The PREVIEW New Zealand study: Prevention of Type 2 Diabetes through Lifestyle Intervention in a Cohort of Overweight Adults with Pre-Diabetes

Amy Yee Liu

A thesis submitted in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy (Biomedical Science),
in the Department of Medicine,
The University of Auckland

December 2018

Abstract

The prevalence of obesity worldwide has increased to a pandemic with more than 1.9 billion people classified as overweight and 600 million classified as obese. Obesity is the cause of long-term chronic disease; affecting social and economic costs worldwide. New Zealand is no exception being 3rd in the OECD for obesity, behind USA and Mexico. More than two-thirds of New Zealanders are overweight and from which 50% are classified as obese. Obesity contributes directly to the cause of T2D; hence, the increasing obesity leads to the increase in the incidence of T2D. This thesis investigates whether dietary intervention, which is aimed at short-term rapid weight loss and then longer-term weight loss maintenance, can be successful for the prevention of T2D in a cohort of overweight, pre-diabetic adults in Auckland, New Zealand. In particular, investigating whether a higher protein, lower glycaemic index (GI) diet is more successful than a higher carbohydrate (CHO), moderate GI diet for weight loss maintenance, and in turn better T2D related metabolic outcomes. This research was part of the larger international PREVIEW (PREVention of diabetes In Europe and Worldwide) intervention.

The aim of this PREVIEW:NZ study thesis investigates the benefits of short term 8-week acute LED-induced weight loss and longer term (2 year) lifestyle-induced weight change on metabolic parameters associated with risk of T2D in Caucasian, Maori/Pacific and Other ethnicity subgroups. The aim of the GI substudy was to analyse the GI of kumara to be able to make diet recommendations in the lifestyle intervention weight maintenance phase.

The primary objectives for PREVIEW:NZ were to investigate changes to body weight, body composition and metabolic markers during an 8-week low energy diet (LED) rapid weight loss phase and then a 2-year lifestyle weight maintenance phase where the diet recommendations were for lower-fat, higher protein, lower GI versus lower-fat, higher CHO, moderate GI; and also to investigate gender and ethnicity differences. A secondary objective was to investigate the GI of sweet potato/kumara, a high CHO staple commonly consumed in New Zealand and an important food in PREVIEW:NZ. The main hypothesis was that, an *ad libitum* novel low fat, higher protein, lower GI diet would result in better weight loss maintenance and T2D-related metabolic markers when compared to a traditional low fat, higher CHO, moderate GI diet that adheres to current recommendations for T2D prevention.

PREVIEW:NZ comprised of 2 phases. Phase 1 was an 8-week LED weight loss phase where participants attended the clinic every 2 weeks for group counselling and measurement of body weight; followed by Phase 2, a lifestyle weight maintenance phase where higher protein or higher CHO advice was followed and participants attended the clinic every 6 months for 2 years. Clinical investigation days (CIDs) were conducted at baseline (CID1), 2 months (CID2), 6 months (CID3), 12 months (CID4), 18 months (CID5), 24 months (CID6), for anthropometry assessment and blood tests. Recruitment was conducted within the Auckland region. Overweight participants were invited to the Human Nutrition Unit for screening using an oral glucose tolerance test (OGTT) to determine those who were pre-diabetic. During the weight maintenance phase, in addition to

CIDs there were also group-counselling sessions, which followed a fading visit design. In total, PREVIEW: NZ had 8 CID/group visits in the first year and 3 in the second year. Instruction on diet and exercise was provided with additional 'homework' prior to the CID, which included a 4-day self reported food diary to monitor dietary intake.

This thesis presents findings from 3 studies. Chapter 3 presents Phase I of PREVIEW:NZ which is the 8 week LED intended to achieve rapid weight loss goal of ≥8% body weight. Chapter 4 presents Phase II of PREVIEW:NZ which is the 2-year weight loss maintenance lifestyle intervention. Chapter 5 presents a GI sub-study conducted in a group of lean healthy participants.

In total, 321 participants were eligible and registered to start the PREVIEW:NZ study, of which 305 participants attended the first CID1/Baseline visit and 267 completed the 8-week LED and attended CID2/Post LED. The baseline characteristics of the 267 participants who attended CID2/Post LED were predominately female (76%), and Caucasian (58%) when compared to 33% Maori/Pacific and 9% Other ethnicities (including Asian). The 8-week LED weight loss phase resulted in mean (SEM) body weight loss of -11.5 (0.3) kg and -10.7 (0.3) %. 249 out of 267 (39%) who attended CID2 achieved the required ≥8% weight loss goal. Men were significant heavier at baseline and lost the most absolute body weight. Maori/Pacific were significantly heavier than Caucasian and Other at baseline and also lost the most absolute body weight. During the LED phase, there was an improvement in glycaemia in all participants with no gender or ethnic specific differences seen. A greater change in fasting plasma glucose (FPG) was found with a greater change in body weight and FM. Other markers of metabolic health including fasting insulin, insulin resistance assessed through HOMA-IR, beta cell function assessed through C-Peptide, and inflammation assessed through hs-CRP, as well as blood pressure and lipid profile, significantly improved in all participants following weight loss.

