatrist, dietitian, and gynaecologist. The program resulted in a mean weight loss of 6.2kg [187]. The young women had a decrease in insulin and testosterone levels as well as improvement in psychological measures such as self-esteem, anxiety and depression [187, 189]. Those who completed the program also had greater rates of spontaneous ovulation, pregnancy, and live births [188]. Despite these successes, the program is no longer running due to lack of interest from young women seeking fertility treatment through lifestyle modification. Other treatments such as assisted reproductive techniques were preferred, probably due to lower time commitment.

Hoeger et al (2004) conducted a pilot trial in young women with PCOS using a study design adapted from the Diabetes Prevention Trial. Subjects randomised to the lifestyle plus placebo arm participated in a combined lifestyle modification program [190]. This included energy restriction of 500-1000 calorie deficit per day, individualised exercise program of 150 minutes per week and behavioural therapy. The program consisted of 24 weeks weight loss phase followed by 24 weeks weight maintenance phase. Group meetings and progress monitoring took place regularly throughout the entire study period. Six out of the 11 young women randomised to the lifestyle plus placebo arm completed the program. Those who completed the program lost 6.8 kg by the end of the program. Changes in androgen levels, insulin measures, and ovulation did not reach statistical significance, probably owing to the small sample size.

1.2.3 Quantitative or qualitative lifestyle advice

While evidence suggests that a combination of diet, physical activity, and behavioural support is important for long term weight management, the most effective way of delivering the advice has not been extensively researched. Observational data suggests that structure such as having regular meal patterns may assist in weight management [182, 191]. Intervention studies similarly support the role of structure in weight management, suggesting that it may be accountable for the success of some weight loss strategies including meal replacements [192, 193]. However, there is some evidence suggesting that having a rigid set of rules on lifestyle behaviours could be counterproductive [194-198]. Energy restriction has been linked to adverse effects on cognitive function including slower reaction time, poorer immediate recall of words and increased distractibility [199]. It may also contribute to weight cycling as dietary restraint predicts weight gain in women [198]. Some also suggest that food restriction may increase food cravings and result in overeating [195-197]. The problems associated with the structured, quantitative approach led to the rising interest in the 'non-dieting' approaches in obesity management. The 'non-dieting' approaches aimed at producing lifestyle changes through qualitative lifestyle advice. By shifting its focus away from energy restriction and weight loss, 'non-dieting' approaches often result in minimal weight changes [200, 201]. Despite this, studies involving older individuals reported that the qualitative lifestyle advice provided through the 'non-dieting' approaches resulted in similar metabolic improvements (ie in fasting lipids and blood pressure) to the conventional approach involving quantitative advice on energy restriction and physical activity [200, 201]. Moreover, the 'non-dieting' approaches may result in greater psychological benefits compared to the conventional quantitative approach [200, 201]. The effects of qualitative or quantitative lifestyle advice have not been compared in young women. Considering the impact of excess weight on the psychological health of young women [62, 63, 68], the optimal weight management

strategies should not only improve body weight and metabolic risks, but also the psychological well-being of these young women.

1.2.4 Internet as a medium to provide long term weight management support

It was estimated that about 20% of overweight or obese individuals in the general population are successful in maintaining at least 10% weight loss for at least a year [169, 182]. The prevalence of successful weight loss maintenance in young adults is not known. Considering the higher risk of weight gain in young women, successful long term weight management could be rarer this group. It has been noted that the effect of weight loss intervention diminishes after the cessation of treatment, suggesting that long term intervention is required for weight maintenance [202]. However, maintaining frequent contact for long periods of time can be costly and problematic. Recent studies suggest that the internet is an effective and feasible vehicle to provide long term support in weight management [183, 185, 203-205]. The number of Australians accessing the internet has increased dramatically in recent years, with young adults being the greatest user [206]. A national census indicated that 84% of Australian young adults aged 18 to 34 years accessed the internet, with no notable difference between sexes [207]. During this period, numerous commercial self-directed online weight management programs have become available, such as Weight Watchers, Jenny Craig, eDiets.com and many others. Despite the apparent popularity of these programs, the effectiveness of this approach in young women has not been investigated. Poorer compliance to lifestyle advice may affect the effectiveness of this approach in young women [208].

1.2.5 Metformin and weight loss in young women

Metformin is an insulin-sensitising agent traditionally prescribed for patients with type 2 diabetes. It is also commonly prescribed for young women with PCOS [209]. Metformin increases insulin sensitivity in the liver thus decreasing hepatic glucose output [210]. Common side effects include gastrointestinal distress, reduced absorption of dietary vitamin B12 and folic acid, and on rare occasions, lactic acidosis in patients with impaired renal function [211]. Gastrointestinal symptoms occur in 50% of treated patients but usually subside as treatment progresses [212]. Metformin has also been found to improve fasting insulin levels [213-216], fasting glucose levels [213, 214, 217-219], total cholesterol levels [214, 215, 219], LDL-cholesterol levels [214, 220, 221], triglyceride levels [219], HDL cholesterol levels [219, 220, 222], systolic blood pressure and diastolic blood pressure [213, 223]. In addition, it has also been demonstrated to improve menstrual cyclicity, ovulation rate, conception rate, and pregnancy outcome in overweight or obese women with reproductive disorders [46, 209, 214, 216, 224-227]. Considering the pleiotropic effects of metformin in improving metabolic and reproductive symptoms commonly associated with excess weight in young women, metformin may be an ideal candidate as a weight loss drug if proven to have significant weight loss effect in this group.

Mechanism in insulin sensitising

Metformin inhibits endogenous glucose production mainly by decreasing gluconeogenesis [210] and glycogenolysis [228]. This is achieved through a decrease in the activity of gluconeogenic enzymes such as glucose-6-phosphatase and fructose 1,6 bisphosphatase, and an increase in the activity of glycolytic enzymes such as hexokinase [229, 230]. Metformin has also been shown to inhibit mitochondrial respiratory chain activity, thus limiting energy supplies for gluconeogenesis [231]. Metformin also increases glucose

uptake by myocytes and adipocytes through GLUT-1 and GLUT-4 [232]. Activation of AMP-activated protein kinase (AMPK) by metformin contributes to increased muscle glucose uptake [233].

Mechanism in inducing weight loss

Metformin has been shown to decrease hunger and reduce food intake without affecting energy expenditure [210, 234, 235]. It also inhibits hypoglycaemic-induced hunger in healthy lean men [235]. There are several hypotheses explaining the anorectic effects of metformin. First, metformin has been shown to produce a heightened GLP-1 response by inhibiting GLP-1 degradation following oral glucose load in obese non diabetic patients [236]. Second, the anorectic effect of metformin could be mediated through the central effect of insulin. Insulin is a satiety signal which rises acutely after food intake. Insulin is thought to act on IRS-2 in the arcuate nucleus of the hypothalamus to inhibit food intake, possibly through the NPY and melanocortin systems [237]. According to the Central Resistance model, insulin and leptin resistance could occur in the central nervous system, leading to dysfunction in energy regulation and glucose metabolism [238, 239]. Metformin may restore the central anorexic effect of insulin by improving insulin sensitivity in the hypothalamus. In support of this theory, Kim et al (2006) have shown that metformin increased the anorexic effect of leptin in obese rats with leptin resistance [240]. Third, the anorexic effect of metformin could be mediated by reducing AMPK activation in the hypothalamus. In the hypothalamus, AMPK activation leads to an increase in appetite [241] through increases in NPY and AGRP expression [242]. Metformin has been found to inhibit AMPK activation in hypothalamic neurons [243].

Metformin and weight loss: a review of the literature

Metformin has been found to produce modest weight loss when used as a treatment for patients with type 2 diabetes [244, 245]. Its effect on body weight in non diabetic subjects is inconsistent. The findings of the randomised controlled trials on the weight loss effect of metformin in non diabetic subjects and in women with PCOS are summarised in Table 1.7 and Table 1.8 respectively. While some studies found metformin to be effective in inducing weight loss [46, 214, 220, 234, 246-250] and promoting favourable changes to the body composition by increasing lean mass [245, 247] and decreasing fat mass [215, 245, 248, 251], others found that the effect of metformin on weight loss was not significantly different to placebo [44, 213, 216, 217, 222, 223, 226, 227, 245, 252-255]. Only six studies stated changes in body weight or composition as their primary outcomes [248, 249, 251, 256-258]. As a result, most studies had relatively small numbers of subjects which limited their study power. Recently, a meta-analysis which included 31 trials with 4570 participants over the duration from 0.4 to 2 years concluded that metformin resulted in 5.3% reduction in BMI in individuals at risk of diabetes [75].

When all studies are considered, the effect of metformin on weight, metabolic and hormonal outcomes (ie in insulin, glucose, lipids, sex hormones) are inconsistent. Discrepancy between studies could be due to variation in subject's metabolic profiles. Some suggest that baseline BMI and insulin sensitivity could affect treatment efficacy [226, 254], thus heterogeneity of subjects could weaken the observed relationship between metformin and weight loss. Further, a number of studies have reported a preferential decrease in body fat accompanied by no change or an increase in lean mass [210, 234, 245, 247, 248]. An increase in lean mass could have masked fat mass loss, resulting in no net change in body weight.

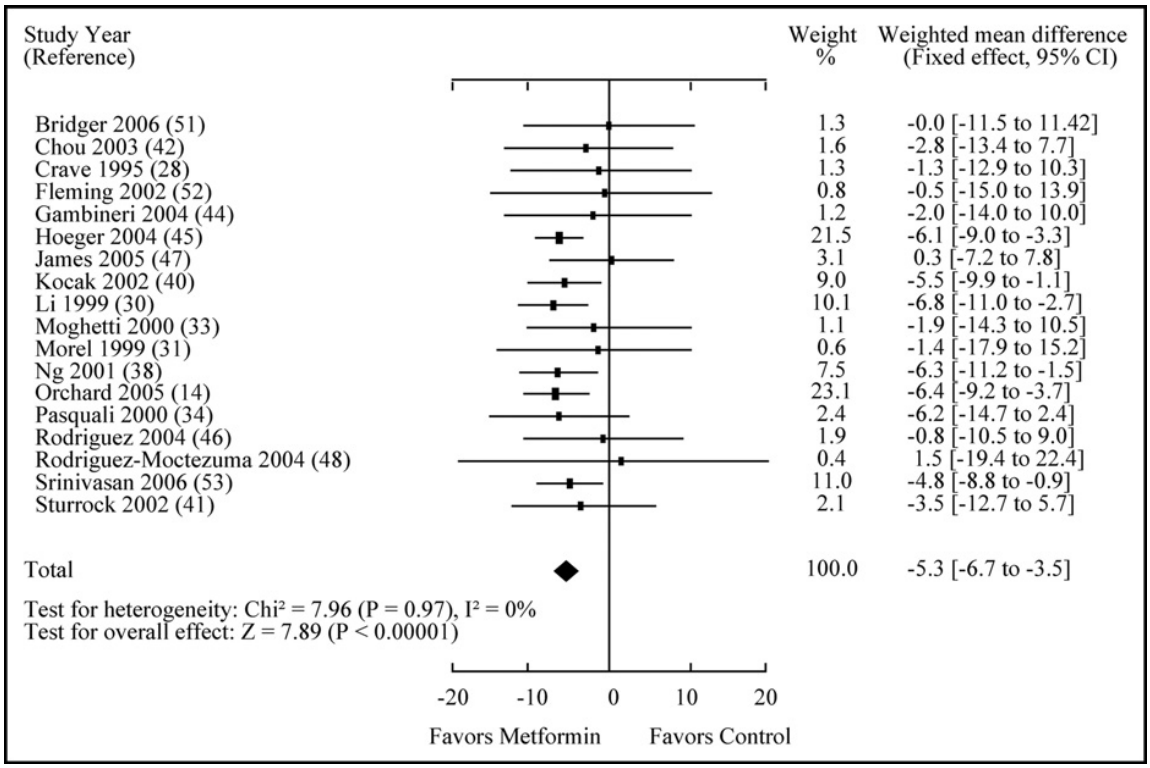


Figure 1.6 Effect of metformin on BMI in non diabetic persons, percentage change. (Taken from Salpeter et al, 2008, p151 [75])

Table 1.7 shows that studies which found a significant benefit of metformin on body weight or body composition tend to have younger participants (under 30 years old), suggesting an effect of age on treatment efficacy. This hypothesis is supported by a recent finding from a secondary analysis on the Diabetes Prevention Program, which found that metformin had greater efficacy in diabetes prevention in younger participants [208]. However, few studies have investigated the effect of metformin in healthy young overweight or obese adults. There were several studies that reported a younger mean age (Table 1.7), but small sample sizes in these studies (ranging from 15 to 30 participants) may have limited their ability to detect significant changes in body weight. Thus, the effect of metformin on body weight in young women is yet to be confirmed in larger trials.

Table 1.7 Randomised-controlled trials on the effect of metformin on body weight in non diabetic individuals

	Subjects	Mean age (years)	Max dosage (mg)	Study duration	Results
Ibanez et al 2006 [247]	22 girls	M: 9.1 P: 9.0	850/day	36 months	Metformin group had significantly less increase in body mass index, total fat mass and abdominal fat mass but larger increase in lean mass compared to placebo group.
Srinivasan et al 2006 [258]	13 boys 15 girls	All: 12.5	1000/day	6 months	Metformin group had greater weight loss (-4.35kg) and greater sc fat loss
Klein et al 2006 [257]	21 boys 17 girls	M: 12.9 P: 13.3	850 od	16 weeks	Metformin group had greater weight loss (-4kg minus placebo)
Freemark and Bursey 2001 [249]	11 boys 18 girls	M: 14.4 P: 15.4	500 bid	6 mo	Metformin group had significant decrease in body mass index (-1.3%) compared to placebo (+2.3%)
Kay et al 2001 [248]	9 boys 15 girls	M: 15.6 P: 15.7	850 bid plus diet	8 weeks	Metformin group had greater weight loss (-6.1 kg vs -3.2 kg) and greater fat loss (-6.0 kg vs -2.7 kg) compared to placebo.
Fruehwald et al 2002 [259]	15 normal weight men	All: 26.7	850 bid	15 days	Non significant weight loss compared to placebo
Wu et al 2008 [260]	64 men 64 women	M: 26.8 P: 25.8	750.day	12 weeks	Metformin group had significantly greater weight loss (-3.2 kg vs +3.1 kg) compared to placebo
Paolisso et al 1998 [234]	13 men 17 women	M: 26.7 P: 28.3	500 bid	15 days	Metformin group had significantly greater weight loss (-2.8 kg vs -0.3 kg) and greater fat loss (-1.4 kg vs -0.3 kg) compared to placebo group
Pasquali et al 2000 [251]	20 women	M: 30.8 P: 32.3	850 bid	6 months	Metformin group had greater decrease in body mass index, body weight, total fat, waist-hip ratio and subcutaneous fat compared to placebo.
Rodriguez et al 2005 [245]	9 men 12 women	M: 36.8 P: 33.6	1700/day	20 weeks	Non significant weight loss compared to placebo
Stakos et al 2005 [261]	159 subjects	M: 40.5 P: 41	500/day	24 months	Non significant weight loss compared to placebo
Munro et al 1969 [256]	90 women	M: 43 P: 42	3000/day	16 weeks	Metformin group had significantly greater weight loss (-6.5kg) compared to placebo (+2.6kg); 80% on metformin lost weight compared to 37% on placebo
Charles et al 2000 [215]	168 men	*M: 45 *P: 46	850 bid	3 months	Non significant weight loss compared to placebo
Caballero et al 2004 [262]	14 men 41 women	M: 47.7 P: 49.3	1000 bid	16 weeks	Non significant weight loss compared to placebo
Giugliano et al 1993 [219]	12 women	All: 47	850 bid	12 weeks	Non significant weight loss compared to placebo
Charles et al 1998 [263]	151 men 306 women	M: 49.7 P: 49.2	850 bid	1 year	Non significant weight loss compared to placebo
Brown et al 2006 [264]	1957 women	M: 49.9 P: 49.5	850 bid	2.8 years	Metformin group had significantly greater weight loss (-1.5 kg vs +0.5 kg) compared to placebo

	Subjects	Mean age (years)	Max dosage (mg)	Study duration	Results
Li et al 1999 [265]	50 men 20 women	M: 49.0 P: 50.0	250 tid	12 months	Metformin group had significantly greater weight loss (-1.4 kg/m2 vs +0.4 kg/m2) compared to placebo
Carlsen et al 1998 [266]	60 men	All: 53	2000/day	12 weeks	Obese subjects had significantly greater weight loss (-3.1kg) with metformin compared to control group
Kantola et al 2002 [217]	15 men 7 women	All: 54	1500/day	8 weeks	Non significant weight loss compared to placebo
Vitale et al 2005 [267]	37 men 28 women	M: 55 P: 54	500 bid	3 months	Non significant weight loss compared to placebo
Jadhav et al 2006 [268]	33 women	M: 55.8 P: 58.1	500 bid	8 weeks	Metformin group had significantly greater weight los (-0.64kg vs +0.48kg) compared to placebo
Snorgaard et al [269]	16 men 9 women	M: 57 P: 52	850 bid/ 500 bid	12 weeks	Non significant weight loss compared to placebo
Lehtorvirta et al 2001 [270]	25 men 15 women	M: 57.3 P: 58.6	500 bid	6 months	Non significant weight loss compared to placebo
Crave et al 1995 [44]	24 women	Not reported	850 bid	4 months	Non significant weight loss compared to placebo
Morel et al 1999 [213]	8 men 11 women	Not reported	850 bid	6 weeks	Non significant weight loss compared to placebo
Schuster et al 2004 [271]	126 subjects	Not reported	500/day	24 months	Metformin group had greater weight loss (-1.4 kg vs +1.4 kg) compared to placebo

M=metformin; P=Placebo; * median age

Table 1.8 Randomised-controlled trials on the effect of metformin on body weight in PCOS women

Source	Subjects (N)	Mean age (years)	Maximum dosage (mg)	Study duration	Results
Tang et al 2006 [255]	143	M: 29.7 P: 29.8	850 bid	6 months	Non significant weight loss compared to placebo
Onalan et al 2005 [254]	139	M: 26 -31 P: 24-28	850 bid	6 months	Non significant weight loss compared to placebo
Jakubowicz et al 2001 [227]	48	M: 27 P: 27	500 tid	4 weeks	Non significant weight loss compared to placebo
Moghetti et al 2000 [222]	23	M: 23.9 P: 21.4	500 tid	6 months	Non significant weight loss compared to placebo
Nestler et al 1997 [216]	31	M: 26 P: 27	500 tid	4-6 weeks	Non significant weight loss compared to placebo
Nestler et al 1996 [218]	24	M; 29 P: 29	500 tid	4-8 weeks	Non significant weight loss compared to placebo
Nestler et al 1998 [272]	61	M: 29 P: 28	300 tid	35 days	Non significant weight loss compared to placebo
Bridger et al 2006 [273]	22	M: 16 P: 16	750 bid	12 weeks	Non significant weight loss compared to placebo
Vandermolen et al 2001 [253]	27	M: 29 P: 30	500 tid	7 weeks	Non significant weight loss compared to placebo
Yarali et al 2002 [252]	32	M: 29.7 P: 28.4	850 bid	6 weeks	Non significant weight loss compared to placebo
Eisenhardt et al 2005 [226]	45	M: 27 P: 29.7	500 tid	12 weeks	Non significant weight loss compared to placebo
Lord et al 2006 [274]	40	M: 27.8 P: 30.7	500 tid	3 months	Non significant weight loss compared to placebo
Kocak et al 2002 [46]	56	All: 26.2	850 bid	32 days	Significant weight loss with metformin but not with placebo
Gambineri et al 2006 [275]	80	M: 28 P: 26	850 bid	12 months	Significantly greater reduction in body weight, waist circumference, fat mass compared to placebo
Pasquali et al 2000 [251]	20	M: 30.8 P: 32.3	850 bid	6 months	Significant decrease in body weight, BMI, visceral fat compared to placebo

M=metformin; P=Placebo

Metformin verses other weight loss drugs

When compared to the existing weight loss pharmaceutical agents, metformin was found to be as effective as orlistat (metformin vs orlistat: -9.9% BMI -9.06% BMI, $P>0.05$) but less effective than sibutramine (-13.57% BMI, $P<0.05$) [276]. Metabolic benefits were found to be comparable between the three agents despite differences in weight loss in this study [276]. This is in contrast to previous findings which suggest that sibutramine is associated with adverse cardiovascular side effects such as increased systolic and diastolic blood pressure and increased pulse rate due to its nor-adrenergic effects [277, 278]. In terms of restoring reproductive function, Lazurova et al (2004) found that metformin was more effective in restoring ovarian function in obese women even though sibutramine induced a greater weight loss [279]. The favourable effects metformin have on the metabolic and reproductive function suggest that it may be a highly desirable weight loss drug for overweight or obese young women with metabolic and reproductive disorders, if shown also to be effective in weight loss.

Metformin versus other insulin sensitising agents

There are three types of treatment for diabetes in the market, namely insulin sensitising agents, insulin mimetics and insulin releasing agents (sulfonylureas and others). Insulin sensitisers include metformin, rosiglitazone, pioglitazone. Both rosiglitazone and pioglitazone cause weight gain [280].