Chapter 4 presents Phase II, the 2-year weight maintenance phase. Regression analysis was conducted 'blinded' to diet group in 2 ways; categorical and continuous multivariant analysis. Information on randomised diet groups was not available for data analysis in this thesis, as the international multi-centre PREVIEW intervention had not yet been completed. The categorical analysis compared the higher protein vs. the higher CHO diet groups, differentiated using reported diet data from the 4-day food diary at CID3/6 months. The continuous multivariant analysis used 3 methods of statistical analysis, (i) observed data only, plus imputation using (ii) last-value-carried–forward and (iii) multiple imputation The categorical analysis showed both diet groups maintained some of the anthropometric and metabolic improvements of the LED, remaining below the pre-trial baseline by the end of the 2-year follow-up; but notably with no difference between the 2 diet groups. The continuous analysis using observed data showed a small but significant inverse relationship with protein content of the diet, where an increase in 10en%protein was associated with better weight loss maintenance of ~1kg during Phase II. There were no gender differences, however Maori/Pacific was found to have more rapid weight regain, 3 kg over 2 years, when compared to Caucasian. Over time, there was also an increase in total

energy intake over the 2-year follow-up. The results from the continuous multivariant analysis using imputation showed similar findings.

Chapter 5 presents results from 2 kumara and GI substudies, each conducted in 10 lean, healthy individuals, and using the International GI methodology protocol with monosaccharide glucose as the control food. The statistical analysis used AUC for glucose (0 to 120 min), delta change, and incremental AUC glucose. *Post hoc* testing was performed using Tukey's pair-wise comparison at time 0, 15, 30, 45, 60, 90 and 120 minutes. The first kumara and GI study used calculated available CHO values, and found kumara to be a very high-GI food item. The unexpectedly high results led to this study being repeated using measured available CHO values, analysed at a local accredited food analysis company. Substudy 1 using the calculated values showed that kumara has a high GI of 99 units, reduction of GI was found when consumed hot and with skin due to the changes to resistant fibre. Substudy 2 using the analysed values, and confirmed the very high-GI value of kumara, as shown in both studies.

In conclusion, this thesis demonstrated a number of important outcomes. Firstly, an 8-week meal replacement LED was an effective method of short-term rapid weight loss for those overweight and at high risk of developing T2D, when assessed in a multi-ethnic cohort of adults from the Auckland region. It was able to achieve significant improvements in both anthropometry and glucose-related and other metabolic markers, with some evidence that men may have greater health improvements than women. Surprisingly however, there were no ethnic differences in terms of metabolic improvements. Secondly, 2 years of lifestyle intervention for weight loss maintenance had some success, with those who achieved ≥8% body weight loss during the LED having some rebound weight regain, but not returning to pre-trial levels of overweight during the 2 years of this thesis. This also was seen in the metabolic endpoints, with gradually worsening glucose and other markers. Unexpectedly, there was no evidence that recommendations to replace dietary fat with higher levels of protein rather than CHO had a clinically relevant effect on body weight or metabolic endpoints, with +10en% protein increase expected to result in only ~1kg better weight loss maintenance over 2 years. Changes in GI were difficult to achieve, with GI response to foods quite unpredictable, and so may not be a useful tool for diet education. There were no clear differences between men and women, but Maori/Pacific regained more weight when compared to Caucasian during weight maintenance. Use of an LED followed by regular support during the weight maintenance phase with inclusion of a 'rescue' protocol to promote compliance and sustained weight loss maintenance may improve the outcomes from low-fat higher protein diet regimes, which require further research before they can be recommended for T2D prevention.

Acknowledgements

Firstly, I would like to express my sincere gratitude to my advisor, supervisor and mentor, Professor Sally Poppitt for the continuous support of my PhD study and related research, for her patience, motivation, and immense knowledge. Her guidance helped me in all of the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my PhD study.

I would also like to express my gratitude to Associate Professor Clare Wall as my other supervisor for her insightful comments and encouragement throughout my PhD.

Besides my supervisors, I would also like to give a special thanks to Dr Marta Silvestre for your constant stimulating and insightful comments, which incented me to widen my research from various perspectives. I would also like to thank Dr Yannan Jiang, Senior Clinical Statistician for your advice and expertise.

A very special gratitude goes to my Professional Dietetics Leader, Kerry McIlroy, who introduced Professor Sally Poppitt to me to enable me to commence this amazing research.

I thank my past and current research colleagues at Human Nutrition Unit. Thank you all for the stimulating discussions, for the long days we were working together for the clinical investigation days, packing the LEDs, evening and weekend group meetings, and for all the fun we had in the last 4 years. Special acknowledgements to the Health Research Council for providing the funding for the PREVIEW:NZ study.

I am also grateful to the past and current colleagues at Auckland Diabetes Centre for your support and motivation throughout my PhD studies. In particular, I am grateful to Dr Paul Drury for enlightening me the first glance of clinical research.