1.3 Summary and gaps in knowledge

Population studies suggest that young women are at high risk of weight gain and that weight gain in young women could be detrimental in both the short and long term. Changes in lifestyles such as an increase in energy intake through poor quality diet and a decrease in physical activity during early adulthood could account for weight gain in this group. These changes have been found to be associated with other significant changes in young women's lives, such as getting married, having children and starting work. Despite the extent of the problem, no weight loss study has been conducted in healthy overweight or obese young women.

Previous research showed that hormonal and psychological factors such as hyperandrogenemia or stress may affect the eating behaviour of young women. However, the relationship between hyperandrogenemia or stress and food craving in young women is not known.

Metformin is commonly prescribed for young women with PCOS to improve insulin resistance and reproductive symptoms. While some studies suggest that it could produce weight loss, results from past studies have been inconsistent. The effect of metformin on body weight and metabolic outcomes of healthy overweight or obese young women has not been investigated.

A combination of diet, exercise and behavioural therapy is recommended for obesity management. However, this has not been trialled for weight loss in healthy overweight or obese young women. In addition, the most effective way of delivering the lifestyle advice

has not been extensively researched. Quantitative lifestyle advice has been shown to be effective in producing weight loss but some argued that it may have adverse psychological effects. On the other hand, qualitative lifestyle advice has been demonstrated to produce psychological improvements but weight loss with this approach was minimal. The effect of qualitative and quantitative lifestyle advice on body weight and psychological outcomes has not been compared in young women.

Attrition is an important issue in weight loss interventions in young women. Young women are more likely to drop out of weight loss interventions but the reasons for attrition among young women are not known.

Long term weight loss maintenance is a challenge, possibly even more so in young women. The internet could be a viable means to provide long term support on weight management. Young adults are frequent users of the internet but the effectiveness of internet-based lifestyle program on long term weight management in young women is not known.

1.4 Objective

The overall objective of this thesis was to investigate the effect of various interventions on weight management in young women to develop appropriate weight management guidelines for this group.

1.5 Aims

The specific aims of the chapters in this thesis are:

- To determine the relationship between hyperandrogenemia, psychological distress and food cravings in young women
- To compare the effectiveness of metformin plus qualitative lifestyle advice, placebo plus qualitative lifestyle advice and structured lifestyle intervention with quantitative lifestyle advice on weight management in young women
- To compare the weight and psychological effects of quantitative and qualitative lifestyle advice in young women
- To determine the long term effects of a quantitative lifestyle intervention delivered through the internet on body weight in young women

1.6 Hypotheses

The specific hypotheses of the chapters in this thesis are:

- Food cravings will increase in the presence of hyperandrogenemia or psychological distress
- Metformin will be more effective than placebo in producing weight loss, but lifestyle intervention will be more effective than metformin on weight loss in young women.
- Quantitative lifestyle advice will result in greater weight loss in young women, but qualitative lifestyle advice will result in greater improvement in psychological outcomes
- The quantitative lifestyle intervention delivered through the internet will result in a net weight loss between baseline and week 48 in young women

Chapter 2 Hyperandrogenemia, psychosocial distress, and food cravings in overweight and obese young women

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STATEMENT OF AUTHORSHIP

Siew Lim (Candidate)

Developed protocol, prepared ethics application, delivered dietary interventions, assisted with laboratory analyses, performed statistical analyses, interpreted data, wrote manuscript and acted as corresponding author.

Signed……..Date……

Peter Clifton

My contribution to this paper involved:

Assistance with statistical analyses, data interpretation and manuscript evaluation.

I give consent to Siew Lim to present this paper for examination towards the Doctor of Philosophy

Signed……..Date……

Robert Norman

My contribution to this paper involved:

Assistance with statistical analyses, data interpretation and manuscript evaluation.

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My contribution to this paper involved:

Contribution to study design and assistance with statistical analyses, data interpretation and manuscript evaluation.

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2.1 Abstract

Reproductive disorders and psychological distress are common co-morbidities of obesity in young women. Psychological and reproductive disturbances may also be associated with increased food cravings but the relationships between these factors have not been explored. This study aimed to explore the pattern of food cravings and to determine the relationship between psychological distress, reproductive health and food cravings in overweight and obese young women using baseline data in a weight loss trial. A total of 198 young women were included in this analysis (BMI 33.3 $\pm$ 0.3 kg/m^2, age 28 $\pm$ 0.3 years). The most frequently craved food item was chocolate (3.9 $\pm$ 0.08 i.e. sometimes-often). The most frequently craved food categories were fast foods (2.6 $\pm$ 0.07) and sweets (2.5 $\pm$ 0.05). Psychological distress was significantly correlated with food cravings (R^2=0.18, P<0.05). High fat (r=0.2), sweets (r=0.17) and overall cravings (r=0.20) were significantly correlated with energy intake (P<0.05). Psychological distress did not correlate with energy intake (P>0.05). Participants with menstrual disturbances had greater fast food cravings independent of age, BMI and PCOS status (P<0.05). Participants with hyperandrogenemia had greater high fat food cravings independent of age, BMI and PCOS status (P<0.01). Energy intake did not differ with menstrual disturbances or hyperandrogenemia (P>0.05). These results suggest that psychological distress, hyperandrogenemia and menstrual disturbances are associated with greater food cravings. Further investigations are required to elucidate the relationship between hyperandrogenemia and food cravings in young women.

Keywords: Psychological distress, hyperandrogenemia, food cravings.

2.2 Introduction

A food craving is defined as having an intense desire directed at a specific food or drink [281]. Food cravings reportedly occur in up to 97% of young women and 68% of young men [79]. Craved foods are usually higher in energy density and fat content and lower in fiber compared to habitual diet [80]. Commonly craved foods include chocolate, chips, dessert and fast foods [282]. Cravings have been found to predict intakes of specific foods [283, 284]. Cravings of high fat foods such as chips were associated with obesity [281, 285]. On the other hand, those who indulged in food cravings less frequently also had greater weight loss [80]. These findings suggest that cravings may play an important role in the etiology and treatment of obesity.

The origins of cravings are not well understood. Food cravings are unlikely to be a metabolic signal for a particular nutritional deficit [196]. It is also distinct from hunger as less than 40% of food cravers reported being hungry while experiencing food cravings [286]. The experience of food cravings include visual, gustatory and olfactory senses, suggesting that cravings may reflect a desire for specific sensory experiences [287]. Significant relationships between depression and food cravings have also been reported, suggesting that mood states may also be involved in eliciting food cravings [288, 289].

Hyperandrogenemia and menstrual abnormalities are common co-morbidities of obesity in young women. Hyperandrogenemia is one of the main features in polycystic ovaries syndrome (PCOS), in addition to menstrual disturbances and polycystic ovaries. PCOS is a common endocrinological disorder among overweight and obese young women [29]. It was suggested that obesity contributes to these reproductive abnormalities through hyperinsulinemia [29]. However, hyperandrogenemia or other co-existing metabolic

derangements may have also perpetuated the obese state in these women. Altered appetite regulation has been reported in women with PCOS including impaired ghrelin and cholecystokinin secretion [69, 137]. Little is known about the effect of hyperandrogenemia on food cravings in women.

Obesity can have significant psychological impact in young women [68, 290]. The relationship between obesity and psychological health could be bi-directional. While obesity may lead to poorer mental health by producing greater body dissatisfaction and lower self-esteem [290, 291], stress may also contribute to obesity by altering eating patterns [125, 140]. Stress has been associated with greater preference for foods high in fat and sugar [124-126]. It has been suggested that cortisol which is released during stress may increase energy intake by reducing the inhibitory effect of leptin on food intake and by stimulating the release of neuropeptide Y [138, 292]. The relationship between stress and food cravings has not been described.

The primary purpose of this study was to determine the relationships between food cravings, psychological distress and reproductive health (ie hyperandrogenemia and menstrual disturbances). We hypothesized that food cravings will increase in the presence of high psychological distress, hyperandrogenemia or menstrual disturbances.

2.3 Methods

Subjects

This study included a sub-sample of the participants (n=198) in a 12-week weight loss trial. Those who completed a Food Craving Inventory at baseline and provided blood samples for the determination of hyperandrogenemia were included in this study. Other

inclusion criteria for the trial were young women aged between 17 to 37 years with a BMI between 25.1 kg/m^2 to 44 kg/m^2, who had access to the internet and were able to attend the clinic for outpatient visits. Exclusion criteria were: significant illnesses including kidney disease, liver disease, malignancy, uncontrolled hypertension, diabetes or thyroid disease; pregnancy or lactation; intention to conceive during the study duration, or current rapid weight loss (>0.5kg/week). This study was approved by the CSIRO Human Nutrition and Adelaide University Ethics Committee Boards. Data was collected from participants who provided written informed consent. This trial was registered with the Australian Clinical Trials Registry (ACTRN012607000213448).

Clinical measurement

At baseline participants attended the CSIRO clinic after an overnight fast, during which weight, height and psychosocial variables were measured followed by the collection of venous blood samples to determine steroid hormone binding globulin (SHBG) and testosterone. Body weight was measured at baseline while participants wore light clothing and no shoes with the use of a calibrated electronic digital scale (Mercury, AMZ 14, Tokyo, Japan). Body height was measured using a stadiometer while participants were barefoot (SECA, Hamburg, Germany). Food intake was measured by analysing 3-day (2 week days and 1 weekend) food diaries collected at baseline using Foodworks (Xyris Software 1998, Highgate Hill, Australia).

Participant characteristics, food cravings and psychological measures

All questionnaires were administered through a computer in a quiet, temperature-controlled room (see Appendix). Participants' characteristics such as age, dieting history, marital status, parity, smoking status, presence of menstrual disturbances, and polycystic ovary syndrome (PCOS) status were collected in the first part of the questionnaires.

Menstrual disturbances are defined as having cycle length <21 days or >35 days or variation between consecutive cycles of more than 3 days [293].

Food cravings were measured using a modified version of the Food Craving Inventory [281]. The questionnaire measures the frequency of craving for 27 food items. The questionnaire was modified to reflect Australian foods. Modifications include the replacement of cornbread with pie or pastie, the deletion of cookies from the food items, and the re-location of biscuits from carbohydrates subscale to sweets subscale. As in the original version, the food items were prefaced by the question '*over the past month, how often have you experienced a craving for the following food item?*". Craving was defined as having an intense desire for the particular food item. Response options were *never*, *rarely*, *sometimes*, *often*, and *always/almost everyday* (Score 1 to 5 respectively). Overall craving score represented the average rating of all food items. Mean subscale score were calculated as the average rating of all food items in the subscale. There were four subscales, including high fat foods (fried chicken, sausage, gravy, fried fish, bacon, pie or pastie, hot dog, steak), sweets (brownies, candy, chocolate, biscuits, donuts, cake, cinnamon rolls, ice cream), carbohydrates (rolls, pancake or waffle, sandwich bread, rice, baked potato, pasta, cereal) and fast foods (hamburger, french fries, chips, pizza). Cronbach's α coefficients for the total and subscale scores in the current version were between 0.8 and 0.9.

Psychological distress was assessed using the 12-item General Health Questionnaire (GHQ) scored by the Likert method [294]. GHQ is a screening instrument commonly used to detect psychiatric disorders. This questionnaire has been validated in young adults [295]. Cronbach's α coefficient for this instrument is 0.81 [296]. This questionnaire is useful in

identifying emotional states such as anxiety, depression or general psychological distress. Scores ranged from 0 to 36, with higher score representing greater psychological distress.

Biochemical and nutrient analyses

Serum was isolated by centrifugation at 2000 *g* for 10 minutes at 5 ^{o}C (Beckman GS-6R centrifuge, CA, USA) and frozen at -80 ^{o}C. Serum testosterone and SHBG was analysed as previously described [297]. The intra-assay coefficient of variation for SHBG ranged from 4.0% to 5.5% and the inter-assay coefficient of variation ranged from 3.3% to 6.9%. For testosterone, the intra-assay co-efficient of variation ranged from 6.7% to 8.1% and the inter-assay coefficient of variation ranged from 5.7% to 10.5%. Free androgen index (FAI) was calculated from SHBG and testosterone levels (100 x testosterone/SHBG). Hyperandrogenemia is defined as having FAI of greater than 4.97 [298]. This cut-off has been suggested for the diagnosis of PCOS [298].

Statistical analyses

The relationship between psychological distress and energy intake was assessed using Pearson's correlation. The relationship between psychological distress and food cravings were assessed using multiple regression, with sweet cravings, fast food cravings, carbohydrate cravings, high fat food cravings, age, BMI and PCOS status as predictors. Differences in food cravings between participants with and without menstrual disturbances, and between participants with and without hyperandrogenemia, were assessed using one-way ANOVA. These analyses were repeated using ANCOVA to correct for age, BMI, PCOS status and psychological distress. All calculations were performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, IL, USA). A P-value of less than 0.05 was considered statistically significant. Unless otherwise specified, all data were presented as mean $\pm$ SE.

2.4 Results

Participants

Baseline characteristics of the participants were as shown in Table 2.1. Thirty-one percent of the participants had menstrual disturbances, 33% had hyperandrogenemia and 9% had PCOS. Food cravings did not differ with marital status, parity, or dieting history.

Patterns of food craving

When considering single food items, the most frequently craved food was chocolate (3.9 $\pm$ 0.08 i.e. sometimes-often), followed by candy (2.9 $\pm$ 0.09 ie rarely-sometimes), chips (2.84 $\pm$ 0.09), bread (2.74 $\pm$ 0.09) and pasta (2.73 $\pm$ 0.08). In terms of food categories, most frequent cravings were reported for fast foods (2.6 $\pm$ 0.07) and sweets (2.5 $\pm$ 0.05), followed by carbohydrates (2.3 $\pm$ 0.06) and high fat foods (2.0 $\pm$ 0.04).

Hyperandrogenemia, food cravings, psychological distress and energy intake

Those with hyperandrogenemia had significantly greater high fat food cravings, $F(1,196)=10.416$, P=0.001 and carbohydrate cravings, $F(1,196)=4.001$, P=0.047 compared to those with lower FAI values (Figure 2.1). High fat food cravings remained significantly greater in participants with hyperandrogenemia after correcting for age, BMI, and PCOS status, $F(1,193)=8.556$, P=0.004. When psychological distress was added to the model, high fat food cravings remained significantly greater in participants with hyperandrogenemia, $F(1,192)=8.887$, P=0.003. Psychological distress was not different between participants with and without hyperandrogenemia. Dietary intake (total energy intake and intakes of protein, fat and carbohydrate) were also similar between the groups.

Menstrual disturbances, food cravings, psychological distress and energy intake

Those with menstrual disturbances had significantly higher overall food cravings, $F(1,196)=3.961$, P=0.048, high fat food cravings, $F(1,196)=3.932$, P=0.049 and fast food cravings, $F(1,196)=5.156$, P=0.024, when compared to those who without menstrual disturbances (Figure 2.2). Fast food cravings remained significantly higher among those with menstrual disturbances after correcting for age, BMI and PCOS status, $F(1,193)=5.183$, P=0.024. When psychological distress was added to the model, fast food cravings remained significantly greater in participants with menstrual disturbances, $F(1,192)=4.052$, P=0.046. Psychological distress was not different between participants with and without menstrual disturbances. Dietary intake (total energy intake and intakes of protein, fat and carbohydrate) were not significantly different between the groups.

Psychological distress, food cravings and energy intake

Multiple regression indicated that sweet cravings and fast food cravings predicted psychological distress (Table 2.2). Psychological distress did not correlate with energy intake (r=0.05, P=0.46).

2.5 Discussion

This is the first study that explored the relationships between food cravings, stress and reproductive abnormalities. Hyperandrogenemia and menstrual disturbances were significantly associated with greater food cravings independent of age, BMI and PCOS status. Psychological distress was also significantly related to higher food cravings after corrected for age, BMI and PCOS status.

Hyperandrogenemia was associated with greater high fat food craving while menstrual disturbances was associated with greater fast food craving after correcting for age, BMI

and PCOS status. This is the first time a relationship was reported between reproductive abnormalities and food cravings. The underlying mechanism for the relationship is unclear. Although there has been a lack of research investigating the association between reproductive disturbances and cravings, previous studies have found that reproductive dysfunction may be associated with altered eating behavior. Women with PCOS were found to have higher prevalence of abnormal eating behavior including bulimic behavior [299]. Women with bulimia nervosa, a condition defined by characteristics such as an uncontrollable desire to eat, also had higher androgen levels compared to healthy controls [300]. Anti-androgen or androgen antagonist treatment improved bulimic behavior in women with bulimia nervosa [73, 301]. Together, these findings suggest that hyperandrogenemia may contribute to greater impulsivity in food intake. It is unclear if reproductive abnormalities may also be associated with increased food cravings in a similar way.

Although the macronutrient profiles of high fat foods and fast foods may be similar, different results were seen between these two categories. The food categories were statistically determined using factor analysis with an oblique (PROMAX) rotation [281]. The analysis yielded the four-factor structure as seen in the Food Craving Inventory used in this study. The analysis indicated that food items such as hamburger, chips, fries and pizza belong to a factor different from the high fat foods category. The authors who developed the questionnaire attributed these unexpected findings to the availability or situational specificity of fast foods [281]. In support of this, a recent study in children found that foods with branded fast food packaging received higher taste preference scores compared to identical foods presented in unbranded packaging [302]. Thus, the social identity of fast foods may affect the desirability of the food item itself independent of

nutritional or biochemical factors. This may explain the differences in cravings for fast foods as compared to the other high fat foods.

Our findings suggest a relationship between reproductive function and food cravings. However, reproductive disturbances appeared to have no association with self-reported energy intake. In contrast, a recent study involving the analysis of 7-day food diaries found that women with PCOS had greater percentage energy intake from fat and higher saturated fat intake compared to age- and weight-matched controls [303]. In support of this finding, the current study reported that reproductive abnormalities were associated with greater fast food and high fat food cravings. The lack of dietary effect seen in the current study could be due to the limitations of 3-day food diaries in capturing the wide range of eating patterns in this age group [304]. In addition, the accuracy of food diaries is known to be poor especially in women [305]. Women have been shown to underreport their energy intake by 30% in food diaries [305]. Those with higher body mass index are also more likely to underreport [305]. On the other hand, less severe reproductive abnormalities in the current study may also be associated with milder alterations in food cravings that may be insufficient to produce a noticeable difference in eating behavior.

This study reports for the first time that psychological distress may be associated with food cravings. Stress has been shown to increase drug cravings by increasing the reinforcing qualities of drugs [139]. It is unclear if chronic stress may also contribute to greater food cravings in a similar way. Previous studies also reported that individuals with high levels of stress had greater energy or fat intake [124-126, 140]. In contrast, we did not find a significant relationship between energy intake and psychological distress in the current study. This is possibly due to the limitations of food records as discussed above.

This study has several limitations. First, this is a cross-sectional study. Causal relationships between the variables could not be determined based on the current findings. Second, the food craving inventory developed for the general population may not include all the foods that are frequently craved by young women. The development of age- and population-specific food craving inventories may be necessary to improve the sensitivity of the tool. Due to the rapidly changing food supply, the inventory may also need frequent updating to reflect current food trends. Third, as this analysis was part of a weight loss intervention, only overweight and obese young women were included. Involvement of women from a wider BMI range may result in stronger relationships between the variables. Fourth, participants completed the food craving questionnaire at different points in their menstrual cycle. Stronger relationships may be observed if all participants completed the questionnaires in the same menstrual phase (i.e. luteal or follicular phase). On the other hand, the determination of menstrual phase could be difficult in participants with severe menstrual disturbances. These limitations need to be considered when interpreting the results of this study.

Conclusion

This is the first study reporting a relationship between psychological stress, reproductive disorders and food cravings. Reproductive disorders such as hyperandrogenemia and menstrual disturbances were associated with increased cravings for certain foods such as high fat foods and fast foods independent of age, BMI, PCOS status and psychological distress. Psychological distress was also associated with sweets craving and high fat foods craving. However, it is unclear if increased food cravings are associated with increased habitual energy intake. Further investigation should be conducted to elucidate the role of hyperandrogenemia and psychological distress in the etiology of food cravings.