To my life-coach, my late mother, Ann Liu: because I owe it all to you. Thank you for your constant encouragement to aim high but also do the things I love the most.

Last but not the least, I would like to thank my complaisant partner, Darryl Carey and my loving father, Tommy Liu for your constant encouragement, understanding and support; and for doing all the household chores during my thesis. Also thank you to my family and friends for your constant support, both physically and emotionally throughout this thesis and in my life in general.

Thanks for all your encouragement.

Table of Contents

List of Figures

List of Tables

List of Appendices

Abbreviation/Glossary

2h-PPG	2-hour Postprandial Plasma Glucose
ADA	American Diabetes Association
Adipose	Fat
AHA	American Heart Association
BMI	Body Mass Index
BP	Blood Pressure
BW	Body weight
C	Control
CHO	Carbohydrates
CID	Clinical Investigation Day
CODEX	Codex Alimentarius, or "Food Code"
CRF	Clinical Record Forms
CRP	C-reactive protein
DBP	Diastolic Blood Pressure
DioGENES	Diet, Obesity and Genes European multicentre trial
DiRECT	Diabetes in Remission Controlled Trial
DPP	Diabetes Prevention Program
DPPOS	DPP Outcome Study
DPS	Diabetes Prevention Study
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eCRF	Electronic case record form
EDIPS-Ncl	UK European T2D Prevention Study-Newcastle
EI	Energy Intake
en%CHO	Percentage energy of carbohydrate
en%fat	Percentage energy of fat
en%protein	Percentage energy of protein
en%saturated fat	Percentage energy of saturated fat
F/U	Follow-up
FDA	Food and Drug Administration
FFA	Free Fatty Acids
FFM	Fat Free Mass
FDRS	Finnish Diabetes Risk Score
FM	Fat Mass
FPG	Fasting Plasma Glucose
FSANZ	Food Standards Australia and New Zealand
GD	Gestational Diabetes
GGT	Plasma γ-glutamyltransferase
GI	Glycaemic Index
HDL-C	High Density Lipoprotein Cholesterol
H-GI	High Glycaemic Index
HNU	Human Nutrition Unit
HOMA-IR	Homeostasis Model Assessment for Insulin Resistance
HC	Higher Carbohydrate
HP	Higher Protein
HR	Hazard Ratio
IANZ	International Accredited New Zealand
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance

IHD	Ischaemic Heart Disease
IL-6	Interleukin-6
Insulin	Fasting Serum Insulin
IR	Insulin Resistance
JDPP	Japan Diabetes Prevention Program
kcal	kilocalories (energy)
kJ	kiloJoules (energy)
Kumara	Sweet Potatoes
LDL-C	Low Density Lipoprotein Cholesterol
LED	Low Energy Diet or Low Calorie Diet (LCD)
L-GI	Low Glycaemic Index
Look AHEAD	Look Action for Health in Diabetes study
LP	Lower protein
MC	Moderate Carbohydrates
M-GI	Medium Glycaemic Index
MJ	MegaJoules (energy) (1MJ = 1000kJ)
MOH	Ministry of Health (New Zealand)
MRFIT	Multiple Risk Factor Intervention Trial
NCD	Non-Communicable Disease
NG	Normoglycaemic
NZSSD	New Zealand Society for the Study for Diabetes
O/W	Overweight (BMI ≥25kg/m^2)
OECD	Organisation for Economic Cooperation and Development
PA	Physical Activity
RCT	Randomised Controlled Trial
RR	Relative Risk
RYGB	Roux en-Y Gastric bypass
SBP	Systolic Blood Pressure
SFA	Saturated Fatty Acids
SLIM	Study on lifestyle-intervention and impaired glucose tolerance Maastricht
SMART	Specific, Measurable, Achievable, Realistic and Time-bound goals
T2D	Type 2 Diabetes
TC	Total Cholesterol
TC:HDL ratio	Total Cholesterol: High Density Lipoprotein Cholesterol Ratio
TDR	Total Diet Replacement
TE	Total Energy Intake
TG	Triglycerides
TNF-α	Tumour necrosis factor
UK	United Kingdom
USDPP	US Diabetes Prevention Program
USD	American Dollars (currency)
USDA	US Department of Agriculture
VLED	Very Low Energy Diet or Very Low Calorie Diet (VLCD),
WC	Waist Circumference
WHO	World Health Organisation

Chapter 1 Introduction

The prevalence of obesity is increasing worldwide with the number of those overweight (O/W) and obese having almost doubled from year 1980 to 2008, creating a worldwide obesity pandemic. More than 1.9 billion people are classified as O/W and 600 million are classified as being obese (Swinburn et al., 2011; World Health Organization, 2017). Obesity is a major contributor to the overall chronic disease burden and disability, with significant social and economic impact (World Health Organization, 2017). Obesity is the leading modifiable risk to health and it has been associated with chronic conditions, health complications, overall death and rising economic health costs (Heymsfield & Wadden, 2017; Swinburn et al., 2011). There is strong evidence suggesting that obesity increases comorbidities linked to metabolic syndrome. These include stroke, hypertension, cardiovascular disease, cancers (prostate, breast, liver, kidney, colon, ovarian and endometrial) and Type 2 Diabetes (T2D) (Calle et al., 1999; Calle et al., 2003; Deng & Scherer, 2010; Guiducci et al., 2013; Penn. et al., 2009; Perez, 2013). As the obesity prevalence increases so does the incidence of these chronic conditions, leading to increased health costs and economic expenditure.

The International Diabetes Federation (IDF) claims that 415 million (or 8.8% of the global population) adults have T2D worldwide, with 318 million with pre-T2D or impaired glucose tolerance, expected to increase to 642 million (or 10.4% of the global population) and 482 million, respectively by 2040 (Cefalu et al., 2016). In order to prevent the rising numbers of these obesity-driven conditions, it is essential to target the global obesity challenge. It is estimated that the global cost of obesity is $2.1 trillion USD per year, which equates to the combined cost of armed violence, war and terrorism and is linked to 5% of all annual deaths (Dobbs et al., 2014). From 1975 to 2014, there has been a six-fold increase in obesity. The World Health Organisation (WHO) aims to stop the rise of obesity rates to “virtually zero”, from year 2010 to 2025 (NCD Risk Factor Collaboration, 2014). As well as dietary and exercise lifestyle interventions, effective communication, expansion of regulation and fiscal policies are some other strategies suggested to tackle obesity (OECD, 2017).

1.1 Obesity

1.1.1 Global Obesity Pandemic - Prevalence and Aetiology of Obesity

The prevalence of obesity is on an upward trend worldwide and has almost doubled between 1980 and 2008. In 1980, only 5% of men and 8% of women had a BMI ≥30kg/m^2. Currently, one in two adults and nearly one in six children are O/W or obese, which equates to an increased 10% in men and 14% in women (OECD, 2017; World Health Organization, 2017). It is estimated that 1.9 billion adults and 41 million children were O/W in 2014, of these 600 million adults were obese (BMI≥30kg/m^2) (World Health Organization, 2017), a number that has increased six-fold from 1975 to 2014 (NCD Risk Factor Collaboration, 2014) and is projected to increase further by year 2030 (OECD, 2017). Current global pandemic has more than 50% of the world’s population classified as O/W (39% O/W and 13% obese) (World Health Organization, 2017). O/W is

classified as having excessive weight of at least 20% higher than what it should be against height (m^2), with a BMI of 25.0-29.9kg/m^2, whereas obesity is classified as having a BMI of ≥30kg/m^2. The global pandemic of this obesity issue has many detrimental effects on health factors, social aspects and the rising economic cost to the health budget due to the positive correlation to the development of many chronic conditions such as cardiovascular effects, T2D and some cancers (Blackstone, 2016; Chan, 2017; Gittelsohn & Trude, 2017; Guiducci et al., 2013; Nichols et al., 2013; Palou & Bonet, 2013; Rigby, 2013; Ruan et al., 2013; Statistics New Zealand, 2016; Wing et al., 2004). Adult obesity rates are highest in United States, Mexico and New Zealand with 1 in 3 adults (>30%) being obese, while lowest in Japan and Korea at 3.7 and 5.3%, respectively (OECD, 2017). Over the past decade, the obesity prevalence has increased in Mexico, United States, Canada, France and Switzerland, but has stabilised in England, Italy, Spain and Korea (OECD, 2017). However, Korea and Switzerland are the two countries projected to increase at a faster rate with projected rates of obesity of 9 and 15%, respectively, in year 2030 (OECD, 2017). The obesity levels are projected to be 47%, 39% and 35% by 2030 for United States, Mexico and England, respectively (OECD, 2017).

Policies and initiatives to tackle obesity have occurred over the last few years around the world. These strategies include pricing and fiscal measures, such as taxation of unhealthy food (e.g. sugar tax) to increase the price of potentially unhealthy food options, and aim to drive the consumer to healthier, cost effective options. These measures have been introduced in Mexico, Belgium, Chile, Finland, France and Hungary (OECD, 2017). Other strategies include reformation of products and restricting portion sizes using specific guidelines, work-based and school-based lifestyle intervention and intervention in primary care and within the community (OECD, 2017). Other policies around communication address the need to improve health literacy, specialised marketing regulations and food label requirements to assist with consumer understanding and buying power, such examples include changes to food labelling of nutrient list, traffic light system and use of information logo (OECD, 2017). Echini et al suggest the benefits of the 'traffic-light' system increasing healthier option section by 17.95%, and a 3.59% reduction in calorie intake (Cecchini & Warin, 2016). This unsustainable economic costs and pressure to the healthcare system is preventable or reduced by delaying the diagnosis of chronic conditions and micro- and microvascular complications (Arena et al., 2017; Buhler et al., 2013; Knowler et al., 2009; Zhang et al., 2013). Withrow et al estimates an increase of 30% in health cost of people who are O/W, when compared to the healthy weight population (Withrow & Alter, 2011).