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2.6 Figures and tables

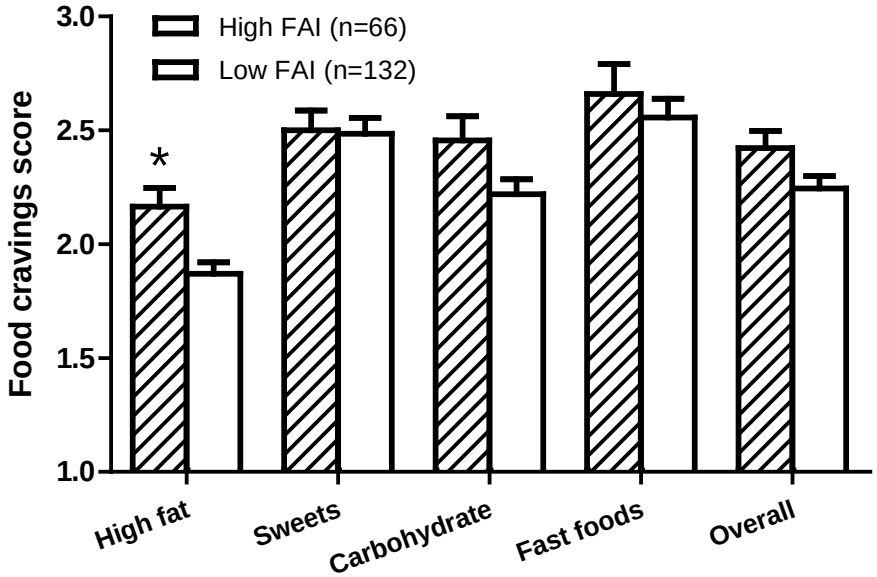

Figure 2.1 Food cravings score (means ± SE, n=198) in young women with or without hyperandrogenemia (defined as Free Androgen Index > 4.97). * P<0.05 between groups after correcting for age, BMI and PCOS status.

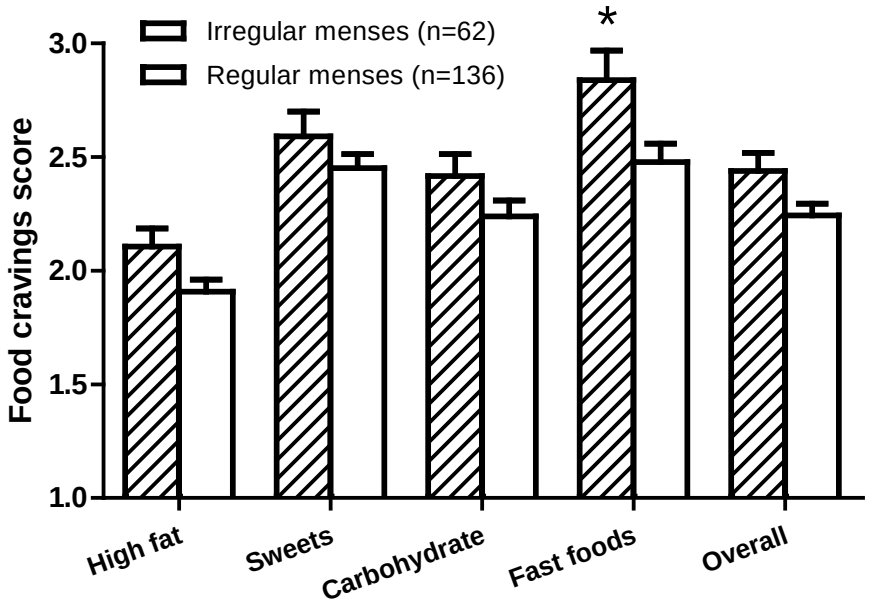

Figure 2.2 Food cravings score (means + SE, n=198) in young women with or without menstrual disturbances (MD). * P<0.05 between groups after correcting for age, BMI and PCOS status.

Table 2.1 Characteristics of study participants (n=198)

	Mean (standard error)
Age, years	27.9 (0.3)
BMI, kg/m^2	33.3 (0.3)
Testosterone, nmol/L	1.76 (0.05)
SHBG, nmol/L	66.9 (4.3)
Psychological distress	13.4 (0.4)
Free androgen index	5.2 (0.4)
Energy intake, KJ	8587 (182)
General cravings	2.3 (0.04)
High fat cravings	2.0 (0.04)
Sweets cravings	2.5 (0.06)
Carbohydrate cravings	2.3 (0.06)
Fast food cravings	2.6 (0.07)
	%
Married or cohabiting	50
Have had at least 1 child	35
Dieted in the past for weight loss	90

Table 2.2 Regression coefficients for food cravings[a] in predicting psychological distress[b] (n=198)[c]

Variable	B	SE (B)	β	t	P-value
High fat cravings	0.147	0.830	0.017	0.178	0.859
Sweets cravings	1.229	0.580	0.176	2.120	0.035
Carbohydrate cravings	-0.772	0.643	-0.114	-1.20	0.232
Fast food cravings	1.865	0.504	0.337	3.70	<0.0005
R^2=0.18					

[a] Food cravings were measured using modified Food Cravings Inventory, a 27-item scale, higher scores indicate greater frequency of craving.
[b] Psychological distress was measured using General Health Questionnaire, a 12-item scale, higher scores indicate greater psychological distress.
[c] Model included high fat cravings, sweets cravings, carbohydrate cravings, fast food cravings, age, BMI, and PCOS status.

Chapter 3 The effect of comprehensive lifestyle intervention or metformin on obesity in young women

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Abbreviated title: Metformin or comprehensive lifestyle in young women

Keywords: Lifestyle modifications, women, weight loss, clinical trials, drug treatment.

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STATEMENT OF AUTHORSHIP

Siew Lim (Candidate)

Developed protocol, prepared ethics application, delivered dietary interventions, assisted with laboratory analyses, performed statistical analyses, interpreted data, wrote manuscript and acted as corresponding author.

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Peter Clifton

My contribution to this paper involved:

Monitoring of drug adverse effects during trial and assistance with statistical analyses, data interpretation and manuscript evaluation.

I give consent to Siew Lim to present this paper for examination towards the Doctor of Philosophy

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Robert Norman

My contribution to this paper involved:

Assistance with statistical analyses, data interpretation and manuscript evaluation.

I give consent to Siew Lim to present this paper for examination towards the Doctor of Philosophy

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Manny Noakes

My contribution to this paper involved:

Contribution to study design and assistance with statistical analyses, data interpretation and manuscript evaluation.

I give consent to Siew Lim to present this paper for examination towards the Doctor of Philosophy

Signed……..Date……

3.1 Abstract

Background and aim: Young women are at high risk of weight gain but few weight management interventions have been investigated in this group. This study aimed to determine the effect of metformin on body weight, body composition, metabolic risk factors and reproductive hormone levels in overweight or obese young women compared to placebo and comprehensive lifestyle intervention.

Methods and results: 203 overweight or obese young women (BMI 33.2±0.3 kg/m^2, age 28±0.3 years) were randomised to 1500mg/day metformin (M) plus general lifestyle advice, placebo (P) plus general lifestyle advice or comprehensive lifestyle intervention including structured diet, exercise and behavioural therapy (L) for 12-weeks. At 12-weeks, linear mixed models found that L group had greater weight loss (-4.2±0.4 kg) compared to M (-1.0±0.4 kg) and P groups (-0.2±0.3 kg) (P<0.0001). Weight loss between M and P groups were not significantly different. Attrition rate was 48% for L, 34% for M and 29% for P (P=0.08). Intention-to-treat analysis showed that 10% (8/79) of the subjects in P group had gained weight (>3%), compared to 3% (2/65) from M group and none (0/59) from L group (P<0.001). The L group had the greatest decrease in waist circumference (-5.2±0.7 cm) and fat mass (-5.4±0.7 kg) compared to the other groups (P<0.05). No significant time-by-group effects were seen in plasma lipids, SHBG, testosterone, blood pressure, serum folate, serum ferritin and serum vitamin B12.

Conclusion: Lifestyle intervention was more effective in reducing body weight and improving body composition compared to metformin among healthy overweight or obese young women.

3.2 Introduction

The majority of the adults in the western world are now overweight or obese. The National Longitudinal Survey of Youth in the United States reported that more than 80% of those who were obese by their mid-thirties became obese in early adulthood [5]. Young women were twice as likely to gain weight compared to young men [3]. Weight gain in young women increases the risk of a range of diseases including cardiovascular disease, diabetes and cancer [11, 14]. In the short term, obesity also increases the risk of irregular periods, infertility, or polycystic ovaries syndrome (PCOS). Despite the extent of the problem, there has been a paucity of research on weight management in young women.

Few successful strategies have been reported for weight management interventions in young women. Young adults are less likely to participate in a weight loss intervention. Thus, most weight loss intervention trials report a mean participant age of 40 to 60 years old [306]. Younger and female participants are also more likely to drop out of weight loss interventions [134]. Lower participation rate and higher attrition rate in young women suggest that they may be under-represented in obesity research despite high levels of interest in weight management by this group.

Metformin has been shown to reduce body weight and improve metabolic outcomes in individuals at risk of diabetes [75]. It is also prescribed for polycystic ovary syndrome (PCOS), a common endocrinological disorder affecting young women particularly those with central obesity [209]. Some studies suggest that metformin may induce weight loss, possibly by reducing hunger [14, 15]. In the Diabetes Prevention Program, weight loss with metformin compared to weight gain with placebo explained 64% of the reduction in diabetes risk with metformin [307]. On the other hand, intensive lifestyle intervention has

been shown to induce significantly greater weight loss compared to metformin , although with lower effectiveness among younger participants [208, 250]. To our knowledge, the effect of comprehensive lifestyle intervention compared to metformin or placebo on body weight in healthy, overweight or obese young women is unknown.

The aim of this study was to compare the effect of comprehensive lifestyle intervention to metformin or placebo on body weight in overweight or obese young women. In addition we also evaluated changes in body composition, metabolic risk factors and reproductive hormone levels across the treatment groups. We hypothesised that metformin would result in greater weight loss and metabolic improvements compared to placebo, but lifestyle intervention would result in the greatest improvements in these outcomes.

3.3 Methods and procedure

Participants

We recruited 297 overweight or obese young women through public advertisement. Inclusion criteria were women aged between 17 to 37 years with a BMI between 25.1 kg/m^2 to 44 kg/m^2, access to the internet and able to attend the clinic for outpatient visits. All participants completed an online medical screening questionnaire. Exclusion criteria include: significant illnesses including kidney disease, liver disease, malignancy, uncontrolled hypertension, self-reported diabetes or thyroid disease; pregnancy or lactation; or current rapid weight loss (>0.5kg/week) were excluded. This study was approved by the CSIRO Human Nutrition and Adelaide University Ethics Committees. Data was collected from participants who provided written informed consent.

Study design

The participants were block-matched for age, menstrual irregularity and body mass index and then randomised to one of the three treatment groups: metformin plus general lifestyle advice (M), placebo plus general lifestyle advice (P), or comprehensive lifestyle program (L). Randomisation was conducted by an independent observer using the program CLINSTAT (St George's Hospital Medical School, London, United Kingdom). Two of the three groups received either metformin or placebo packed in identical bottles according to the treatment codes provided by the Royal Adelaide Hospital Pharmacy. The code was randomised in blocks of 20 (1:1) and were concealed from the experimenters until data collection and laboratory analyses was completed, thus achieving double-blinding in the tablet arms. All participants were instructed to attend the CSIRO Human Nutrition outpatient clinic every two weeks for 12 weeks to review progress. This trial was registered with the Australian Clinical Trials Registry (ACTRN012607000213448).

Metformin or placebo

Extended-release metformin (Diabex XR 500mg, Alphapharm Pty Ltd) was used to improve compliance. To maximise tolerance, dosage was increased gradually across three weeks by one tablet a week to achieve the maximum dose of 1500mg a day. Compliance was monitored every two weeks during the study by checking the pill diary kept by participants. Pill-counts were conducted at the end of the 12 week period to obtain an objective measure on compliance. At Week 0, participants in the metformin or placebo arms were provided with general lifestyle advice according to the Australian Guide to Healthy Eating and National Physical Activity Guidelines for Australian Adults websites [308, 309]. Participants were seen every two weeks at the CSIRO outpatient clinic.

Comprehensive lifestyle program

The comprehensive lifestyle program includes a hypocaloric high protein diet (6000KJ; 40% carbohydrate, 30% protein, 30% fat), a structured exercise program involving a gradual increase in physical activity to achieve 60 minutes of aerobic and resistance exercise per day as suggested for long term weight maintenance [310], and other support for behavioural modification. This program has been shown to result in 7-10% weight loss and improvement in reproductive and metabolic health in young women with PCOS [153]. Participants were advised to keep food and exercise checklists daily, which were reviewed by a qualified dietitian every two weeks to address barriers to the lifestyle program.

Clinical measurements

Body weight was measured every 14 days while participants wore light clothing and no shoes with the use of a calibrated electronic digital scale (Mercury, AMZ 14, Tokyo, Japan). Body height was measured at week 0 using a stadiometer (SECA, Hamburg, Germany). Waist circumference was measured at weeks 0 and 12 using a flexible tape. Body composition was measured at week 0 and 12 using a bioelectrical impedance analyser (SFB7™, Impedimed Pty Ltd, Brisbane, Australia). At weeks 0 and 12, participants attended the CSIRO clinic after an overnight fast, during which systolic and diastolic blood pressure were measured followed by the collection of venous blood samples to determine blood lipids, glucose, insulin, vitamin B12, folate, steroid hormone binding globulin (SHBG) and testosterone. Hirsutism was determined at weeks 0 and 12 using the Ferriman-Gallwey scores. Metabolic syndrome was determined using the ATP III definition [311]. Food intake was measured by analysing 3-day (2 week days and 1 weekend) weighed food diaries collected at weeks 0 and 12 using Foodworks (Xyris Software 2007, Highgate Hill, Australia). Physical activity levels were assessed using the

short format of the International Physical Activity Questionnaire collected at weeks 0 and 12 [312].

Biochemical analyses

Plasma or serum was isolated by centrifugation at 2000 g for 10 minutes at 5 ^{o}C (Beckman GS-6R centrifuge, CA, USA) and frozen at -80 ^{o}C. Serum total and HDL cholesterol, triglyceride, ferritin and plasma glucose were measured on a Hitachi centrifugal analyser (Roche Diagostics, Indianapolis, IN, USA) using standard enzymatic kits (Roche Diagostics, Indianapolis, IN, USA). Insulin was measured using a commercial enzyme immunoassay kit (Mercodia, Uppsala, Sweden). LDL cholesterol was calculated using a modified Friedewald equation [313]. The homeostasis model assessment (HOMA) was as a measure of insulin sensitivity [fasting insulin (μU/L) x fasting glucose (mmol/L)/22.5] [314]. Serum testosterone and SHBG was analysed as previously described [297]. Free androgen index (FAI) was calculated from SHBG and testosterone levels (100 x testosterone/SHBG). Vitamin B12 and folate were measured by a certified commercial laboratory (Institute of Medical and Veterinary Science, Adelaide, South Australia).

Study outcomes

The primary outcome was changes in body weight. Secondary outcomes were changes in body composition, waist circumference, metabolic risk factors and reproductive hormone levels.

Statistical analyses

Data which were not normally distributed (ie triglyceride, insulin, HOMA, ferritin, SHBG, FAI, physical activity) were logarithmically transformed. Baseline differences between treatment groups were analysed using one-way ANOVA for continuous variables and Chi-

square tests for categorical variables. In the primary analyses, treatment outcomes were assessed using linear mixed models on all participants who commenced the interventions [315]. Models included time, treatment and time-by-treatment as fixed factors. Mixed models analyses assumed that data were missing at random. Differences between groups were determined by post hoc tests when a significant time-by-group interaction was present. When a significant time-by-group interaction was found (ie for insulin, glucose, and HOMA outcomes), analyses were repeated with weight change added as a covariate in the models to determine the effect of weight loss on metabolic changes. In the secondary analyses, completers' and baseline-carried-forward analyses were carried out on continuous variables using repeated measure ANOVA. Categorical outcomes such as attrition rate, prevalence of metabolic syndrome, and the percentage of participants who gained (>3%), maintained ($\pm$ 3%) or lost weight (>3%) in each group were assessed using Chi-square analyses [316]. Categorisation of weight change was based on last-observation-carried-forward method. All calculations were performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, IL, USA). A P-value of less than 0.05 is considered statistically significant. Unless otherwise specified, all data are presented as estimated mean$\pm$SEM.

Assuming an alpha of 0.05, the current study had at least 85% power to detect a significant difference of 6 kg in weight loss between metformin and placebo, or between metformin and comprehensive lifestyle intervention.

3.4 Results

Participants

At baseline, participants had a mean age of 28$\pm$0.3 years and BMI of 33.3$\pm$0.3 kg/m^2. A total of 50% (100/203) of the participants were married or in a de facto relationship, 66%

(131/203) never had children, and 40% (131/203) had a university degree. One possibly had newly discovered diabetes (fasting blood glucose >7.0 mmol/L) and four had impaired fasting glucose (fasting blood glucose 6.1-6.9 mmol/L). Clinical characteristics at baseline did not differ between the groups, except for testosterone, which was higher in M group (2.05±0.11 nmol/L) compared to L (1.58±0.08 nmol/L) or P groups (1.70±0.08 nmol/L) ($P<0.01$). Completers did not differ from dropouts in marital status, parity, age and education.

Of the 297 participants randomised to the treatment groups, 203 commenced the treatments. One hundred and thirty young women completed the 12-week intervention. Of the 73 who discontinued, 33 stopped attending visits and could not be contacted while 24 cited work or family commitment issues as reasons for withdrawal (Figure 3.1). There was a trend towards a higher attrition rate in the L group (48%) compared to M (34%) or P (29%) groups among those who commenced the interventions although differences did not reach statistical significance ($P=0.08$).

Adherence to intervention

Based on pill counts, 86% in the M group and 87% in the P group took at least 80% of the tablets. Based on the self-reported pill diary, 95% of the M group and 94% of the P group took at least 80% of the tablets. Total energy intake decreased significantly in all groups, by 2799±455 KJ in the L group, 1437±388 KJ in the M group, and 1234±353 KJ in the P group ($P<0.01$). The decrease in energy intake in the L group was significantly greater than M or P groups (Table 3.1). Physical activity increased in all groups without group differences (366±191 MET-minutes/week for the combined group).

Adverse events

The treatments were generally well-tolerated. There were 6 reported adverse events in the M group (3 had gastrointestinal discomfort, 2 developed a rash, 1 could not be contacted further). Adverse events were also reported by 5 participants in the P group (2 had gastrointestinal discomfort, 1 had dizziness, 1 had chest pain, and 1 developed a rash). No treatment-related adverse events were reported in the L group.

Body weight

There was a significant time-by-group interaction for body weight when analysed using linear mixed models ($P<0.001$). Weight loss in the L group was significantly greater than that achieved by the M or P group ($P<0.001$) (Figure 3.2). Completers' and baseline-carried-forward analyses reported similar results for weight loss ($P<0.001$ for time-by-group). There was a wide range of responses in each treatment group. Intention-to-treat analysis showed that 46% of the participants in the L group who commenced the intervention had lost weight (>3% of baseline weight) compared to 12% in the M group and 11% in the P group ($P<0.001$) (Figure 3.3). On the other hand, 10% from the P group had gained weight throughout the 12-week study period, compared to 3% from the M group and none from the L group ($P<0.001$).

Waist circumference, fat mass, fat-free mass

There was a significant time-by-group interaction on waist circumference according to linear mixed models ($P<0.001$, Table 3.1). The L group (6%) had greater decrease in waist circumference compared to the M (2%) or P groups (2%) ($P<0.001$). L group had a significantly greater decrease in fat mass (16%) compared to M (3%) or P groups (2%) ($P<0.001$). Changes in fat-free mass were not significant by time or group. The completers'

and baseline-carried-forward analyses produced similar results for waist circumference ($P<0.05$ for time-by-group) and fat mass ($P<0.001$ for time-by-group).

Metabolic outcomes

No significant time-by-group interactions were seen on plasma lipids when analysed using linear mixed models (Table 3.1). Over the 12-week study period, the L group had a significant decrease in total cholesterol (6%), decrease in HDL cholesterol (6%), decrease in triglyceride (8%), and a decrease in LDL cholesterol (8%) ($P<0.05$), but these changes were not significantly different from M or P groups (Table 3.1). Completers' and baseline-carried-forward analyses similarly did not detect any significant time-by-group effects on lipids.

Significant time-by-group interactions were observed for insulin ($P=0.03$), glucose ($P=0.047$) and HOMA ($P=0.03$) (Table 3.1). Decrease in fasting glucose level (2%) in M group was significantly different to the P group ($P=0.02$), but not to the L group ($P=0.06$). Decrease in fasting insulin (18%) and HOMA (17%) in L group (18%) was significantly different to the P group ($P<0.05$) but not to the M group. Completers' and baseline-carried-forward analyses similarly reported a significant time-by-group effect for insulin ($P<0.05$), glucose ($P<0.05$) and HOMA ($P<0.05$). When weight was added as a covariate into the mixed models, time-by-group interactions were no longer significant for insulin, glucose and HOMA ($P>0.05$).

Mean baseline levels of ferritin, vitamin B12, folate, systolic blood pressure and diastolic blood pressure were all within the normal range. There were no significant time-by-group effects for ferritin, serum vitamin B12 and folate. While all groups experienced a decrease

in systolic and diastolic blood pressures, no significant group differences were seen. Completers' and baseline-carried-forward analyses produced similar results.

Sex hormones and hirsutism

Changes in testosterone were not different between groups (P=0.09). SHBG increased in all groups without significant time or group effect (Table 3.1). There was no time or group effects on FAI or the Ferriman-Gallwey scores. Completers' and baseline-carried-forward analyses produced similar results.

3.5 Discussion

This is the first prospective randomised trial to compare the effect of lifestyle intervention to metformin or placebo in healthy overweight or obese young women. The comprehensive lifestyle intervention produced greater weight loss compared to metformin. Metformin may be more effective than placebo in weight gain prevention. However, a trend towards higher attrition in the comprehensive lifestyle group suggests that longer term studies are required to determine the long term sustainability and effectiveness of these strategies in this group.

Previous studies have shown that metformin may reduce body weight and improve body composition [14, 27]. However, when all trials were considered, the effect of metformin on body weight is inconsistent. In the current study, metformin resulted in a modest weight loss of 1 kg over 12-weeks, which was not significantly different from placebo. However, metformin may be effective in short term weight gain prevention compared to placebo. Similar findings were recently reported in psychiatric patients receiving antipsychotic medications, which is also a high risk group for weight gain [260]. The role of metformin on weight gain prevention in young women could be investigated in longer term trials.

The current study found that comprehensive lifestyle advice resulted in greater weight loss compared to metformin or placebo in young women (mean age 28 years). This is consistent with the findings of the Diabetes Prevention Program conducted in older participants (mean age 51 years) [250]. Despite greater weight loss, the current study reported a trend towards higher levels of attrition in the comprehensive lifestyle group compared to the metformin or placebo groups. Such differential drop-out between the treatment groups was not reported by the Diabetes Prevention Program [250], possibly owing to younger participants in the current study. Younger age (<50 years) has been associated with greater attrition in weight loss intervention [134]. The mostly commonly cited reasons for withdrawal in the current study were related to family or work. Commitments in these areas are likely to place a high demand on the time availability of young women. Perceived time pressure has been reported as a potential barrier to healthy eating and physical activity among women [317]. Interventions that could be fitted around the busy schedules of young women should be investigated in the future.

This study found that metformin had greater effect in decreasing fasting glucose but lifestyle intervention produced greater improvement in fasting insulin and HOMA levels compared to placebo. These were no longer significant after correcting for weight loss, which suggests that improvements in these outcomes were at least in part due to weight loss achieved. The comprehensive lifestyle group showed a significant but small decrease in HDL, which was not significantly different to the changes seen in the other groups. Similar decrease in HDL cholesterol have been previously described in active weight loss phase whereas sustained weight loss leads to increased HDL cholesterol [318].

This study has several limitations. First, a substantive proportion of participants who registered for the trial did not attend any clinic visits. However, as these individuals were not aware of their allocation at the time of withdrawal, no bias was introduced by the pre-commencement drop outs. At commencement, the demographic and clinical characteristics across the groups were similar aside from testosterone. Another limitation of this trial relates to its short duration. It is not known if in a longer term metformin may exert a greater accumulated effect on weight loss, or that compliance with lifestyle program may falter over time resulting in a greater weight loss with metformin instead. These limitations need to be considered in interpreting the results of this trial.

To our knowledge, this is the largest trial on weight management in young women. We found that metformin may be effective in weight gain prevention, but lifestyle intervention was more effective than metformin in reducing body weight. However, we also found that young women are a challenging group in terms of retention in weight loss interventions. These findings suggest that population-specific research is required to develop appropriate weight management strategies for young women.

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Disclosure

The authors declared that no conflict of interest exists.

3.6 Figures and tables

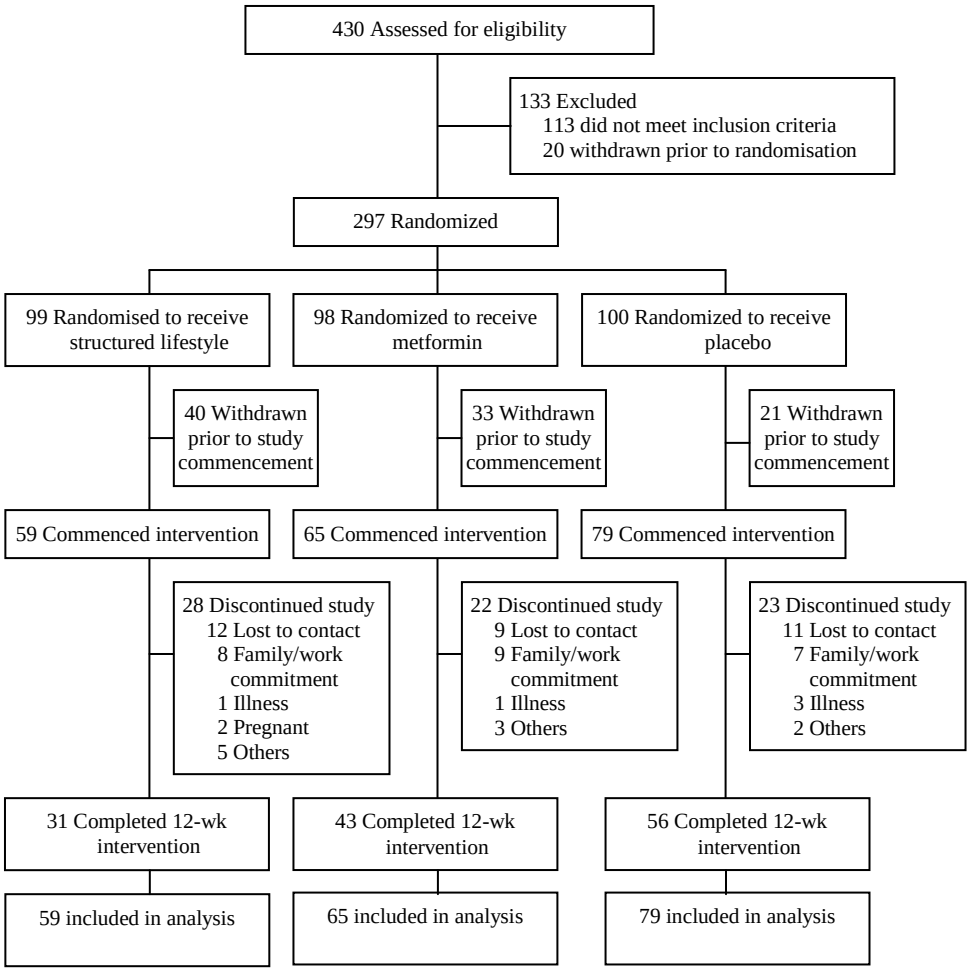

Figure 3.1. Flow diagram of participants' recruitment, randomization and completion of the interventions.

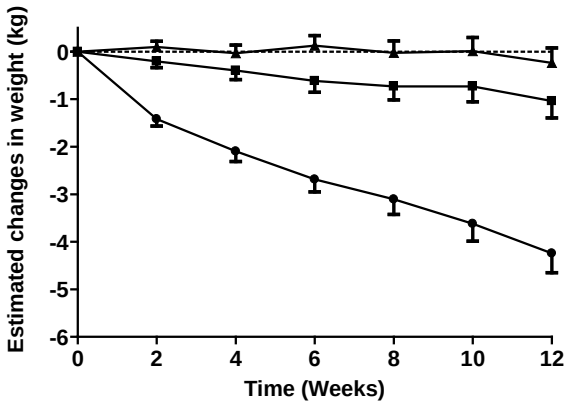

Figure 3.2 Estimated weight changes (± standard error) in participants randomised to comprehensive lifestyle program (circles, n=59), metformin plus general lifestyle advice (squares, n=65), or placebo plus general lifestyle advice (triangles, n=79). P<0.05 between changes in comprehensive lifestyle group compared to metformin and placebo groups.

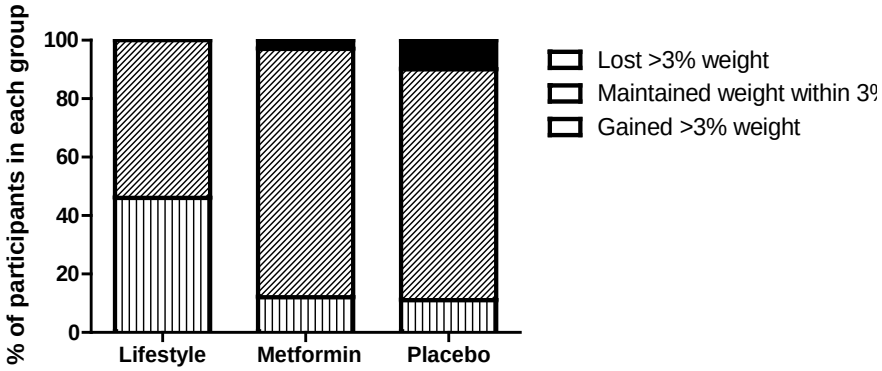

Figure 3.3 Weight outcomes of participants after 12-weeks on comprehensive lifestyle program (n=59), metformin (n=65), or placebo (n=79). P<0.05 for chi-square analysis.

Table 3.1 Estimated means and changes on clinical and metabolic outcomes[a]

	Baseline	Week 12	Change	P-value between groups
Weight, kg				<0.001
Comprehensive lifestyle	91.1 (1.9)	86.8 (1.9)[b]	-4.2 (0.4)[c]	
Metformin	93.7 (1.8)	92.6 (1.8)[b]	-1.0 (0.4)	
Placebo	91.4 (1.6)	91.2 (1.6)	-0.2 (0.3)	
BMI, kg/m^2				<0.001
Comprehensive lifestyle	32.4 (0.6)	30.6 (0.6)[b]	-1.7 (0.2)[c]	
Metformin	34.1 (0.6)	33.7 (0.6)[b]	-0.4 (0.1)	
Placebo	33.5 (0.6)	33.4 (0.5)	-0.1 (0.1)	
Waist, cm				<0.001
Comprehensive lifestyle	94.0 (1.5)	88.8 (1.6)[b]	-5.2 (0.6)[c]	
Metformin	97.2 (1.5)	95.1 (1.5)[b]	-2.1 (0.5)	
Placebo	94.2 (1.3)	92.1 (1.4)[b]	-2.1 (0.5)	
Fat mass, kg				<0.001
Comprehensive lifestyle	33.3 (1.3)	28.0 (1.4)[b]	-5.3 (0.7)[c]	
Metformin	34.7 (1.3)	33.9 (1.3)	-0.7 (0.7)	
Placebo	34.2 (1.1)	33.1 (1.2)	-2.2 (0.6)	
Fat-free mass, kg				0.11
Comprehensive lifestyle	56.7 (1.0)	57.4 (1.0)	0.7 (0.6)	
Metformin	59.0 (0.9)	58.6 (1.0)	-0.3 (0.5)	
Placebo	56.6 (0.8)	57.7 (0.9)	1.1 (0.4)	
Cholesterol, mmol/L				
Comprehensive lifestyle	5.00 (0.12)	4.71 (0.14)[b]	-0.28 (0.11)	0.20
Metformin	5.14 (0.12)	5.04 (0.13)	-0.10 (0.09)	
Placebo	4.92 (0.11)	4.88 (0.11)	-0.05 (0.08)	
HDL cholesterol, mmol/L				0.12
Comprehensive lifestyle	1.26 (0.04)	1.18 (0.05)[b]	-0.07 (0.03)	
Metformin	1.24 (0.04)	1.23 (0.04)	-0.01 (0.03)	
Placebo	1.24 (0.03)	1.26 (0.04)	0.01 (0.03)	
Triglyceride, mmol/L[d]				0.11
Comprehensive lifestyle	1.17 (0.03)	1.03 (0.03)[b]	-0.14 (0.03)	
Metformin	1.19 (0.02)	1.23 (0.03)	0.04 (0.02)	
Placebo	1.02 (0.02)	0.97 (0.02)	-0.05 (0.02)	
LDL cholesterol, mmol/L				0.50
Comprehensive lifestyle	3.18 (0.11)	3.02 (0.12)[b]	-0.15 (0.09)	
Metformin	3.30 (0.10)	3.20 (0.11)	-0.09 (0.08)	
Placebo	3.17 (0.09)	3.14 (0.10)	-0.02 (0.07)	
Fasting glucose, mmol/L				0.047
Comprehensive lifestyle	5.03 (0.06)	5.07 (0.07)	0.03 (0.05)	
Metformin	5.12 (0.06)	5.03 (0.06)[b]	-0.09 (0.04)[c]	
Placebo	5.14 (0.05)	5.18 (0.06)	0.04 (0.04)	
Fasting insulin, mU/L[d]				0.03
Comprehensive lifestyle	9.10 (0.03)	7.38 (0.04)[b]	-1.72 (0.03)[c]	
Metformin	9.10 (0.03)	8.51 (0.03)	-0.59 (0.03)	
Placebo	8.34 (0.03)	8.57 (0.03)	0.23 (0.02)	
HOMA[d]				0.04
Comprehensive lifestyle	2.03 (0.03)	1.65 (0.04)[b]	-0.38 (0.03)[c]	
Metformin	2.01 (0.03)	1.90 (0.04)	-0.17 (0.03)	
Placebo	1.90 (0.03)	1.96 (0.03)	0.07 (0.02)	

Ferritin, ng/ml[d]				0.90
Comprehensive lifestyle	45.08 (0.05)	40.09 (0.05)[b]	-4.99 (0.03)	
Metformin	59.29 (0.04)	54.08 (0.05)	-5.22 (0.02)	
Placebo	52.00 (0.04)	47.75 (0.04)	-4.25 (0.02)	
Vitamin B12, pmol/L				0.65
Comprehensive lifestyle	284.63 (15.31)	272.75 (18.28)	-11.87 (14.62)	
Metformin	283.32 (14.71)	287.43 (16.34)	4.10 (12.47)	
Placebo	299.35 (13.34)	290.61 (14.53)	-8.73 (10.94)	
Folate, nmol/L				0.81
Comprehensive lifestyle	18.06 (1.16)	18.25 (1.43)	0.20 (1.26)	
Metformin	17.45 (1.11)	17.92 (1.25)	0.47 (1.08)	
Placebo	16.96 (1.00)	16.54 (1.11)	-0.43 (0.95)	
Testosterone, nmol/L				0.09
Comprehensive lifestyle	1.58 (0.10)	1.45 (0.11)	-0.13 (0.08)	
Metformin	2.05 (0.10)	1.84 (0.10)[b]	-0.22 (0.07)	
Placebo	1.70 (0.08)	1.69 (0.09)	-0.01 (0.06)	
SHBG, nmol/L[d]				0.48
Comprehensive lifestyle	59.29 (0.04)	66.07 (0.05)	6.78 (0.03)	
Metformin	41.69 (0.04)	42.36 (0.04)	0.68 (0.03)	
Placebo	52.36 (0.04)	57.28 (0.04)	4.92 (0.02)	
Systolic BP, mmHg				0.80
Comprehensive lifestyle	116.5 (1.2)	114.1 (1.6)	-2.4 (1.5)	
Metformin	117.3 (1.2)	115.6 (1.4)	-1.7 (1.3)	
Placebo	116.4 (1.1)	113.6 (1.2)[b]	-2.9 (1.1)	
Diastolic BP, mmHg				0.66
Comprehensive lifestyle	65.2 (1.0)	62.9 (1.3)	-2.3 (1.3)	
Metformin	64.9 (1.0)	62.5 (1.1)[b]	-2.4 (1.1)	
Placebo	64.6 (0.9)	63.4 (1.0)	-1.2 (1.0)	

[a]Data presented as estimated means (SEM) obtained from linear mixed effect models, which included all data points contributed by the non completers (n=203).
[b] P<0.05 between baseline and Week 12.
[c] P<0.05 compared to changes in placebo.
[d]Data was log transformed for analysis. The presented estimated means were anti-log transformed.

Chapter 4 The psychological effects of prescriptive vs general lifestyle advice for weight loss in young women

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Abbreviated title: Prescriptive lifestyle advice for weight loss in young women

Keywords: Prescriptive, psychological effects, young women

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STATEMENT OF AUTHORSHIP

Siew Lim (Candidate)

Developed protocol, prepared ethics application, delivered dietary interventions, assisted with laboratory analyses, performed statistical analyses, interpreted data, wrote manuscript and acted as corresponding author.

Signed……..Date……

Peter Clifton

My contribution to this paper involved:

Assistance with statistical analyses, data interpretation and manuscript evaluation.

I give consent to Siew Lim to present this paper for examination towards the Doctor of Philosophy

Signed……..Date……

Robert Norman

My contribution to this paper involved:

Assistance with statistical analyses, data interpretation and manuscript evaluation.

I give consent to Siew Lim to present this paper for examination towards the Doctor of Philosophy

Signed……..Date……

Manny Noakes

My contribution to this paper involved:

Contribution to study design and assistance with statistical analyses, data interpretation and manuscript evaluation.

I give consent to Siew Lim to present this paper for examination towards the Doctor of Philosophy

Signed……..Date……

4.1 Abstract

This study aimed to investigate the effects of prescriptive lifestyle advice with quantifiable dietary and physical goals compared to general lifestyle advice on weight and psychological outcomes in overweight or obese young women. A total of 203 women (BMI 33.3±0.3 kg/m^2, age 28±0.3 years) received either prescriptive or general lifestyle advice for weight loss over 12 weeks. Linear mixed models found that the prescriptive lifestyle advice group had significantly greater weight loss (4.2±0.4 kg vs 0.6±0.2 kg, P<0.001) compared to the general lifestyle advice group. However, the prescriptive lifestyle advice group also had greater attrition (48% vs 31%, P<0.05) compared to the general lifestyle advice group. Linear mixed models found that the prescriptive lifestyle advice group had greater improvement in psychological distress (-3.0±0.04 vs -1.1±0.01, P<0.05) and in self-esteem (+3.2±0.8 vs -0.04±0.04, P<0.001) compared to the general lifestyle advice group. Changes in psychological distress and self-esteem remained significantly different between groups after correcting for weight loss. Food cravings decreased significantly over time without group differences (P<0.001 for time). Weight locus of control remained unchanged in either group (P>0.05). Drop-outs had greater baseline psychological distress (15.1±0.7 vs 12.5±0.4, P<0.01) and higher food cravings (2.42±0.07 vs 2.24±0.05, P=0.049) compared to completers. In conclusion**,** a prescriptive approach is associated with greater weight loss and greater improvements in psychological outcomes in young women compared to general lifestyle advice. However, these quantitative targets should be accompanied with qualitative advice on how they could be met in a variety of circumstances.

4.2 Introduction

Food restriction such as consuming less fat or reducing energy intake is the most popular method for weight control [131, 319-321]. Although effective in short term weight loss, food restriction has been criticized for eliciting adverse psychological effects such as impaired cognitive function, slower reaction time, poorer immediate recall of words and increased distractibility [199, 322, 323].

Non-dieting approaches may reduce the negative effects of food restriction by shifting the focus from prescriptive energy restriction (e.g. 1430 kcals/day) to general lifestyle advice (e.g. nutritionally balanced diet, increased physical activity). One study found that a non-dieting intervention resulted in better improvements in depression and self-esteem compared to a prescriptive approach involving energy restriction [201]. In the 'non-dieting' interventions, dietary modification was achieved through general, health-focused advice instead of a conventional calorie-focused approach [200, 201]. In contrast, the traditional behavioral modification approach focuses on quantitative goals such as reducing energy intake by 500kcal a day to achieve weight loss of 0.5 kg a week. By shifting its focus away from weight loss and energy restriction, non-dieting interventions usually achieve minimal weight loss [200, 201, 324-326]. This reduces the metabolic benefits of non-dieting interventions. It is unclear if the introduction of weight loss as a treatment goal to a general or non-dieting approach would eliminate its psychological advantages.

The main objective of this study was to compare the effect on body weight and psychological outcomes of prescriptive lifestyle advice compared to general lifestyle advice for weight loss in overweight and obese young women. We hypothesized that prescriptive lifestyle advice would result in greater weight loss, greater psychological improvements and lower attrition compared to general lifestyle advice.

4.3 Methods

A total of 297 overweight or obese young women (age 17 to 37 years; body mass index [BMI] 25.1 kg/m^2 to 44 kg/m^2) were recruited from the metropolitan area of Adelaide, Australia, through newspaper and television advertisement. Exclusion criteria include significant illnesses (eg, cancer, thyroid disease etc), pregnancy or lactation; or rapid weight loss (>0.5kg/week). This study was approved by the CSIRO Human Nutrition and University of Adelaide Human Research Ethics Committees. Data was collected from participants who provided written informed consent.

Participants were block-matched for age, BMI and menstrual irregularity and then randomized using the Clinstat software (1996, St George's Hospital Medical School, London, United Kingdom) to metformin plus general lifestyle advice, placebo plus general lifestyle advice, or prescriptive lifestyle advice for 12 weeks. Participants in the metformin or placebo groups received their allocated treatment following a double-blind procedure. As both metformin and placebo groups achieved similar average weight loss and had similar psychological outcomes, these groups were combined and regarded as the general lifestyle advice group in this study.

Body weight, food intake and psychological variables were measured at weeks 0 and 12. Food intakes were assessed through the analyses of three-day weighed food diaries (two week days and one weekend) (Foodworks, version 5.0, Xyris Software 2007, Highgate Hill, Australia) by a registered dietitian. Physical activity levels were assessed using the short format of the International Physical Activity Questionnaire [312]. Body weight was measured using a calibrated electronic digital scale (Mercury, AMZ 14, Tokyo, Japan).