Obesity is a complex condition influenced by multiple factors including genetics, physiological, metabolic, social, environmental and psychological factors (Ogden et al.; Swinburn et al., 2011; Wadden & Stunkard, 1993; World Health Organization, 2017). Gender differences, education and socio-economic background are linked to obesity (OECD, 2017). Women have higher rates of obesity than men, but the rate of obesity in men is increasing. Less educated women are 2-3 times more likely to be O/W than those with a higher level of education, however in United States, obesity rates have been increasing most rapidly among high educated people (OECD, 2017). Within the labour market, obese people have poorer job prospects and contribute to reinforcing

existing social and health inequalities (Devaux & Sassi, 2015). People who are obese have been reported to earn 10% less than those who are not obese with negative labour market outcomes i.e. less productivity, more sick days and fewer worked hours (OECD, 2017). Obesity is associated with the metabolic syndrome and is linked with insulin resistance (IR) (Lee. et al., 2013; Singleton et al, 2003; Zimmet. & Baba, 1990; Zócalo et al., 2017). Impaired glucose tolerance (IGT) is one of the factors for metabolic syndrome and is a state of insulin resistance (IR) shown to predict both large- (macrovascular) and small-vessel (microvascular) outcomes (Singleton et al., 2003). Microvascular outcomes can contribute from chronic impaired glucose control e.g. renal disease (nephropathy), diabetes related eye disease (retinopathy) and nerve damage (neuropathy). Macrovascular complications include coronary artery, cerebrovascular and peripheral vascular disease (Lee. et al., 2013; Zócalo et al., 2017). An obese state leads to increased release of free fatty acid and adipocytokines from adipocytes causing inhibition of nitric oxide-medicated vasodilation leading to direct metabolic injury of endothelial and end-organ cells all contributing to vascular damage (Singleton et al., 2003).

1.1.2 Classification of Overweight and Obesity

O/W and obesity are classified by using body weight (BW) (kg) and height (m), following the equation weight (kg) / height squared (m^2). Optimum health is determined with having a body mass index (BMI) of 21 to 23kg/m^2 in the adult population, while the goal for individuals should be to maintain BMI in the healthy range of 18.5 to 24.9kg/m^2 (World Health Organization, 2017). There is increased risk of co-morbidities for those O/W (with a BMI of 25.0 to 29.9kg/m^2), and moderate to severe risk of co-morbidities for those obesity (with a BMI ≥30kg/m^2) (World Health Organization, 2017) (see Table 1 below). Previously, WHO had ethnic specific BMI but this was removed, even though a lower cut-off is suggested for Asian population and a higher cut-off for the Maori/Pacific population due to adipose distribution (Fantuzzi, 2005; Rush et al., 2007; Rush et al., 2009; Vazquez et al., 2007).

$$\text{BMI} = \frac{\text{WEIGHT (kg)}}{\text{HEIGHT (m)}^2}$$

Table 1: BMI classification in adults

Classification	Underweight	Healthy Weight	O/W	Obesity Class I	Obesity Class II	Obesity Class III
BMI range (kg/m^2)	<18.5	18.5-24.9	25-29.9	30-34.9	35-39.9	>40

BMI, Body Mass Index = the weight (kg) divided by the square of the height (m) = kg/m2, extrapolated from WHO BMI classification (World Health Organisation, 2016), O/W, overweight

Adipose tissue is required for normal pathological and physiological functions, to regulate energy expenditure, insulin sensitivity, endocrine and reproductive system, metabolism of bone, immunity, appetite and inflammation (Genoni et al, 2013; Liu et al, 2005). BMI is an index of adiposity, that provides a simple measure of O/W and obesity, which in large cohorts is strongly related to disease risk. Obesity, calculated using BMI, is associated with increased mortality shown in an U-shaped curve (Carmienke et al., 2013). However, ectopic fat or central fat

distribution has a stronger association with mortality showing a J-(WHR) shaped curve (Carmienke et al., 2013). The site of lipid deposition appears to be critical to morbidity and mortality risk (Carmienke et al., 2013).