Body height was measured at week zero using a stadiometer (SECA, Hamburg, Germany). Psychological distress was assessed using the 12-item General Health Questionnaire (GHQ) [294]. Self-esteem was measured using the Bachman revision of Rosenberg's Self-Esteem scale [327, 328]. Weight locus of control was measured using the Dieting Beliefs Scales [329]. Food cravings were measured using a modified version of the Food Craving Inventory [281].

All participants visited a food and nutrition professional at weeks 0, 2, 4, 6, 8, 10, 12 to review weight loss progress. Online newsletters on cognitive-behavioral topics such as stimulus control, coping with relapse and other related topics were sent to all participants every 2 weeks.

Prescriptive lifestyle advice

Participants were advised to follow a hypocaloric high protein diet (1430 kcal; 40% carbohydrate, 30% protein, 30% fat) and a structured exercise program (gradual increase in physical activity up to 60 minutes per day) [153, 310]. An online forum was developed to facilitate peer support. Participants were advised to keep food and exercise checklists daily, which were reviewed every two weeks by a qualified food and nutrition professional. Participants in the prescriptive lifestyle advice group did not receive any tablets from the study.

General lifestyle advice

General lifestyle advice was administered using the Australian Guide to Healthy Eating and National Physical Activity Guidelines for Australian Adults developed by the Australian Department of Health and Aging [308, 309]. Participants were encouraged to have a nutritionally balanced diet through frequent consumption of nutritious food (e.g.

fruits and vegetables) and the avoidance of 'extra' foods (e.g. chocolate, chips). Participants were also advised to achieve at least 30 minutes of moderate intensity physical activity on most days in the week. Specific details such as energy restriction, types of physical activity (i.e. aerobic or resistance), the definition of 'moderate intensity' and the total duration of physical activity per week were not provided. All participants in the general lifestyle advice group were instructed to consume the metformin or placebo tablets provided by the study.

Baseline differences between treatment groups and between completers and non completers were analyzed using one-way analysis of variance. Attrition rate between the groups was compared using Chi-square analysis. In the primary analyses, treatment outcomes were assessed using linear mixed models. After a significant time-by-treatment effect was found, weight change was added as a covariate to determine the effect of weight loss on psychological changes. In the secondary analyses, completers and baseline-carried-forward analyses were conducted using repeated measure analysis of variance. Analyses of covariance were performed to assess changes in outcomes correcting for baseline values. All calculations were performed using SPSS for Windows 16.0 (version 16.0, 2007, SPSS Inc, Chicago, IL). All data are presented as estimated mean$\pm$standard error of the mean.

This study had more than 90% power to detect a significant difference of 4 kg in weight loss, a significant difference of 2.2 unit of the scores in psychological distress changes, a significant difference of 1.0 unit of the scores in self-esteem changes, a significant difference of 6.5 unit of the scores in weight locus of control changes, and a significant difference of 0.7 unit of the scores in food cravings changes between the groups. These calculations assumed an alpha of 0.05.

4.4 Results and discussion

The participants had a mean age of 23±0.3 years and a mean BMI of 33.3±0.3 kg/m^2. Fifty percent of the participants were married or living with a significant other, 46% were never married, and 4% were separated. Thirty-nine percent had a university degree; 59% had diploma, trade or high school qualifications; and 2% had no formal qualifications. Sixty-six percent had no children. Of the 203 participants who commenced the treatments, 130 of them completed the 12-week intervention (Figure 4.1). Attrition was significantly higher in the prescriptive lifestyle advice group (48%) compared to the general lifestyle advice group (31%) (P<0.05). Baseline characteristics were not significantly different between treatment groups. Completers and drop-outs did not differ in age, BMI, marital status, education, parity and weight locus of control. However, drop-outs had significantly higher psychological distress (15.1±0.7 vs 12.5±0.4, P=0.001) and higher food cravings (2.42±0.07 vs 2.24±0.05, P=0.049) at baseline. There was also a trend for lower baseline self-esteem (38.4±0.9 vs 40.3±0.6, P=0.06) in the dropouts compared to the completers. When stratified according to the treatment groups, dropouts in the prescriptive lifestyle advice group had more internal weight locus of control compared to the completers (71.14±1.36 vs 66.87±1.15, P=0.019). In the general lifestyle advice group, dropouts had higher baseline psychological distress (15.21±0.92 vs 12.33±0.49, P=0.003) and higher baseline food cravings (2.44±0.10 vs 2.18±0.06, P=0.023).

At 12 weeks, the linear mixed models found that the prescriptive lifestyle advice group lost 4.2±0.4 kg while the general lifestyle advice group lost 0.6±0.2 kg (P<0.001). There was a significantly greater decrease in self reported total energy intake in the prescriptive lifestyle advice group (666±108 kcal) compared to the general lifestyle advice group (314±62 kcal) (P<0.01) according to mixed model analyses. Physical activity increased in both groups without group differences (366±191 MET-minutes/week). Analyses which

included only participants who successfully completed the study produced similar results as the mixed models. The baseline-carried-forward analyses reported similar results for weight loss ($P<0.001$) and physical activity ($P>0.05$) but the time-by-treatment effect was only marginally significant for energy intake ($P=0.055$).

Mixed model analyses found a significant time-by-treatment effect in psychological distress and self-esteem (Table 4.1). The prescriptive lifestyle advice group had a greater decrease in psychological distress (Table 4.1, $P<0.05$) and a greater improvement in self-esteem (Table 4.1, $P<0.001$) compared to the general lifestyle advice group. After correcting for weight loss in the mixed models, the time-by-treatment effect for psychological distress ($P<0.05$) and self-esteem ($P<0.01$) remained significant. Analyses which included only participants who completed the study reported similar results for psychological distress ($P<0.05$), self-esteem ($P<0.01$). The baseline-carried-forward analyses yielded similar results for self-esteem ($P<0.01$) but not for psychological distress, in which the time-by-treatment effect were no longer significant ($P=0.08$). Similar results were obtained with analysis of covariance which corrected for the baseline values of each variable.

Mixed model analyses found that food cravings decreased significantly over time in both groups without a significant time-by-treatment effect (Table 4.1). Analyses which included only those who completed the study and baseline-carried-forward analyses showed similar results for food cravings. Weight locus of control remained unchanged in either group in all analyses ($P>0.05$).

These results indicate that prescriptive lifestyle advice on quantitative approaches to achieving an energy deficit resulted in greater weight loss and psychological improvements

compared to general lifestyle advice in young women who completed the program. However, this approach was also associated with greater attrition.

The structured, prescriptive lifestyle advice resulted in greater weight loss than general lifestyle advice which is consistent with previous intervention studies [200, 201, 324-326]. Participants in both groups received similar cognitive-behavioral lessons through emails and were seen by a dietitian at the same frequency throughout the study period. The prescriptive lifestyle advice group also had the opportunity for peer support through online forum discussion but low utilization of the website (less than 30% of the participants used the forum) suggests that this did not contribute to the treatment outcomes. Although it was intended that both groups were seen for the same duration at the review visits, the prescriptive lifestyle group received more detailed quantitative advice on lifestyle modification at the individual counseling sessions. This may explain the success associated with the prescriptive approach.

This study found that a structured, prescriptive approach to lifestyle modification involving energy restriction results in greater improvement in psychological outcomes compared to a general, qualitative approach. This finding also adds to the increasing evidence that a combination of diet, exercise and behavioral modification therapy produces positive psychological effects [330-333]. The current findings are in contrast with studies which reported that non-dieting approaches resulted in psychological outcomes similar to or better than that of dieting approaches [200, 201, 325, 334]. The current study differed from these studies in that weight loss was an explicit treatment goal in both interventions and size-acceptance was not part of the general lifestyle intervention [200, 201].

Consistent with previous findings, the prescriptive, energy restricted approach resulted in greater attrition compared to the general approach [200, 201]. Previous studies suggest that participants receiving prescriptive advice were more likely to express feelings of failure. They were also less likely to report that the program helped them feel better about themselves compared to the group receiving general advice, which may explain their withdrawal from the study [200, 201]. In contrast, the current study found that the prescriptive approach had higher attrition despite achieving greater weight loss and psychological improvements. Greater attrition with the prescriptive approach in this study could be due to its rigid structure which may be less compatible with the lifestyles of young women. A study comparing the eating patterns of American adults between 1971-1975 and 1999-2002 reported a trend towards more unstructured eating patterns especially among women [335]. This may explain poorer long term compliance to structured lifestyle interventions among younger women. Prescriptive lifestyle advice could be implemented with strategies to achieve greater flexibility to meet the needs of this group.

There are several limitations in this study. First, a substantive proportion of participants who registered for the trial did not attend any clinic visits. However, as these individuals were not aware of their allocation at the time of withdrawal, no bias was introduced by the pre-commencement drop outs. At commencement, the demographic and psychological characteristics were similar across the groups. Second, post-intervention psychological outcomes could only be obtained from participants who completed the intervention. It is unclear if the improvement in psychological outcomes were limited to the completers. Third, causal relationships between psychosocial changes and weight loss could not be verified from the cross-sectional analysis. Fourth, the effect of taking tablets on dietary compliance in the general lifestyle advice group is unclear. The potential effect of metformin on hunger reduction was explained to the all participants prior to randomization

as one of the mechanisms by which metformin may induce weight loss. Thus, the general lifestyle advice group could be more successful in restraining themselves due to placebo effect. However, this was not observed because there was insignificant weight loss observed in this group. On the other hand, they may be less motivated to modify their lifestyles if they perceive the tablets as the primary means to weight loss.

4.5 Conclusions

This is the first trial to compare the psychological outcomes of weight loss through a prescriptive approach compared to general lifestyle advice in young women. The prescriptive approach resulted in significantly greater weight loss and greater improvements in psychological outcomes in women who completed the program. However, the rigidity of this approach also resulted in greater attrition. Prescriptive lifestyle advice implemented with strategies for flexibility may be considered for weight loss in young women. During weight loss counseling, food and nutrition professionals should provide quantitative details of recommended servings for each food group as targets to assist clients in implementing the advice. These targets should be accompanied by qualitative advice on how to meet them in a variety of circumstances. Although such an approach has not yet been formally evaluated for effectiveness, it is important to acknowledge that younger clients may have eating patterns that may not be as structured as those of older adults.

4.6 Figures and tables

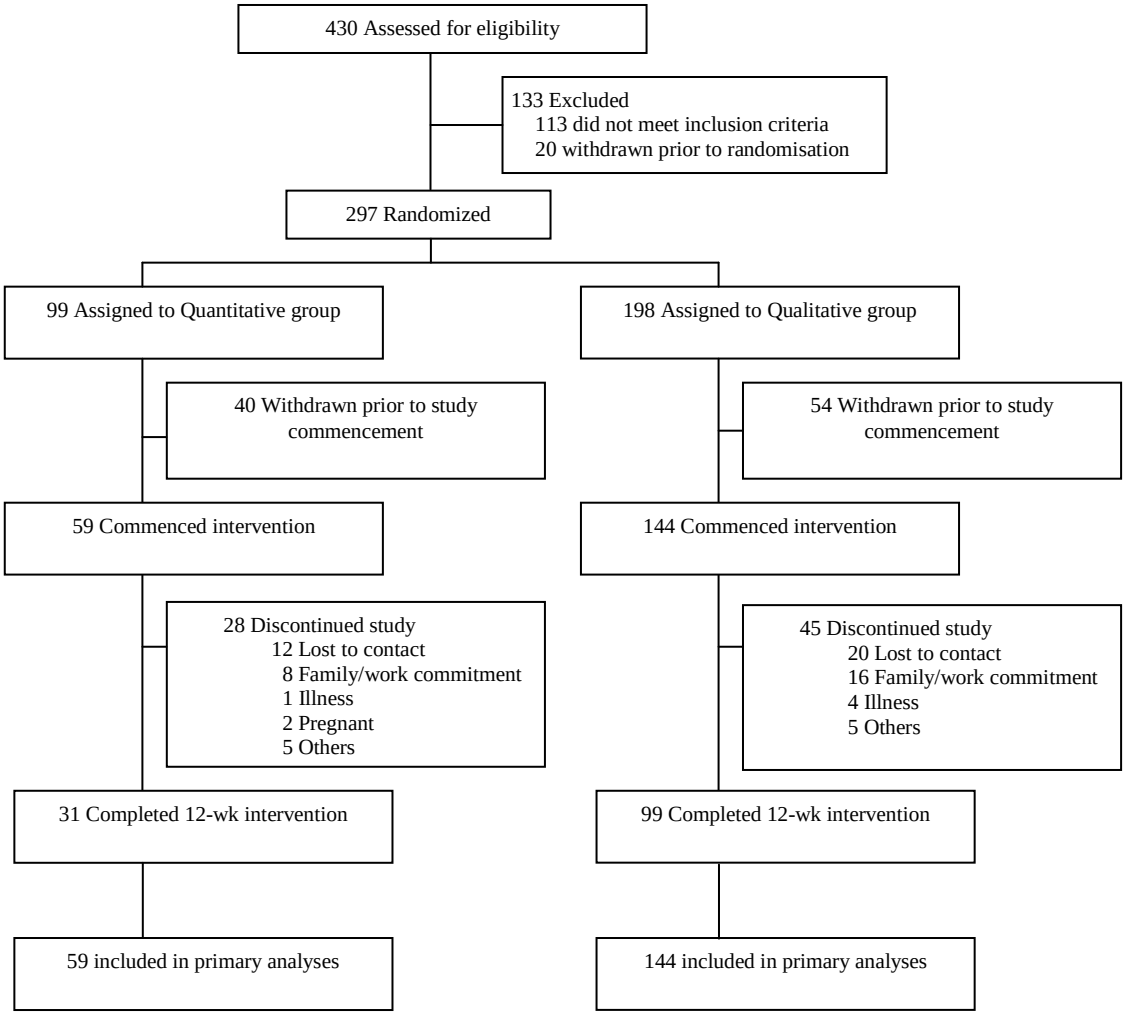

Figure 4.1 Flow diagram of participants' recruitment, participation and completion of the interventions.

Table 4.1 Estimated means and changes for psychological measures for the prescription lifestyle advice (PLA) group (n=59) and the general lifestyle advice (GLA) group (n=144)

	Baseline[a]	Week 12[a]	Change[a]	P-value for changes across time	P-value for time-by-treatment
Psychological distress score (GHQ)[b]					0.013
PLA group	13.95 (0.70)	10.91 (0.90)	-3.04 (0.89)	<0.001	
GLA group	13.21 (0.45)	12.37 (0.52)	-0.84 (0.52)	0.054	
Self-esteem (RSE-B)[c]					<0.001
PLA group	38.66 (0.87)	41.85 (1.01)	3.19 (0.77)	<0.001	
GLA group	39.97 (0.57)	39.93 (0.61)	-0.04 (0.04)	0.929	
Weight locus of control (DBS)[d]					0.947
PLA group	69.00 (1.00)	67.98 (1.27)	-0.92 (1.21)	0.447	
GLA group	67.61 (0.65)	66.78 (1.27)	-0.83 (0.70)	0.238	
Food cravings (FCI)[e]					0.261
PLA group	2.42 (0.08)	2.10 (0.10)	-0.32 (0.10)	0.001	
GLA group	2.26 (0.05)	2.08 (0.06)	-0.19 (0.06)	0.001	

Chapter 5 Long term weight management through internet program in young women

5.1 Abstract

Background: Young women are at high risk of weight gain yet few studies have examined the long term effectiveness of weight loss programs in this group. Young women are one of the greatest users of internet which provides a potential medium to deliver weight loss programs and provide longer term social support. This chapter examines the effect of an internet delivered weight loss program on body weight, energy intake and physical activity in young women, and the relationship between the frequency of website access and weight loss.

Methods A total of 203 young women (BMI 33.4±0.3 kg/m^2, age 27.8±0.3 years) received qualitative lifestyle advice with in-person support (QL) or quantitative lifestyle advice with in-person support for 12-weeks (QT), followed by quantitative lifestyle advice delivered via the internet for 36 weeks. Body weight, energy intake and physical activity were measured at baseline, week 12, week 24 and week 48.

Results: Mixed model analyses found that the QT group had greater weight loss compared to the QL group from baseline to week 48 (-4.8±0.8kg vs -1.3±0.4 kg, $P<0.0005$). Changes from week 12 to week 48 were not significantly different between the groups ($P>0.05$). Utilisation of the website was low, with 10% of the completers accessing the information pages at least once a month and 20% of the completers accessing the forum at least once a month. Frequency of website access did not predict weight loss ($P>0.05$). A total of 53 (26%) participants completed the intervention. Those who were married or had children were more likely to drop out of the program. A post-intervention survey showed low adherence to the self monitoring components of the program with only 53% of the

participants weighing themselves at least once a week, 18% recording their dietary intake at least weekly and 14% recording their physical activity levels at least weekly.

Conclusions: The internet-based weight loss program quantitative lifestyle advice was effective in maintaining weight loss over 36 weeks. Utilisation of the website was low and the frequency of access did not predict weight loss. Attrition was high especially among those who were married or had children. Further developments that address the specific barriers in young women are required to improve the sustainability of the internet-based quantitative lifestyle intervention in this group.

5.2 Introduction

Internet-based weight loss programs have been shown to be effective in maintaining long term weight loss in older adults [203, 204, 336]. The effectiveness of internet-based weight loss programs was further enhanced by the addition of behavioural support tools such as weight charts, food diary and exercise diary [183, 185]. However, internet-based interventions may be less effective among younger participants. A study conducted in adolescents found that an internet-based weight loss program resulted in body fat loss in the first 6 months, but fat mass was regained in the following 18 months due to reduced use of the website overtime [184, 337]. The long term effectiveness of internet-based weight management program in young women is not known.

While the internet provides an alternate medium to deliver long term support in weight management, decreased website usage over time has been previously seen in internet-based weight loss programs [337-339]. One study suggested that continuous use of technology-based behavioural intervention resulted in significantly greater weight loss compared to intermittent use [340]. As internet-based weight loss interventions have not been investigated in young women, it is unclear how often the website would be accessed by this group, and if the frequency of access would be related to weight outcomes.

In Chapter 4, we have described the weight outcomes of a cohort of young women who received either quantitative (i.e. prescriptive) lifestyle advice or qualitative (i.e. general) lifestyle advice for a period of 12 weeks. The current chapter reports on their weight loss progress in the following 36 weeks during which quantitative lifestyle advice was administered to all participants through the internet.

The primary aim of this study was to describe the effect of the internet-based program on long term weight outcomes, energy intake and physical activity in young women. The secondary aim of this study was to investigate if greater frequency of access to the website would be associated with greater weight loss. We hypothesised that the internet-based program would maintain the weight loss achieved in the first 12 weeks. We also hypothesised that those who accessed the website more frequently would have greater weight loss.

5.3 Methods

Subjects

Participants were recruited as described in Chapter 4. All participants who commenced the intervention at baseline were included in the primary analysis of the study to determine the effect of the internet-based program on weight loss, energy intake and physical activity. Participants who provided information on the frequency of website access were included in the secondary analysis of the study, which was to determine the effect of frequency of website access on weight outcomes. This study was approved by the CSIRO Human Nutrition and Adelaide University Human Ethics Committee Boards. Data was collected from participants who provided written informed consent.

Study design

Participants received either qualitative lifestyle advice or quantitative lifestyle advice through in-person clinic visits in the first 12 weeks, as described in Chapter 4. From week 13 to 48, all participants received quantitative lifestyle advice based on the CSIRO Total Wellbeing Diet via the internet.

This study was conducted on an outpatient basis over 48-weeks. All participants attended the CSIRO outpatient clinic every fortnight in Phase I (week 0 to 12), and at weeks 24 and 48 in Phase II (week 13 to 48) (Table 5.1). Participants completed 3–day weighed food diaries (2 week days and 1 weekend) at weeks 0, 12, 24 and 48 which were analysed using Foodworks (Xyris Software 1998, Highgate Hill, Australia). Physical activity levels were assessed using the short format of the International Physical Activity Questionnaire collected at weeks 0,12, 24 and 48 [312].

QT group

At baseline, the QT group received intensive in-person support on quantitative lifestyle advice, which included a combination of energy restriction, physical activity, behavioural support and social support as described in Chapter 4. In addition, each participant in the QT group were also given a unique login and password at week 0 to access a self-directed website, which included dietary and exercise information from the manual, a weight and waist tracker, and a forum for peer support. Participants received electronic newsletters every fortnight in Phase I and monthly in Phase II through email on cognitive-behavioural topics such as stimulus control, coping with relapse, managing social cues, controlling negative thoughts and other related topics. Participants met with a dietitian to discuss progress in weight loss every fortnight in Phase I and at Weeks 24 and 48 in Phase II.

QL group

In Phase I, the QL group received in-person support on *qualitative lifestyle advice* as described in Chapter 4. At week 13 (ie the commencement of Phase II), participants in the QL group were introduced to the quantitative lifestyle advice through the website described for the QT group. Participants in the QL group received a manual and unique

login and password to access the program website in a single face-to-face session with a dietitian. As with the QT group, participants in the QL group received electronic newsletters on cognitive-behavioural topics every fortnight in Phase I and every month in Phase II and met with a dietitian every fortnight in Phase I and at Weeks 24 and 48 in Phase II to discuss weight loss progress.

Anthropometric measure

Body weight was measured as previously described (see Chapter 4).

Demographic and internet-related characteristics

At baseline, demographic characteristics such as age, marital status, education level were obtained. Participants were also asked to provide information on their usual location for accessing internet for personal use, their comfort level with using the internet, and their computer abilities.

Frequency of website access and behavioural measures

At week 48, a questionnaire was administered to determine the frequency of website access and behavioural changes in young women. Utilisation of the various components in the intervention was assessed in four questions (eg *how often did you access the study website).* Response options were *never, less than once a month, once a month, few times a month, weekly, more than once a week.* There were three questions on goal-setting (eg *how often did you set yourself a specific exercise goal eg 2 hour a week*). Response options were *I did not have specific exercise goals, less than once a month, monthly, fortnightly, weekly.* Frequency of self monitoring was assessed in three questions (eg *how often did you weigh yourself*). Response options were *less than once a week, once a week, once every*

few days, once a day, more than once a day. Two questions assessed lifestyle planning behaviours (eg *how far ahead do you usually plan your meals*). Response options were *further than a week ahead, a week ahead, one to several days ahead, on the day itself, I don't plan my meals*).

Statistical analyses

Baseline differences between treatment groups and between completers and non completers were analysed using one-way ANOVA. Attrition rate between the groups was compared using Chi-square tests. In the primary analyses, changes from baseline to week 48 and changes from week 12 to week 48 were assessed using linear mixed models [315]. Mixed models assumed that data were missing at random. Time, treatment and time-by-treatment effects were included as fixed factors in the models. Completers' and last-observation-carried-forward analyses were conducted using repeated measure ANOVA. Weight loss differences between frequent users (i.e. those who accessed the study website at least once a month) and occasional users (i.e. those who accessed the study website less than once a month) were analysed using analysis of covariance, with weight loss in Phase 1 as a covariate. Predictors of weight loss were determined using linear regression. Variables entered as predictors include age, BMI, psychological measures, internet-related characteristics, and adherence behaviours obtained in the questionnaires. All calculations were performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, IL, USA). A P-value of less than 0.05 is considered statistically significant. Unless otherwise specified, all data are presented as estimated mean $\pm$ SEM.

5.4 Results

Participants

The characteristics of participants were described in Table 5.2. A total of 53 participants completed the 48 weeks intervention (Figure 5.1). Attrition rate by week 48 was high (159/203; 78%) without significant differences between the groups (Table 5.4). At 48 weeks, completers and dropouts did not differ with baseline age, psychological distress, self-esteem, location of internet access (ie home, work or other places), comfort with internet and computer ability. However, dropouts by week 48 had higher baseline BMI (33.9 ± 0.39 vs 31.8 ± 0.62, P=0.04), were more likely to be married (81% of married participants dropped out compared to 67% of single participants, P=0.036) and more likely to have at least one child (86% of those who had at least one child dropped out compared to 68% of those who did not have any children, P=0.007).

Body weight

At week 12, QT group had significantly greater weight loss compared to the QL group (Table 5.3). A significant time-by-treatment effect was also observed for body weight from baseline to week 48 according the mixed model analysis (P<0.0005), in which QT group had greater weight loss compared to the QL group (Table 5.3, Figure 5.2). Completers analysis similarly found that weight loss in the QT group were significantly greater than weight loss in the QL group (-6.9 ± 1.3 kg vs -1.2 ± 1.1 kg, P=0.013). Last-observation-carried-forward analysis also found a significant time-by-treatment effect for weight loss (-3.3 ± 0.5 kg vs -0.7 ± 0.3 kg for QT and QL group respectively, P<0.0005). Changes from week 12 to week 48 were not significantly different between the groups (P>0.10 for time-by-treatment effect by mixed models analysis, completers analysis and last-observation-carried-forward analysis).

Energy intake and physical activity

At week 12, QT group had significantly greater decrease in energy intake compared to the QL group, but physical activity increased in both groups without differences. A significant time-by-treatment effect was reported for both energy intake (P=0.005) and physical activity (P=0.02) from baseline to week 48 according to mixed model analysis. At week 48, the QL group had a greater decrease in energy intake and greater increase in physical activity from baseline compared to the QT group (Table 5.3). Changes from week 12 to week 48 were also found to have significant time-by-treatment effects for both energy intake (P=0.009) and physical activity (P=0.022) according to mixed model analysis. Completers' and last-observation-carried-forward analyses did not find significant time-by-treatment effects for energy intake and physical activity for changes between baseline and week 48 (P>0.05). For changes between week 12 and week 48, completers' analysis found a significant time-by-treatment effect for energy intake (P=0.038) but not for physical activity (P>0.05) while last-observation-carried-forward analysis found significant time-by-treatment effects for both energy intake (P=0.001) and physical activity (P=0.043)

Usage of the internet program

At week 48, seventy percent of the completers reported having accessed the diet and exercise information pages on the study website at least once in the past 24 weeks, with 10% having accessed these pages at least once a month. Half of the participants (53%) accessed the forum at least once in the past 24 weeks, with 20% accessed the forum at least once a month. Most of the participants (88%) have read the monthly electronic newsletter, of which 65% reported having read them on a monthly basis. None of these variables predicted weight change. Similarly, analyses of covariance found that weight change from week 12 to week 48 did not differ between frequent users and occasional users of the

information pages, forum, or newsletter after correcting for weight loss achieved in Phase I ($P>0.05$).

Goal-setting, self-monitoring, and planning

Most of the participants who completed the intervention had a specific weight loss goal (67%), dietary goal (78%) and physical activity goal (82%). About half of the participants (53%) weighed themselves at least once a week. Most of them did not monitor their diet and physical activity, with only 18% recording their dietary intake and 14% recording their physical activity levels at least once a week. About half of the participants planned their meals and physical activity ahead of time: 53% planned their meals at least a day ahead, and 49% planned their activities at least a day ahead. None of these behaviours predicted weight change.

5.5 Discussion

Internet weight loss interventions have been shown to be effective in older adults but their efficacy in young women is not known. In this study, we found that an internet-based weight loss program with quantitative lifestyle advice administered by a research institute was successful in maintaining weight loss in young women for 36 weeks, although attrition was high especially among those who were married or had children.Overall website usage was low and the frequency of access did not predict weight loss.

Both groups successfully maintained a significantly lower body weight compared to baseline by week 48. A net weight loss over the period of 48 weeks in overweight and obese young women is a significant achievement considering their high risk for weight gain [3, 5, 9]. Previously, a weight gain prevention program conducted in young women at

risk of weight gain (i.e. with at least one obese parent) reported that the no intervention control group gained 2.6 kg in 1 year [142]. The current finding suggests that an internet-based weight management program administered by a research institute may be efficacious in preventing weight gain in young women.

In the current study, the group which received quantitative lifestyle advice from baseline to week 12 achieved a significantly greater weight loss by week 48, when compared to the group which received qualitative lifestyle advice in the first 12 weeks. Weight change from week 12 to week 48 did not differ significantly between the groups, suggesting that the greater weight loss seen in the quantitative lifestyle advice group at week 48 was due to their greater weight loss in the first 12 weeks of intervention. This is consistent with past observation that the pattern of weight regain is independent of the initial weight loss achieved so that those who with greater weight loss initially would sustain a greater weight loss for up to one year after treatment [341]. Thus, having more intensive initial treatment to induce greater initial weight loss could result in better weight outcomes in the medium term.

The group which received qualitative lifestyle advice in the first 12 weeks reported greater decrease in energy intake and greater increase in physical activity from week 12 to week 48. Despite this, their weight loss over this period was not greater than the group which received quantitative lifestyle advice in the first 12 weeks of the study. This suggests a preferential misreporting of energy intake and physical activity by the qualitative lifestyle advice group. It is known that those with greater BMI are more likely to underreport their energy intake [342]. At week 12, the qualitative advice group had significantly greater BMI than the quantitative advice group (33.20 ± 0.46 vs 30.11 ± 0.89, P=0.002). In addition, fear of negative evaluation was also a predictor for underreporting in women

[342]. Less weight loss achieved in the first 12 weeks by the qualitative advice group may have elicited greater feelings of under-performance and consequently a greater fear for negative evaluation in this group, which eventually increases the risk for misreporting in energy intake and energy expenditure. A greater tendency towards misreporting may explain the discrepancy between the self-reported energy intake levels and weight loss in the qualitative lifestyle advice group.

While past studies suggest that greater website usage is correlated with greater weight loss [185, 339, 340], the current study failed to find a significant relationship between self-reported frequency of website access and weight loss. The frequency of website access in the current study, even among the 'frequent users', were low. The highest self-reported frequency of the study website was few times a month. No participants reported having accessed the website at least once a week. Such overall low frequency of access may limit the study's ability to detect a relationship between usage and weight loss. Small sample size in the current study may further reduce the likelihood of detecting a significant different in weight loss between 'frequent' users and 'occasional' users.

Attrition rates as high as 66% have been reported in long term weight management studies involving lifestyle modification in older participants [343]. The attrition rate in this study was higher than that seen in previous studies involving older participants [203, 204, 338, 339]. As this is the first long term study on weight loss in young women, a high attrition rate could be a characteristic of this group. Young age and being female were predictive of attrition in weight loss interventions [134, 136]. The literature suggests that greater drop outs among young women could be due to greater perceived time pressure in this group [123]. Women were more likely to be time-pressured compared to men, and the likelihood of being time pressured increased with marriage and having children [123]. In addition,

other factors related to their roles as wives or mothers such the prioritization of children's needs above their own and the desire to accommodate food preferences of family members were also cited by young women as barriers to lifestyle modification [127]. This is consistent with the current findings that those who were married and those who had at least one child were more likely to drop out of the intervention. Development of simple, convenient and time-saving lifestyle modification strategies may be important in improving the sustainability of weight loss interventions in young women.

Studies to date suggest that structured lifestyle plans, regular self-monitoring, frequent self-weighing and regular meal patterns between weekdays and weekends are associated with successful long term weight loss maintenance [182, 344-346]. However, the post-intervention survey in this study found that compliance to these behaviours was poor even among the completers. Additionally, these behaviours did not predict weight outcomes in the current study, possibly owing to the small number of participants who complied with these behaviours. The current study found that only half of those who completed the intervention planned their meals and activities at least a day ahead. It was also previously reported that younger adults have less structured eating patterns compared to older adults, such as more frequent meal-skipping, greater frequency of snacking, and greater number of meals per day [347]. The spontaneous and irregular lifestyle pattern of young adults may be one of the reasons for their poor compliance and high attrition in conventional weight loss interventions [134, 136, 208]. Lifestyle program with greater flexibility may be required for weight management in young women.

Other facilitators of successful long term weight loss maintenance based on studies in the general population include greater social support, good coping strategies, greater ability to handle stress, flexible control of eating behaviour, and greater self-efficacy [345, 348]. On

the other hand, some of the barriers to long term maintenance in weight loss include a history of weight cycling, greater disinhibition, lower restraint, binge eating, emotional eating and passive reactions to problems [182, 345]. In young women, factors relating to motivation, time, cost, emotional coping, social support and self-efficacy have been reported as perceived barriers to healthy eating and physical activity [117, 127]. The effect of these factors on long term behavioural change in young women has not been investigated.

This study has several limitations. First, no control group was present in this study, thus the benefit of this self-directed internet program compared to no intervention could not be determined. Second, this study was over-represented by young women with higher levels of education, which may not be the group most affected by obesity. Third, low utilisation of the website may have reduced the study's ability to detect a relationship between website usage and weight loss. Fourth, the high attrition rate limited the study's ability to identify behavioural predictors of weight change associated with this program.

To our knowledge, this is the largest study investigating the long term effects of lifestyle intervention in young women. This study found that internet-based weight management program administered by a research institute was efficacious in maintaining weight loss in young women. However, attrition was high and utilisation of the website was low. Further research is required to improve the effectiveness of internet-based programs for young women.

5.6 Figures and tables

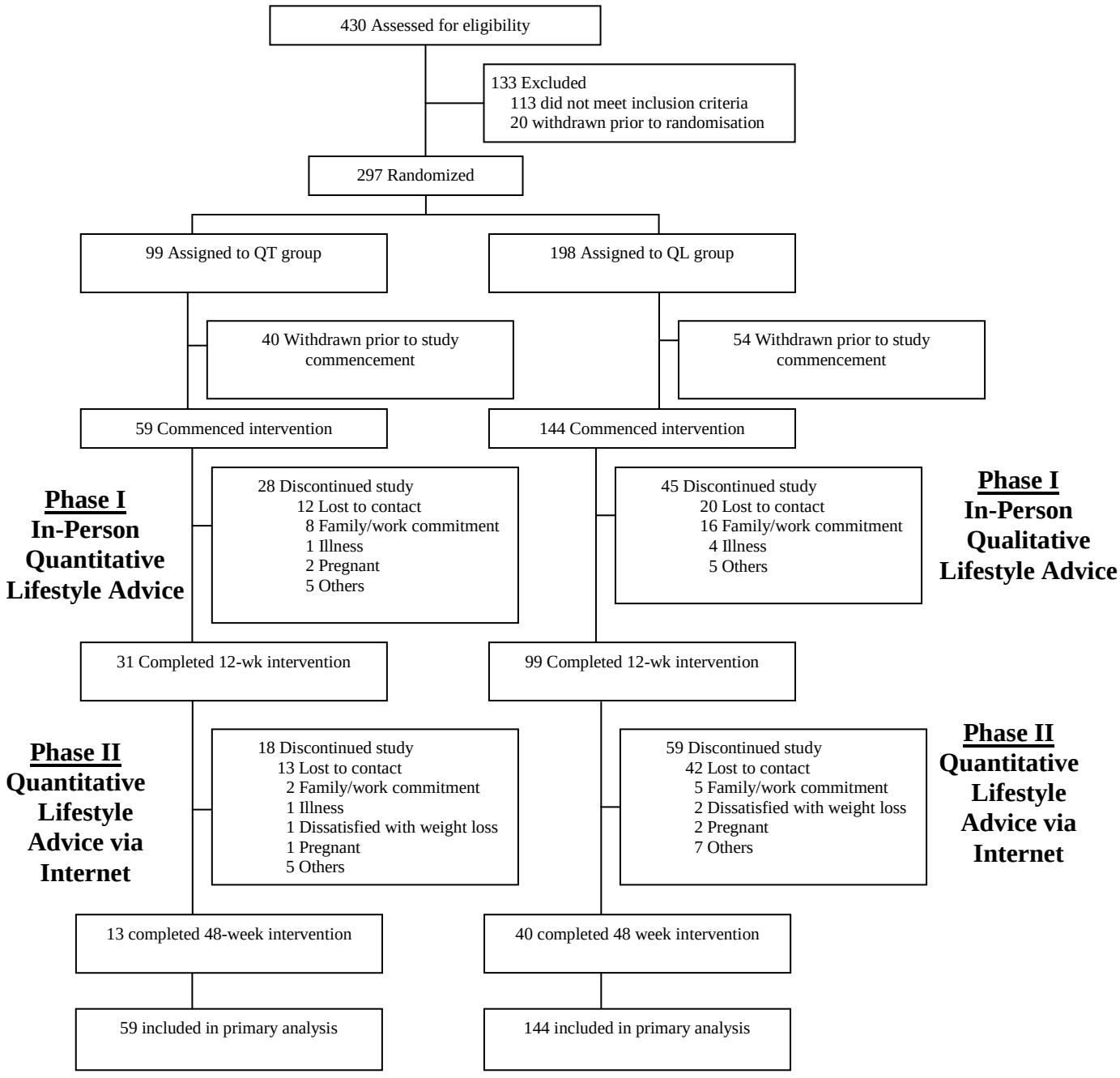

Figure 5.1 Flow diagram of participants' recruitment, randomization and completion of the interventions.

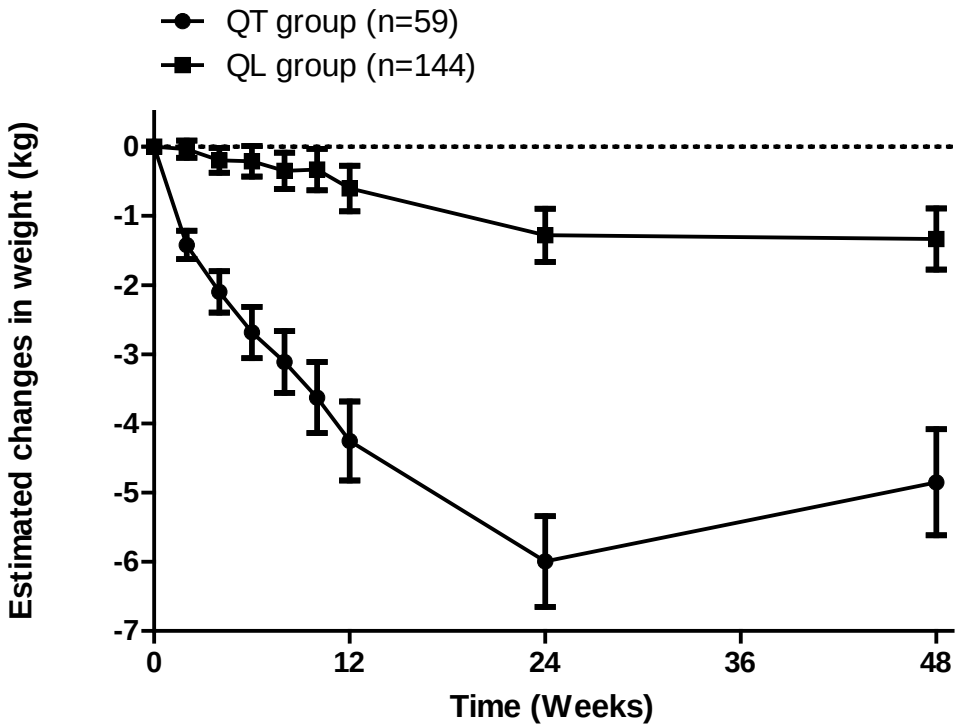

Figure 5.2 Estimated weight changes (±SEM) of the groups receiving quantitative lifestyle advice (QT) or qualitative lifestyle advice (QL) from week 0 to 12 according to mixed model analyses. Both groups received online quantitative lifestyle intervention from week 12 to 48. Time, treatment and time-by-treatment were fixed factors in the linear mixed models. P<0.0005 for time-by-treatment effect.

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Table 5.1 Treatment conditions in Phase I (week 0 to 12) and Phase II (week 13 to 48)

		QT group	QL group
Phase I	Weigh-in	Fortnightly	Fortnightly
	Therapist contact	Fortnightly	Fortnightly
	Diet	High protein, hypocaloric diet	Qualitative advice
	Physical activity	Up to 60 mins a day	Qualitative advice
	Behavioural support	Fortnightly e-newsletter	Fortnightly e-newsletter
	Peer support	Online peer group forum	None
	Website support	Weeks 0 to 48	Weeks 13-48
Phase II	Weigh-in	Weeks 24 and 28	
	Therapist contact	Weeks 24 and 28	
	Diet	High protein, hypocaloric diet	
	Physical activity	Up to 60 mins a day	
	Behavioural support	Monthly e-newsletter	
	Peer support	Online peer group forum	

Table 5.2 Baseline characteristics of participants (n=203)

	Means ± SE
Age, years	27.8 (0.3)
BMI, kg/m^2	33.4 (0.3)
Weight, kg	92.0 (1.0)
	%
Marital status	
Married/de facto	50
Separated, never married	50
Education	
No formal qualifications	2
High school	31
Trade/apprentice/certificate/diploma	28
University degree	39
Internet access for personal use	
Home	21
Work	72
Others	7
Internet comfort	
Comfortable	98
Undecided/uncomfortable	2
Computer ability	
Little or no experience	2
Experience with basic software applications and internet	61
Advanced understanding	28
Computer professional	9

Table 5.3 Body weight, energy intake and physical activity outcomes by treatment condition from baseline to Week 48[a]

	Baseline	Week 12	Week 48	Change from baseline to week 48	P-value to time	P-value for time-by-treatment
Weight, kg						<0.0005
QT group	91.1 ± 1.9	86.8 ± 1.9	86.2 ± 1.9	-4.8 ± 0.1	<0.0005	
QL group	92.4 ± 1.2	91.8 ± 1.2	91.1 ± 1.2	-1.3 ± 0.4	0.003	
Energy intake, KJ						0.005
QT group	8633 ± 300	5798 ± 406	7770 ± 657	-863 ± 713	0.227	
QL group	8484 ± 189	7156 ± 231	6745 ± 383	-1739 ± 421	0.000	
Physical activity, met-min/week						0.020
QT group	1971 ± 398	2291 ± 506	2606 ± 811	635 ± 882	0.472	
QL group	2072 ± 258	2426 ± 290	3292 ± 449	1219 ± 502	0.015	

[a] Data presented as estimated mean ± SE. Missing values imputed by linear mixed models from available data. Models included time, treatment and time-by-treatment as fixed factors (n=203; QT group, n=59, QL group, n=144).