1.1.3 New Zealand - Prevalence of Obesity

New Zealand, like other countries is also following the same trend of obesity rates and is currently rated third when compared to the rest of the 'Organisation for Economic Cooperation and Development' (OECD) countries, behind only US and Mexico (OECD, 2017). The New Zealand Health Survey reported that two-thirds (65%) of New Zealanders are O/W, half (or 32.2% of the total, increased from 26.5% in 2006) are classified as obese, with 31% of New Zealand children classified as O/W or obese (Ministry of Health, 2016; Statistics New Zealand, 2016). A breakdown in ethnicity shows 50.2% of Maori adults and 15% Maori children were obese and 68.7% of Pacific adults and 30% Pacific children were obese (Ministry of Health, 2016; Ministry of Health, 2017) . Poverty has been shown to increase risk of obesity with 1.7 times more likely for adults and 5 times for children to be obese who live in the highest deprivation, when compared to the least deprived (Ministry of Health, 2011; Ministry of Health, 2016; Ministry of Health, 2017). The Pacific population has the highest rate of obesity of 68.7%, from 61.4% in 2011/12 and 63.4% in 2006/07 (Ministry of Health, 2017). The Maori population has the second highest rate of obesity at 50.2%, also increased from 44.1% in 2011/12 and 41.6% in 2006/07 (Ministry of Health, 2017). The rate of obesity for the European population is 30.5%, increased from 25.7% in year 2011/12 and 22% in 2006/07 (Ministry of Health, 2017; Statistics New Zealand, 2016). The obesity rates in the Asian population have over doubled over the past decade with some stability, from 6% in 2006/07, 15.9% in 2011/12 to 14.8% in 2016/17 (Ministry of Health, 2017; Statistics New Zealand, 2016). Table 2 shows the increasing obesity trend over the past ten years. The main issue in New Zealand and around the world is that obesity is rising in the younger population, whereas 1 in every 10 (12.3%) children aged 14 years and under is now classified as obese, according to the 2016/2017 New Zealand Health Survey. Table 3 shows the increase in extreme obesity (BMI >40kg/m^2) in the adult New Zealand population (Ministry of Health, 2011; Ministry of Health, 2016; Ministry of Health, 2017; Ministry of Social Development, 2016).

Table 2: Obesity rates (BMI>30kg/m^2) in New Zealand from 2006 to 2017

Obesity Rates	2006/07	2011/12	2016/17
Adult population	26.5%	28.6%	32.2%
- European	22.0%	25.7%	30.5%
- Maori	41.6%	44.1%	50.2%
- Pacific	63.4%	61.4%	68.7%
- Asian	6.0%	15.9%	14.8%
Children (0-14 years)	8.4%	10.7%	12.3%
- Maori (obese / O/W)	11.8 / 41.6%	16.7 / 44.1%	18.1 / 46.5%
- Pacific (obese / O/W)	23.1 / 63.4%	25.0 / 61.4%	29.1 / 66.2%

New Zealand data: table extrapolated from Ministry of Health, 2017

Table 3: Extreme obesity rates (BMI>40kg/m^2) in New Zealand from 2006 to 2017

Obesity Rates (BMI>40kg/m^2)	2006/07	2011/12	2016/17
Adult population	3.4%	4.0%	5.5%

BMI, Body Mass Index (kg/m^2); New Zealand data: table extrapolated from Ministry of Health, 2017

Table 4 shows the adjusted rate ratio of obesity risk (BMI ≥ 30kg/m^2) for the adult population from the Statistics New Zealand data (Statistics New Zealand, 2016). This shows small differences between genders, with significantly increased risk in ethnic minority groups of 1.7 and 2.4 for Maori and Pacific, respectively. Deprivation shows an increased obesity rate ratio of 1.7 compared to those not affect by deprivation (Ministry of Health, 2017; Statistics New Zealand, 2016).

Table 5 shows the adjusted rate ratio of obesity (BMI ≥30kg/m^2) for the children population from the Statistics New Zealand data (Statistics New Zealand, 2016). This shows small differences between genders, with significantly increased risk in ethnic minority groups of 1.6 for Maori and an astounding 3.9 risk ratio for Pacific children. Deprivation shows a much higher rate ratio of 3.0 for children (Statistics New Zealand, 2016).

Table 4: New Zealand Adult Obesity rates adjusted rate ratio between ethnic groups

Adult obesity rates (BMI ≥30kg/m^2)	Adjusted rate ratio
Men vs. women	0.9
Maori vs. non-Maori	1.7*
Pacific vs. non-Pacific	2.4*
Asian vs. non-Asian	0.5*
Most vs. least deprived	1.7*

*P<0.05; extrapolated from Statistics New Zealand, 2016

Table 5: New Zealand Child Obesity rates adjusted rate ratio between ethnic groups

Child obesity rates (BMI ≥30kg/m^2)	Adjusted rate ratio
Boys vs. girls	0.9
Maori vs. non-Maori	1.6*
Pacific vs. non-Pacific	3.9*
Asian vs. non-Asian	0.7
Most vs. least deprived	3.0*

*P<0.05; extrapolated from Statistics New Zealand, 2016

1.1.4 Causes of Obesity

Multiple non-modifiable, modifiable and other factors are shown to contribute to the increasing rates of O/W and obesity worldwide. Non-modifiable risk factors include ethnicity, genetic predisposition, endocrine-related medical conditions and changes to stages of life i.e. post menopause and ageing (Mahan et al., 2007; World Health Organization, 2017). Lifestyle is one of the modifiable factors through energy imbalances. Excess weight is developed over time when energy intake exceeds energy expenditure. Excessive consumption of calories, especially

through fat, sugar and alcohol can lead to weight gain over the long-term (Chan, 2017; Chan et al., 1994; Guiducci et al., 2013; McLean et al., 2009; OECD, 2017). Poor nutrition and physical inactivity leads to excess adipose tissue, local adipose inflammation, which over time may develop into chronic systemic inflammation, IR, hypertension, arterial dysfunction plaque, abnormal cell growth, ultimately increasing chronic disease risk (Arena et al., 2017; Pedersen, 2009).