Table 5.4 Attrition by treatment condition over time [a]

	QT group	QL group	P-value between groups
Baseline to Week 12	28/59 (48%)	45/144 (31%)	0.036
Week 12 to Week 48	18/31 (58%)	59/99 (60%)	0.520
Baseline to week 48	46/59 (78%)	104/144 (72%)	0.483

[a] Data presented as participants (% estimated mean ± SE. Differences between groups were evaluated using chi-square tests

Chapter 6 Discussion and conclusion

The prevention of weight gain and obesity in young women appears to be a critical time to intervene to prevent future weight gain. To our knowledge, this is the first weight loss study focussing on healthy overweight or obese young women. In this thesis, we have explored the short term and long term behavioural, nutritional and metabolic outcomes of three strategies on weight management in young women. The strategies involved the use of a quantitative structured lifestyle intervention program, a qualitative lifestyle approach and the same approach with the addition of an insulin sensitising agent, metformin. The use of the internet as a strategy to maintain long term weight loss was also investigated. This thesis identifies significant challenges in assisting young women to adopt healthier lifestyles as well as reveals important potential strategies for future research in this group.

6.1 Drug or diet

In Chapter 3, it was demonstrated for the first time in healthy young women that metformin may have a small effect on weight gain prevention, but lifestyle modification was more effective in weight reduction. The hypothesised effects of metformin on body composition were not demonstrated. The overall results were in agreement with the Diabetes Prevention Program (DPP) which reported a weight change of -1.5$\pm$7.6 kg with metformin, +0.5$\pm$6.7 kg in placebo and -3.4 $\pm$8.2 kg with lifestyle modification after mean trial duration of 2.9 years in women aged 50 $\pm$10 years [264]. Similar results achieved in our study shows that younger women are not metabolically different to older women in regards to weight loss. However, age may result in significant behavioural differences. The DPP reported an overall completion rate of 92.5% [250]. In contrast, our study reported an attrition rate of 48% in the lifestyle group and 30% in the tablets group (P=0.08 between

groups). A greater efficacy but higher attrition in the lifestyle arm suggests that the current approach in lifestyle modification for weight loss is in need of further development to meet the unique needs of young women.

6.2 Restraint or freedom

Structure, rules and flexible restraint may be essential parts of weight control in contemporary society where food is abundant, highly palatable, inexpensive and ubiquitously available. Population studies have found that those with greater structure in their life had better weight control [182]. While some argue that restrictions may have negative psychological effects [197, 322], our findings in Chapter 4 suggest that energy restriction resulted in psychological improvements.

Quantitative, energy restricted approaches are usually more successful in producing weight loss compared to qualitative approaches [200, 201, 349]. However, proponents of the qualitative approaches suggest that the imposition of quantitative rules increases stress while produces short-lived results as dieters binge when given the opportunity [197, 322]. On the contrary, our findings suggest that at least in the context of this study which provided professional support, restraint imposed by quantitative lifestyle advice produced greater improvements in psychosocial outcomes. This could be due to a greater sense of achievement from greater weight loss, and possibly less anxiety associated with the ambiguity of requirements within the qualitative lifestyle advice.

Although our study found that structured, quantitative advice is important for weight loss and psychosocial improvements, we also found that many young women could not cope with this approach as apparent from the higher attrition rate with the quantitative lifestyle group (48% vs 31%, P=0.036). A recent study comparing the eating patterns in adult

Americans between 1971-1975 and 1999-2002 suggest a trend towards more unstructured eating patterns especially among women [335]. During this period, the number of eating episodes increased in women but not in men. The percentage of energy intake from snacks also increased in women but not in men. These suggest a secular trend towards more unstructured lifestyles, which may explain poor long term compliance to structured lifestyle interventions. In view of this recent trend in eating patterns, lifestyle interventions may need to evolve accordingly so that they provide relevant and helpful advice that allows individuals to make better choices within an unstructured lifestyle. This is especially important in addressing the issue of obesity in the younger population who may have greater exposure to unstructured lifestyles. To achieve this, restraint should be implemented through strategies with high levels of flexibility and low requirements for planning and preparation. The positive effects of flexible restraint was demonstrated in a study which reported that both having no restraint at all or having rigid restraint such as being on a strict diet were associated with overeating, while flexible restraint implemented through strategies such as having a daily calorie limit was associated with the absence of overeating and lower body mass [350]. Thus, strategies which encourage flexible restraint should be considered in future investigations for weight management in young women.

6.3 Stress, hyperandrogenemia and food cravings

Many young women eat in response to negative emotions [63, 351]. Stress increases energy intake among emotional eaters [351]. Stress-driven eaters were also found to have higher intakes of energy dense foods such as sausages, hamburgers, pizza and chocolate compared to non stress-driven eaters [126]. Stress-driven eating is significantly associated with obesity in women (OR 3.24 95%CI 2.19-4.79) but not in men [126]. Greater food intake during stress could be due to the effects of HPA activation on the brain reward

pathways [352]. While stress has been found to increase cravings for alcohol and other substance of abuse [138, 353], the effect of stress on food cravings have not been described. Our findings in Chapter 2 reported that psychological distress was significantly correlated with the frequency of food cravings in all subscales in young women. While these results imply that stress-reduction may be helpful in producing weight loss, a recent study found that a non-dieting stress reduction program resulted in improved stress management with no effect on weight loss [324]. As stress only increases food intake in individuals with high cortisol reactivity [138], further studies could investigate the effect of stress reduction on body weight specifically in individuals with a high cortisol response to stress.

In addition, we also reported a novel relationship between hyperandrogenemia and food cravings. A co-existence of eating disorders and hyperandrogenemia has been reported among patients with bulimia nervosa and women with PCOS [299, 300]. Alterations in satiety signalling was also reported in women with PCOS [69, 354]. The current study extended these findings by suggesting that food cravings may also be altered in women with reproductive dysfunction. This may reflect possible aberrations in the food reward system in this group. The relationship between androgen and food cravings could be due to alterations in the appetite regulation pathway which interact closely with the brain reward pathway [138, 355], or the direct pharmacological effect of androgen on the brain reward pathway [356, 357]. The role of hyperandrogenemia in the development of obesity in young women warrants further investigation. Intervention studies have shown that food restriction is successful in reducing food cravings among completers [358, 359]. It is unclear if similar outcomes would be observed among drop-outs.

6.4 Internet-based weight management program

Providing support for long term weight maintenance is a challenge, possibly even more so in young people. Although young adults are the greatest users of the internet in Australia, the effects of internet-based weight management programs have not been investigated in young women. In Chapter 5 we reported that minimal intervention through a self-directed website could be effective in maintaining weight loss in a minority of young women. However, utilization of the website was low and only one in five young women remained in the intervention study to the 48-week completion. The attrition rate of the current study was considerably higher than that reported by the other studies on internet-based lifestyle intervention conducted in older participants, which reported attrition rates ranging from 7% to 34% for intervention periods ranging from 12 to 18 months [338, 339, 360].

In the current study, a high attrition in both in-person (baseline to week 12) and online (week 13 to 48) interventions suggests that the mode of delivery is not the main reason for attrition in this group. Greater drop out among those who were married or had children were consistent with previous literature, suggesting that these events predict weight gain in young women. Further, marriage and parenting also increases the odds of being time-pressured. Thus, lack of time could be one of the most important barriers to lifestyle modification in young women. Considering the importance of family responsibilities in the lives of young women, family based programs may be an alternative strategy for future investigation.

6.5 Young women and weight management

In these studies, we have explored a range of strategies including medication, quantitative lifestyle advice, qualitative lifestyle advice and internet-based support. In the quantitative

lifestyle advice, we have taken an evidence-based approach on weight management strategies including regular self-monitoring, frequent therapist support, structured diet and physical activity plans, and peer support. Yet despite this, attrition was high. Due to the range of options we have investigated, we could state rather confidently that the existing weight loss approaches appear not to suit a majority of young women. This is perhaps not a surprising finding considering that weight loss research to date was mostly conducted in mid-age men and women.

Although it was known that young women are more likely to drop out, the reasons for such phenomenon have not been described. A psychologist in our team conducted exit interviews among young women who withdrew from the study (Appendix 3). Whilst the young women stated that they felt positive about the weight loss program, they cited a plethora of personal reasons for withdrawal such as illness of family members, or difficulty in fitting the program around work or study or parenting requirements. There were also suggestions for recipes that can be accepted by the whole family so that they don't have to cook separate meals, suggesting that lack of social support was also one of the barriers.

The main reason for attrition appeared to be that personal motivators such as health or the desire to look and feel better lost their priority to more pressing issues in young women's lives, such as family, work and study. The desire for lifestyle change in these young women was evident from their registration and participation in the trial. However, their desires appeared to be quickly overruled by other's needs and wants. Their dominant focus seemed to be on individuals other than themselves, such as their husbands, their parents, their children, their friends, and even their colleagues and employers. Even when they do want to lose weight for themselves it could be a thinly veiled desire to obtain affirmation from other individuals [127]. Our studies suggest that targeting young women for lifestyle

changes independent of their social environment can be difficult and strategies that involve these significant others may be worth investigating.

6.6 Limitations

There are a number of limitations in the studies of this thesis. First, this trial was over-represented by young women with higher levels of education, which may not be the group most affected by obesity. Second, this study has seen a high attrition rate prior to study commencement. This is due to the use of an online recruitment method, which had wide reach but low retention for an intervention which requires in-person attendance. Although the pre-study drop out is unlikely to introduce bias differentially across the treatment groups, this could have been prevented by introducing an in-person screening visit to confirm the commitment of the young women in participating in the in-person intervention. Third, most psychological and behavioural data was collected from the completers only, resulting in biased results. Future interventions in young women should consider obtaining post-intervention psycho-behavioural data online from the dropouts. Fourth, as the structured lifestyle intervention included a number of strategies suggested for long term weight maintenance, it is unclear which component of the intervention was accountable for weight loss or attrition in young women.

6.7 Conclusion

Young women are at high risk of weight gain. Excess weight and weight gain in early adulthood is associated with a range of physiological and psychosocial adverse consequences. Despite the extent of the problem, there has not been a study focussing on developing weight loss strategies for young women. To our knowledge, this is the first weight loss study aimed at developing weight management strategies in healthy overweight and obese young women. One of the strengths of this study is the inclusion of various strategies across different disciplines in obesity research. This thesis also reports objective follow-up measures from this challenging group over a period of 48 weeks.

In this study, we found that only a small minority of young women were able to comply with the conventional advice on weight loss in the long term. Although high attrition rates in weight loss treatments have been previously documented in young women, the reasons for attrition have not been described. The current study found that short term attrition (by week 12) was associated with higher baseline psychological distress and food cravings. Thus, strategies in managing stress and cravings may be beneficial in this group. In addition, we also found that long term attrition (by week 48) was higher among those who were married or had children. This may be related to the greater risk of weight gain among married women or women with children shown in the population studies conducted in US and Australia. Past and present findings suggest that stress and 'time poverty' may explain poor outcomes in long term weight management in this group. We also found that quantitative lifestyle advice was associated with greater attrition despite greater weight loss achieved. This suggests that strategies with greater flexibility may be required to improve the acceptability and sustainability of the strategy in this group. Together, these findings

suggest that young women have unique barriers in weight management that are not being addressed by the current evidence-based methods for weight loss. Therefore further research in young women is critically needed to inform the development of weight management programs in this high-risk group.

Based on our findings, we suggest the following as future directions for research in weight management in young women:

- Quantitative lifestyle advice was significantly more efficacious than metformin in weight loss in young women. However a high attrition rate suggests that further development is required to increase the sustainability of lifestyle intervention in young women.
- Quantitative lifestyle advice resulted in greater weight loss and psychological improvements compared to qualitative lifestyle advice. However quantitative lifestyle advice also resulted in higher attrition in young women. Strategies that encourage flexible restraint with minimal time requirements should be considered for future investigations in this group.
- Qualitative lifestyle advice without self-acceptance did not result in greater psychological improvements compared to quantitative lifestyle advice. Further research is required to develop strategies that encourage self-acceptance while promoting weight loss.
- The reasons for attrition in young women were mostly related to work or family requirements. Interventions targeting the social environment of young women such as family, peer groups or workplace may be necessary to facilitate lifestyle change in young women.

- Hyperandrogenemia may be associated with increased food cravings in young women. Further studies are required to increase our understanding on the relationship between hyperandrogenemia and the development of obesity in young women. If the relationship is confirmed to exist, anti-androgenic agents may be potential candidates for obesity drugs in affected individuals.
- Psychological distress was found to be associated with increased food cravings. Future research should investigate the effect of stress management in weight loss interventions for young women.
- This internet-based intervention was effective in maintaining medium term weight loss.
- Delivering lifestyle intervention through the internet does not overcome the issues of high attrition and poor compliance in young women. Further studies should seek to understand and address the potent barriers to lifestyle modification in young women.

Appendix 1. Questionnaires on socio-demographic characteristics, psychological distress (GHQ), self-esteem (RSE-B), food cravings inventory (FCI) and internet usage

1. What is your MAIN occupation?

_____

2. What is your marital status?
    - Married
    - De facto
    - Widowed
    - Separated
    - Divorced
    - Never married

3. Highest qualifications
    - No formal qualifications
    - School certificate (Year 10/12)
    - Trade/apprentice/certificate/diploma
    - University degree

4. How many times have you given birth to a child?
    - Never
    - Once
    - Twice
    - Three times
    - Four or more times

5. Have you ever dieted (ie limiting how much you eat) to lose weight?
    - Yes
    - No

6. If you've answered yes to Question 5, how often have you gone on a diet in order to lose weight in the last year?
    - Never
    - 1-4 times
    - 5-10 times
    - More than 10 times
    - I am always on a diet to lose weight

7. Where do you normally access the internet for personal use? (You may select more than one option)

- o At work
- o At home
- o At other places (Please specify)_____

8. How often are you **able** to access the internet for personal purposes?

- o At least daily
- o 2 or more times per week
- o At least weekly
- o Less than once a week

9. What type of connection does your internet have (ie the internet which you **mainly** use for personal purposes)?

- o Dial up
- o Non dial up ("always on" access, eg Broadband/ADSL)
- o Others (Please specify)_____
- o I don't know

10. How much do you agree with this statement: **I feel comfortable using the internet**

- o Strongly agree
- o Agree
- o Undecided
- o Disagree
- o Strongly disagree

11. Which of the following statements best describe your computer ability?

- o Little or no computer experience
- o Experience using basic software applications
- o Experience using basic software applications and the Internet
- o Hobbyist with more advanced understanding of software and hardware
- o Computer professional

12. How effective do you think the CSIRO Total Wellbeing website will be in providing **information** on this weight loss program?

- o Very effective
- o Quite effective
- o Undecided
- o Quite ineffective
- o Very ineffective

13. How effective do you think the CSIRO Total Wellbeing website will be in providing **social support** (eg chatting with other participants, chatting with dietitian) for this weight loss program?

- o Very effective
- o Quite effective
- o Undecided
- o Quite ineffective
- o Very ineffective

14. I intend to use the CSIRO Total Wellbeing website in the next 12 months

- Very unlikely
- 
- Very likely

15. I predict I would use the CSIRO Total Wellbeing website in the next 12 months

- Very unlikely
- 
- Very likely

16. I plan to use the CSIRO Total Wellbeing website in the next 12 months

- Very unlikely
- 
- Very likely

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do you usual activities.

Q2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

a) <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**

b) Climbing <u>several</u> flights of stairs

Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**

Q3. During the <u>past 4 weeks,</u> how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

a) <u>Accomplished less</u> than you would like

All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**

b) Were limited in the <u>kind</u> of work or other activities

All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**

Q4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a) Accomplished less than you would like

All of the time **Most of the time** **Some of the time** **A little of the time** **None of the time**

b) Did work or other activities less carefully than usual

All of the time **Most of the time** **Some of the time** **A little of the time** **None of the time**

Q5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all **A little bit** **Moderately** **Quite a bit** **Extremely**

Q6. How much of the time during the past 4 weeks...

a) Have you felt calm and peaceful

All of the time **Most of the time** **Some of the time** **A little of the time** **None of the time**

b) Did you have a lot of energy

All of the time **Most of the time** **Some of the time** **A little of the time** **None of the time**

c) Have you felt downhearted and depressed

All of the time **Most of the time** **Some of the time** **A little of the time** **None of the time**

Q7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)

All of the time **Most of the time** **Some of the time** **A little of the time** **None of the time**

We would like to know how your health has been, in general, over the last few weeks.

Please read the questions and each of the four possible answers below, then circle the number for the response that best applies to you.

Have you recently…
a)...been able to concentrate on what you're doing?

better than usual	**same as usual**	**less than usual**	**much less than usual**

b)...lost much sleep over worry?

not at all	**no more than usual**	**rather more than usual**	**much more than usual**

c)...felt that you are playing a useful part in things?

more so than usual	**same as usual**	**less so than usual**	**much less than usual**

d)...felt capable of making decisions about things?

more so than usual	**same as usual**	**less so than usual**	**much less than usual**

e)...felt constantly under strain?

not at all	**no more than usual**	**rather more than usual**	**much more than usual**

f)...felt you couldn't overcome your difficulties?

not at all	**no more than usual**	**rather more than usual**	**much more than usual**

g)...been able to enjoy your normal day to day activities?

more so than usual	**same as usual**	**less so than usual**	**much less than usual**

h)...been able to face up to your problems?

more so than usual	**same as usual**	**less so than usual**	**much less than usual**

i)...been feeling unhappy or depressed?

not at all	**no more than usual**	**rather more than usual**	**much more than usual**

j)...been losing confidence in yourself?

not at all	**no more than usual**	**rather more than usual**	**much more than usual**

k)...been thinking of yourself as a worthless person?

not at all	**no more than usual**	**rather more than usual**	**much more than usual**

l)...been feeling reasonably happy, all things considered?

more so than usual	**same as usual**	**less so than usual**	**much less than usual**

Please read each sentence carefully and then select the response that best indicates how often the sentence is true for you.

		almost always true	often true	some-times true	not often true	never true
Q1	**I feel that I'm a person of worth, at least on an equal plane with others.**					
Q2	**I feel that I have a number of good qualities.**					
Q3	**I am able to do things as well as most other people.**					
Q4	**I feel I do not have much to be proud of.**					
Q5	**I take a positive attitude towards myself.**					
Q6	**I think I am no good at all.**					
Q7	**I am a useful person to have around.**					
Q8	**I feel I can't do anything right.**					
Q9	**When I do a job I do it well.**					
Q10	**I feel that my life is not very useful.**					

Day of cycle (The start of menstruation is Day 1): _____

Study ID

"A craving is defined as an intense desire to consume a particular food (or food type) that is difficult to resist" (White et al 2002)[281]

Over the past month, how often have you experienced a craving for the following food?

	Never	Rarely	Sometimes	Often	Always/almost every day
Fried chicken	**1**	**2**	**3**	**4**	**5**
Sausage	**1**	**2**	**3**	**4**	**5**
Gravy	**1**	**2**	**3**	**4**	**5**
Fried fish	**1**	**2**	**3**	**4**	**5**
Bacon	**1**	**2**	**3**	**4**	**5**
Pie or pasty	**1**	**2**	**3**	**4**	**5**
Hot dog	**1**	**2**	**3**	**4**	**5**
Steak	**1**	**2**	**3**	**4**	**5**
Brownies	**1**	**2**	**3**	**4**	**5**
Candy	**1**	**2**	**3**	**4**	**5**
Chocolate	**1**	**2**	**3**	**4**	**5**
Donuts	**1**	**2**	**3**	**4**	**5**
Cake	**1**	**2**	**3**	**4**	**5**
Cinnamon rolls	**1**	**2**	**3**	**4**	**5**
Ice cream	**1**	**2**	**3**	**4**	**5**
Rolls	**1**	**2**	**3**	**4**	**5**
Pancakes or waffles	**1**	**2**	**3**	**4**	**5**
Biscuits	**1**	**2**	**3**	**4**	**5**
Sandwich bread	**1**	**2**	**3**	**4**	**5**
Rice	**1**	**2**	**3**	**4**	**5**

Baked potato	**1**	**2**	**3**	**4**	**5**
Pasta	**1**	**2**	**3**	**4**	**5**
Cereal	**1**	**2**	**3**	**4**	**5**
Hamburger	**1**	**2**	**3**	**4**	**5**
French fries	**1**	**2**	**3**	**4**	**5**
Chips	**1**	**2**	**3**	**4**	**5**
Pizza	**1**	**2**	**3**	**4**	**5**

Appendix 2. Post intervention questionnaire

These questions refer to your experience on the study in the last 24 weeks

1) How easy or difficult was it for you to follow the diet program?

Very easy			Neither easy nor difficult			Very difficult
1	2	3	4	5	6	7

2) How has your spending on food (including takeaways) changed while on the program?

Decreased a lot			No change			Increased a lot
-3	-2	-1	0	1	2	3

3) How has your time spent preparing food changed while on the program?

Decreased a lot			No change			Increased a lot
-3	-2	-1	0	1	2	3

4) What impact did socializing have on you following the diet program?

Very negative impact			Neither negative nor positive			Very positive impact
-3	-2	-1	0	1	2	3

5) How easy or difficult was it for you to follow the exercise program?

Very easy						Very difficult
1	2	3	4	5	6	7

6) What impact did socializing have on you following the exercise program?

Very negative impact			Neither negative nor positive			Very positive impact
-3	-2	-1	0	1	2	3

7) How easy or difficult was it for you to find the time to exercise?

Very easy						Very difficult
1	2	3	4	5	6	7

8) How helpful was the Total Wellbeing Diet study website in supporting you losing weight?

Not helpful at all						Very helpful
1	2	3	4	5	6	7

9) How helpful was the INTERACTION (ie the Forum) in the website in supporting you losing weight?

Not helpful at all						Very helpful
1	2	3	4	5	6	7

10) How helpful was the INFORMATION on the website in supporting you losing weight?

Not helpful at all						Very helpful
1	2	3	4	5	6	7

11) Have you read the CSIRO Total Wellbeing Diet Book 2?
YES / NO

12) How helpful was the CSIRO Total Wellbeing Diet Book 2 in supporting you losing weight?

Not helpful at all						Very helpful
1	2	3	4	5	6	7

13) How helpful were the monthly newsletters (emails) in supporting your effort in losing weight?

Not helpful at all						Very helpful
1	2	3	4	5	6	7

14) How often did you set yourself a specific weight loss goal (eg 0.5kg in a week)?

I did not have specific weight loss goals	Less than once a month	Monthly	Fortnightly	Weekly
1	2	3	4	5

15) How often did you set yourself a specific diet goal (eg no chips this week)?

I did not have specific diet goals	Less than once a month	Monthly	Fortnightly	Weekly
1	2	3	4	5

16) How often did you set yourself a specific exercise goal (eg 2 hr a week)?

I did not have specific exercise goals	Less than once a month	Monthly	Fortnightly	Weekly
1	2	3	4	5

17) How often did you weigh yourself?

Less than once a week	Once a week	Once every few days	Once a day	More than once a day
1	2	3	4	5

18) How often did you fill in the diet section of your Lifestyle Checklist?

I did not fill in my diet checklist	Less than once a week	Once a week	Once every few days	Daily
1	2	3	4	5

19) How often did you fill in the exercise section of your Lifestyle Checklist?

I did fill not in my exercise checklist	Less than once a week	Once a week	Once every few days	Daily
1	2	3	4	5

20) How far ahead do you usually plan your meals?

Further than a week ahead	A week ahead	One to several days ahead	On the day itself	I don't plan my meals
1	2	3	4	5

21) How far ahead do you usually plan your physical activities?

Further than a week ahead	A week ahead	One to several days ahead	On the day itself	I don't plan my physical activities
1	2	3	4	5

22) How often did you access the diet and exercise pages on the Total Wellbeing Diet study website?

Never	Less than once a month	Once a month	Few times a month	Weekly	More than once a week
1	2	3	4	5	6

23) How often did you access the Forum on the Total Wellbeing Diet study website?

Never	Less than once a month	Once a month	Few times a month	Weekly	More than once a week
1	2	3	4	5	6

24) How often did you refer to the CSIRO Total Wellbeing Diet book 2?

Never	Less than once a month	Once a month	Few times a month	Weekly	More than once a week
1	2	3	4	5	6

25) How often did you read the monthly online newsletters?

Never	Less than once a month	Once a month	More than once a month
1	2	3	4

26) How satisfied are you with the weight loss achieved?

Not satisfied at all						Very satisfied
1	2	3	4	5	6	7

Appendix 3. Exit interview (conducted by psychologist)

Internet, young women and weight loss: Qualitative analyses

Short questionnaire (Those who didn't make baseline) (N-32)

Reasons for applying.

People generally gave more than one response (range 1 to 6), the mean number of reasons were 2.63 (1.04) and a median of 2.

As expected the most prominent issues were people experiencing a problem losing weight (16) and desiring to lose weight (26).

> *"Tried to lose weight but couldn't, thought try this out and see how it goes. Stuff from chemists doesn't work, couldn't lose any weight. Nothing happened [I] can't lose any weight"*

> *"Just I am overweight and thought it would be a good thing to get into…"*

Other common responses included the study or CSIRO being recommended (6) or concerns around general health and being able to maintain a healthy lifestyle (5). There were also related issues of people having a good impression of the TWD (3) and this work also having the potential to assist others and help with research (4).

Reasons why they didn't start

The main reason was not a lack of motivation or desire but rather difficulties meeting the practical requirements of the study. The most common response was work commitments meaning full participation in the study wasn't possible (15). Aligned with this were problems with study (2) and travel time (7) or the care of children, being required to bring children into the city for appointments (7).

Potential areas for future consideration for study planning were perceptions of there being too many appointments (5) and the related issue of there being a limited number of appointments available (4). A reasonable number of people claimed to also be unaware of all of the study requirements prior to agreeing to participate (8). In terms of a process review there were also two people who claimed no to have then been contacted by CSIRO.

> *"The reasons I did was because I live in Craigmore and have two young children, didn't realise it would be so much coming into town and out. The lady said they'd prefer if I didn't bring the children. And I explained I have a 2 and a 3 year old I can't get care for. Couldn't get someone to look after them every time I come into [town] for appointments."*

> *"Didn't realise it was in the city. I live out the north and it's difficult for me to get into the city due to work commitments"*

"The appointment times were all during work hours - impossible. Couldn't afford two hour blocks of time and don't work in the city"

What would they want in a program?

Responses to this can be divided into three main sections (in order of frequency of report): Advice (18), support (12) and monitoring (6) (Though people could report on may have mentioned more than one type of advice or support. Within advice (32 responses), the most frequent topics of interest were food and nutrition, lifestyle advice and tips on timing, how to accommodate for family and children and specific strategies such as menus and quick, healthy meals.

"Has to have food which we can all eat…not gonna do it if I have to make special meals for me"

"How to change the lifestyle to make it easier. My main thing is not just motivation but lifestyle, with so many people in the family its hard, everyone has different tastes and likes food in different ways"

Support (20 responses) generally involved contact with either a mentor (7) of some sort (and some stipulated that this could be via email or phone) or group support with other people in the same situation (8).

"…maybe a support group as such to go through the needs of the group and individuals and to discuss really how everyone's getting on and your own experiences."

"Support wouldn't go astray, not saying I'd need it but wouldn't say no"

Monitoring of progress and adherence to the dietary plans (8 responses) was mentioned by several participants.

"Monitoring. Still comes down to me, we all know what we should eat. But need a diet plan and weigh ins and regular checking"

Long Interview (19)

Executive summary

The majority of participants felt that the programme was well organised, the materials were useful, staff contact was positive and supportive and the monitoring aspects of the programme were beneficial.

The key problems to emerge were issues with including appointments into busy lifestyles as well as the centralised location of CSIRO and problems with travel time and appointments aligning with work and other commitments. There were multiple requests for additional support groups or contact with specialists/mentors. Whether such additions to the programmes would result in increased attendance/efficacy would remain to be seen. The potential to have appointments at regional centres and expanding the hours available

could have a positive impact on retention in the study. It would be interesting to examine the postcode distribution of study participants to see if location was predictive of success or withdrawal. Considering the lifestages of most of the participants it may be more likely that, as young families starting to move into the property market, they could live further away from the city centre and CSIRO Human Nutrition.

Underpinning most of the feedback is the hectic and busy lifestyles of the majority of participants. With young children, work and family commitments taking time to exercise and time to negotiate healthy meals within the context of familial expectations can be a daunting task. If the results are limited, in conjunction with travel time for appointments, it seems less likely that participants will remain in the study. As per most weight loss programmes it seems highly likely that quick/sustained results are a key factor in retaining participants.

Reasons for leaving early

As would be expected, the majority of those who withdrew did so due to life events (illness of family members or participant, pregnancy) (7), other time commitments (increase in work, study, parenting requirements) (11) and problems with travel time for appointments (7).

> *"My son was very sick. Too hard to get in there and concentrate on yourself."*
>
> *"Really busy time for me…..any times in business hours was just unmanageable for six to eight weeks."*
>
> *"Just too busy working, appointment times were difficult and we live in the hills"*
>
> *"At the end, driving in to the city for a two minute appointment. Casual teacher and had to knock back work for the appointment"*
>
> *"Too hard getting into town for a 15 minute appointment (one hour in and one hour out) – petrol costs"*

A small group mentioned side effects from the tablets as reasons for withdrawing (3) with others stating a lack of tangible results was also a contributing factor in leaving the programme (4).

The key issue to emerge from this is the related issues of time and travel commitments. By only having testing or appointments at a centralised location we may be overly limiting the pool of participants we can draw upon or at least sustain throughout the entirety of a program. If appointments or testing could performed at regional community centres or clinics that may help encourage maintenance in the program. The timing of appointments during business hours to cope with people who work full time and may also have travel commitments is an issue to potentially further explore. Though it is acknowledged that working alone after hours raises various security issues.

A number of people stated some form of cost benefit analysis in terms of travel to appointment time. Eg a lot more time spent travelling than in the appointments. It may be that if future studies required centralised testing then involving some form of group

activities or support networks may encourage people who do not live centrally to make that commitment of time.

Interaction with staff

Feedback was overwhelmingly positive regarding people's interaction with CSIRO staff, including clinic staff, receptionists and Siew Lim. Staff were seen as friendly and informative. Only four people mentioned time required to be seen for an appointment. Three of these were very positive in that people were seen very quickly for their appointments. One person made mentioned that the very first appointment took a long time.

> *"Siew was excellent, very easy to get along with"*
>
> *"Really nice, everyone answers questions"*
>
> *"Quick and easy, straight in to see the lady and out again"*

Hence, we can feel reassured that people are leaving the study due to time and work issues as opposed to any form of negative interaction with staff members.

Aspects of the study that were easy

While participants did raise some concerns with other questions within this context no issues were raised. People did not report any real confusion or difficulties with the actual programme itself.

> *"All easy, exercises not strenuous"*
>
> *"Didn't bother me at all – all fine"*

The study seems to have been very well explained as only two participants mentioned being surprised by aspects of the study being easier than expected. One participant lost weight quicker than expected (10-15 kilos) and a second was surprised by how simple the guidelines were.

> *"Didn't think the guidelines would be that simple. Have counted on weight watchers – [it's] hard to begin with. Simple, laid out easily"*

Aspects of the study that were difficult

Six people raised a total of 14 problems experienced with various aspects of the diet. These included practical aspects related directly to the plan such as the requirement to weigh your food and becoming accustomed to the plan and what constitutes a serve.

> *"Weighing food a bother. Can't be bothered."*
>
> *"Cramming all of the food in, in one day was difficult "Oh goodness, still got to eat!", so full after dinner."*
>
> *"Using too much oil during the day"*

There were also practical concerns around following the diet within the wider context of one's life.

> *"Probably say trying to have [a] really healthy diet with a husband and two picky kids"*

> *"If try and get more healthy, spend more money, stretch the budget"*

> *"Struggled going out – only go out during the day but had to watch if pre-buttered bread, if lean ham, was it the right amount of protein etc. Some judgement from shop owners*"

Only one person raised issues of an emotional response to dieting and this related more to this individuals relationship with food rather than anything specific to the programme.

> *"Am an emotional eater – felt like I was restricting myself….Felt even though I want to loose weight I felt like I was punishing myself"*

It is pleasing to note that eight people did not raise any difficulties with the study. The only other concern raised by more than one individual was a restatement of the problems with travel and appointments (3).

Participants seemed well informed as to the processes and the requirements of the study with only three participants being surprised at the difficulty of some of the requirements. Of these three, one lady was surprised by the number of information sessions but did not actually find this difficult. A second participant was surprised by the amount of blood taking but felt that this was explained well and the process went fine. The final participant to be surprised was concerned that there may have been more support from a nutritionist in relation to the food diaries. More participants commented on how everything was thoroughly explained than raised a concern.

> *"Kinda what I expected. Really well explained and easy to follow"*

<u>Tips for study designers</u>

Feedback on the study showed it was very well received, with eight of those participants providing comment not only stating that they could not think of any changes but also that the study was well ran.

> *"No advice, really good the way it is"*

Where advice was provided (five people providing six comments) it was generally within the context of convenience, with people requesting more convenient locations for blood tests, weigh ins and more after business hours appointment times.

> *"More outlets for weigh ins, others also had to drive in"*

> *"If possible, be able to have appointments maybe an hour after business hours. Pretty sure was offered a little after 5."*

"Maybe if you want a broader spectrum, maybe go to the local gribbles for blood tests"

Other comments on potential improvements included advice and support for socialising or convenience foods:

"Actual restaurants that provide CSIRO endorsed food"

"Guidelines on chippies or what's good with take away, eg can we eat the McDonalds heart tick meals?"

One participant also raised the potential for having some group support sessions:

"…can't think of improvements except for groups – no weighing – every two or four weeks"

Total Wellbeing Diet

Those participants who were on the lifestyle programme were asked to comment on the Total Wellbeing Diet.

Feedback was generally positive regarding the book with people finding it a 'good book to read'. Areas of improvement included making the recipes and meal plans more practicable for busy families:

"Beautiful menus but really we're just trying to get a meal on the table"

"Just have some plainer stuff. A lot of the recipes are really fancy, takes time to make. Fruit and veg is also very expensive and meat costs a lot – the cost"

One person did comment that the smaller leaflet was better than the book as it was simple and basic and obviated the need to read the whole book.

What aspects were useful in helping you stick to it?

The monitoring tools provided as part of the study (tablet checklist and food diary) were reported as being useful by participants in the relevant study arms:

"Food diaries were good. Tedious but reinforcing what you had during the day."

"Pretty much the checklist – helped me fix with the tablets. Bit had as lots going on in life."

Within the lifestyle arm the monitoring visits were also seen as being very useful in helping people stick to the diet.

"Definitely think the visits. Were really useful as you feel bad if you don't loose anything at the weigh in. being weighted there is good as you don't believe your own scales"

"Just had to be accountable every two weeks, was really good"

The menu plans in the lifestyle arm were also seen as being useful.

"Did try to follow meal plans. Really like them as I don't have to think. Good to map things out and didn't have to think about serves."

Additional information or support

Participants were asked what additional information or support they might like.
Of the seven responses for more information these covered general information, more advice on exercise and information about food. This dealt with general nutritional information, recipes, how to develop health meals that would also accommodate family members' wants or needs as well as advice on which convenience foods where appropriate.

"I get stuck with things to eat, with recipes. More would be nice. Food that's good but tastes nice. Diet food can be really dull."

"Want easy, fit in around the child. Food for all the family."

"Probably try and let people know what frozen meals are out there. Wanna know that something's ok to eat. Want quick, convenient AND healthy."

17 ideas for additional support were provided. Of these, seven related to additional support regarding exercise, generally focussed on exercise buddy's/support or access to a mentor though some participants did mention problems of access to exercise equipment.

"Set up a physical exercise support group as well"

"Maybe a structured gym thing – have a partnership with a gym so you get training, more variety [of exercise] and in winter you can't go walking and I can't afford a treadmill"

"Someone to monitor exercise or even style an exercise program for you body type and things in your life"

Other ideas for additional support included social/group support, more access to various health specialists, such as nutritionists, assistance with child care and assistance/mentoring with realistic goal setting and the reasons underpinning your weight loss goals as well as negotiating friendship groups.

"Someone, a mentor. One on one. This is where we're at, direction for a week, boss me around, kick me into gear."

"Long term goal and a reason other than looking pretty. I don't think that's enough."

"Only other thing is to look out for diet saboteurs. Stress to friends, this is what I have to do."

"Regular contact with others like you, either daily – giving support during the week. In the same mode, others supporting you in the same situation."

An interesting idea raised by two participants was for assistance with time management and how to plan one's day

"Probably good organisation tips – work and home life. [I] find it difficult as back to full time work and no time to do things at home"

"Scheduling self is really difficult – maybe have someone to help you out the first time to help you plan your day/time efficiently. Eg. Exercise around the kids."

Tips for others

Of those who provided tips for others, motivation was raised by those in the lifestyle arm. These comments addressed issues of maintaining motivation, being initially certain that this is what you want to do and to deal effectively with setbacks.

"Probably, be persistent. Have a bad day, focus on what you've got to do, move on, focus on the diary"

"I'd say it takes effort, not something you can do by half. Be motivated, try not to get downhearted"

Organisation and having sufficient time to commit to the program was also raised by people in both treatment arms.

"Try and go part time while you do it! Try and have enough time to allocate to the study. Every time I'd have a visit I'd try and have a half day at work. I then had to make up the hours after my appointment."

"Recommend not working full time so they can get to the appointments. It's not short either, had to sit and wait. Purely my working hours and their opening hours didn't match"

These comments further reinforce the issues associated with appointment times.

The monitoring aspects of the programme, food diary and appointments, were seen as being useful.

"…stick to diary and appointments, being answerable. If not weighed, no one knows about having a bad week."

Also using the various supports provided – monitoring tools, website and staff contact – were also raised by some participants as being helpful.

"Not really, maybe stay in contact with those running it. If have problems they usually make you feel better/will help. Was really good, people may feel less inclined to quite if feeling bad."

Lifestyle specific

Diet/exercise program

Participants generally commented on the exercise program and this was seen as the more difficult aspect to modify. Common issues were finding the time to commit to the exercise program or when the time was available to exercise, being too tired.

"First month, difficult to fit in. Get home at 6ish, cooking etc. finish at 8:30/9 then bed at 9:30. Difficult to fit in"

"Fitting it in was a little bit difficult, just time and also energy. When had time to myself was either tired or had other stuff to do. Difficult to put self first."

However, there were also numerous comments that when they could find the time the exercise programme itself was quite easy

"From what I had to do, it was pretty easy. Exercises, biking, was easier than going to a gym"

"Good we had a choice [of exercise] as didn't get into the stretching (resistance bands) and we could change this – go for walks"

Staff contact

Reinforcing other comments, this was all seen as very positive.

"Very reassuring and very friendly. Really friendly"

"Good, really good. Siew's really lovely, receptionist lovely"

Monitoring reviews

The reviews were all seen as being positive and helpful experiences with staff being non-judgemental and helping to maintain motivation. The monitoring aspects of the reviews were also seen as supportive.

"Really good, you need to be accountable to someone, good to talk to someone about it and your feelings. [They] didn't judge, were very supportive all the time"

"Very beneficial. Good to ask questions and get answers. Very well explained"

Website – information

The website was not used by all participants who were interviewed. Of those who did use it the responses were positive with questions being answered. The email updates with advice regarding seasonal food issues were pointed out as being particularly useful by one participant.

"Yeah, quite interesting. Didn't look at it a great deal. Email updates were good, had some at Easter time, was good to find out about Easter buns and what we could eat at the time."

Website – social support

Participants did not generally look at this option or felt uncomfortable with adding comments of their own. One participant also reported there not being enough comments or members to make it useful.

"Looked at it but didn't see many. Didn't want to do it, not my thing. Good to have a bit of a read though."

"Used to log on all the time, but no-one else was on when I was. Plus it was early days."

Food/exercise diary

The diaries were generally well received as a useful tool while acknowledging that they could be difficult or tiresome to maintain.

"Good actually as it showed me what I was actually eating (which was surprising) and exercising."

"Painful to do the three day detailed diary. Finding time to do them. The tick boxed one was good."

Socialising on the programme

Barring one participant who did not find any difficulty with socialising participants tended to experience difficulties socialising. This was generally within the context of being difficult with a variety of unhealthy options. One participant did report deliberating limiting their socialising for fear of the effect it would have on the diet.

"Sacred of socialising. Didn't want to go to houses for dinner. Tending more to eat at home and then go around after dinner. Can't get away [with it] all the time. Didn't follow the plan at that time."

"Really, really hard….Try for healthy but lots of stuff doesn't fir in with the diet. Veggies, don't fill me up. Was feeling hungry throughout." (Note: the participant was queried regarding her meat intake and she did report eating this).

Tablet arm specific

Website

The majority of participants did not look at the websites provided and of those who did a few found them useful whereas others felt they did not contain enough information or were too general, ie, no information about pregnancy, no specific information regarding exercises or links as to where one could get involved in such activities.

Remembering /Tablet schedule

No participants reported sustained problems with remembering to take tablets or the schedule.

Tablet checklist

Most participants used the checklist and found it useful. However, there were some issues with remembering to use it or only filling it in before the appointment times.

> *"No (didn't use)..well, filled it out every fortnight."*

> *"Yes. Useful as reminded me to take them."*

Side effects

The majority of people did not report symptoms. Two participants reporting some stomach upset/cramping when they upped their dose but these effects were short lasting.

> *"Cramping (abdomen) at each time I upped the dose. Would go after a few days."*

Staff contact

The positive feedback regarding staff contact was replicated.

Monitoring reviews

Participants were generally positive regarding the monitoring reviews. Specific issues raised included the benefits of receiving feedback via emails and potentially brining in one's one scales to be checked so that weight could be taken at home.

> *"Alright, as got it in my e-mails. Preferred this, was good. Can check whenever I want to."*

> *"Dunno, think an improvement would be if you could take your own scales to see if they're difference and then send in your measurements"*

One participant, who was positive about the contact with staff, actually felt that there was limited monitoring being offered and would have preferred more contact from staff.

> *"Didn't have much monitoring – didn't keep in touch as much as they could. No phone calls or anything. Would be nice tot have people encourage you. Would like someone to talk to on a regular basis, get advice."*

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