Behaviour from mental health disorders can also increase risk of developing obesity through emotional binge eating or cravings for high fat and sugar foods (Palou & Bonet, 2013). Large quantities of food through large portion sizes can also increase overall energy intake leading to O/W and obesity. A reduction in physical activity leads to reduced energy output or energy expenditure, caused from increase in sedentary activity, whilst consuming high energy snacking while watching TV and reduced physical activity or exercise (Reeves et al., 2013). Other causes include endocrine related conditions, medication adverse effects leading to an increase in appetite, mental health condition, smoking cessation leading to increased appetite, sleep deprivation, social factors and surrounding affordability of unhealthy vs. healthy food. How these factors affect the development of obesity is not completely elucidated but some mechanisms have been proposed. With increasing age, the hormonal changes across the perimenopause substantially contribute to increased abdominal obesity leading to physical and psychological morbidity (American Diabetes Association, 2018; Astrup & Rössner, 2000; Baird et al., 1974; de Boer. et al., 2013). Inadequate sleep has been shown to cause a reduction in circulating leptin and an increase in circulating ghrelin, resulting in a reduction of insulin sensitivity (Gangwisch et al., 2005; Yaggi.et al., 2006). Smoking may also enhance the negative health effects of obesity. In the USA, 4.7% of those who are O/W also smoke (Healton et al., 2006). Moreover, major weight gain has been correlated to smoking cessation (Williamson et al., 1991). Obesity and socioeconomic status have also been shown to correlate positively, especially in highly developed countries (McLaren, 2007; Sobal & Stunkard, 1989). In New Zealand, as obesity increases, there is an increased trend in blood pressure, cholesterol levels, arthritis, chronic pain and mood/anxiety disorders, as indicated on Table 6. Table 7 reports the change in macronutrient intake from 1997-2016 with gender and ethnic differences (Ministry of Health, 2006; Ministry of Health, 2016; Parnell et al., 2011).

Table 6: Obesity rates and chronic conditions in New Zealand from 2006 to 2016

	2006/07	2011/12	2015/16
Obesity Rates	26.5%	28.6%	31.6%
High Blood Pressure	13.8%	16.0%	16.3%
High Cholesterol	8.4%	10.5%	11.3%
IHD	5.3%	5.5%	4.6%
Arthritis	14.9%	15.1%	17.0%
Chronic pain	17.0%	16.2%	19.9%
Mood/anxiety disorders	12.7%	16.3%	17.4%

IHD, Ischaemic heart disease

New Zealand data: table extrapolated from Ministry of Health, 2016

Table 7: Intake of macronutrients (grams/percentage TE) in New Zealand from 1997-2016

	1997	2008/09	2015/16
Carbohydrates	165g/46.0%	250g/46.6%	
Male	305g/45.0%	289g/46.0%	
Female	214g/47.0%	213g/47.0%	
Maori - male	42.0%	301g/43.9%	
Maori - female	47.0%	220g/46.6%	
Pacific – male	45.0%	304g/46.8%	
Pacific - female	47.0%	236g/48.1%	
Caucasian – male		288g/46.2%	
Caucasian - female		211g/47.1%	
Protein	88g/15.6%	88g/16.5%	18.6%
Male	105g/15.0%	104g/16.4%	
Female	71g/16.0%	73g/16.5%	
Maori - male		114g/16.8%	
Maori - female		76g/16.3%	
Pacific – male		109g/16.8%	
Pacific - female		81g/16.9%	
Caucasian – male		103g/16.4%	
Caucasian - female		73g/16.4%	
Fat	34.9%	83g/33.7%	%
Male	110g/33.7%	97g/33.7%	
Female	36.0%	70g/33.8%	
Maori - male	34.0%	113g/36.6%	
Maori - female		75g/35.6%	
Pacific – male		103g/34.2%	
Pacific - female		78g/34.7%	
Caucasian – male		95g/33.4%	
Caucasian - female		69g/33.6%7	

New Zealand data: table extrapolated from New Zealand Health Strategy 2016; NHMRC 2006 NZ Adult Nutrition Survey 2008/2009, 2011

1.1.5 Consequences of Obesity

An obese state causes chronic low-grade inflammation, by increasing inflammatory markers, such as, C-reactive protein (CRP), Tumour necrosis factor (TNF-α) and interleukin-6 (IL-6) (Bullo et al., 2013; Clement et al., 2004; Fantuzzi, 2005). These proinflammatory cytokines and hormones are

released by adipose tissue generating a chronic inflammatory profile, which is linked with visceral or central adiposity (Wisse, 2004). Increased fat leads to an increase in the adipocyte-derived secretory factors, adipocytokines (fat (adipo), cell (cyto-) and movement (kines)) – the movement of body fat (also called adipokines). Dysregularity of adipokines leads to a direct impact on the homeostasis of the metabolic system, causing increased risk in obesity, T2D, hypertension and cardiovascular disease (Deng et al, 2010). Obesity and metabolic disorders are both accompanied by low-grade chronic inflammation and insulin sensitivity (Saltiel & Olefsky, 2017). Inflammation can be measured by CRP, using high-sensitivity C-reactive protein (hs-CRP); leading to IR and metabolic disease. Insulin sensitivity can be measured by IR using homeostasis model assessment for insulin resistance (HOMA-IR) calculated from fasting glucose (mg/dl) x fasting insulin (µU/ml)/22.5] (Xydakis et al., 2004). Evidence shows that a reduction of chronic excess intra-organ fat through the twin cycle hypothesis can improve IR and prevent or reverse T2D (Lim et al., 2011; Taylor, 2018; Van Achterberg et al., 2010). An impressive 94% reduction in lower triacylglycerol was observed after 8 weeks of LED through the weight loss phase (Lim et al., 2011).

Excessive weight accumulation results in an increased ectopic fat around the liver and pancreas, leading to pancreatic beta-cell dysfunction and impaired organ function (McCombie et al., 2017). Fat that is centrally distributed, also known as ectopic or visceral abdominally-positioned fat, increases the risk of chronic conditions if excessive. Excessive ectopic fat leads to central adiposity, sometimes termed as 'beer belly or beer gut' and also surrounds organs such as the liver, pancreas, muscle and heart, posing as a high health risk with strong correlation between visceral abdominal fat and mortality (Fantuzzi, 2005; Rush et al., 2007; Rush et al., 2009; Vazquez et al., 2007). Ectopic fat is also linked to hepatic (liver) fat which is indicated using triglycerides (TG) and HDL-cholesterol (HDL-C) (Singh et al., 2017). Liver fat was found to be almost 3 times higher in O/W participants than in the healthy weight ones (Zhyzhneuskaya et al., 2017). Subcutaneous or peripheral fat is the type of adiposity that lies immediately under the skin and is distributed evenly throughout the body, including extremities (fingers and toes) (Fantuzzi, 2005). Increased visceral, organ fat or ectopic accumulation has a more direct effect in rising risk of T2D, dyslipidaemia, hypertension and atherosclerosis, than total body (Fantuzzi, 2005; Rush et al., 2007; Rush et al., 2009; Vazquez et al., 2007).

In summary, obesity links inflammation to IR, leading to a deranged fatty acid metabolism and impaired cellular functions (mitochondrial dysfunction and endoplasmic reticulum stress), which ultimately increases the risk of chronic diseases such as T2D (Eckel et al., 2011). Consequently, the large majority of people who are O/W or obese have an increased risk of developing T2D. 'Diabesity' is the term linking the strong correlation and uprising problem between obesity and T2D (Astrup & Finer, 2000). In order to reduce the exponential rise in the T2D epidemic from becoming a pandemic, there is an urgent public health and economic requirement to instigate the prevention of T2D by reducing obesity and maintaining weight loss management through lifestyle interventions, in a population based setting. Eckel et al reported a gradual age being related with weight gain. There is a need to acknowledge this trend and a need to instigate population based

and individual based approaches to promote weight loss and weight loss maintenance over future years (Eckel et al., 2011). Evidence shows that lowering BW by 5-10% or ~15kg in those severely obesity (≥40kg/m^2) improves obesity related co-morbidities such as reduction in T2D and cardiovascular risk factors, even if the person still remains in the O/W or obese range (Leslie et al., 2017). Nevertheless, weight loss can induce changes in appetite hormones that increase hunger levels in people with obesity for at least 3 years (Purcell et al., 2014). Moreover, weight loss causes a persistent reduction in overall energy expenditure, making weight loss maintenance a challenging task.

1.1.6 Obesity and T2D Risk

One of the primary causes of T2D is IR from weight gain and obesity, with the WHO reporting that 2.3 billion adults were O/W (≥25kg/m^2) and that >700 million were obese (≥30kg/m^2), in 2013 (Khavandi et al, 2013). With excessive adiposity being the major risk factor for metabolic disease, these growing numbers are driving the increase in T2D epidemic (International Diabetes Federation, 2013). A typical phenotype for a person with T2D is generally older in age, O/W or obesity, central adiposity, hyperinsulinaemia, dyslipidaemia and hypertension (American Diabetes Association, 2018; Ferrannini, 2014; Khavandi et al., 2013). Excess adiposity drives the worsening IR and/or beta cell dysfunction that is central to the underlying cause of T2D (Alberti & Zimmet, 2014; Dunkley et al., 2014; Ferrannini, 2014; Gittelsohn & Trude, 2017; Gogebakan et al., 2011; McCombie et al., 2017; New Zealand Guidelines Group, 2011; Perez, 2013; WHO & IDF, 2006). IR is influenced by β-cell degradation leading to metabolic syndrome. In people with T2D, there is an initial increase in β-cell mass, expression and proliferation leading to hyperinsulinaemia. Over time, the β-cell gradually becomes exhausted, reduced numbers and worsen over time leading to β-cell apoptosis (Araujo et al., 2013; Dombrowski et al., 2014).

The United States Diabetes Prevention Program (USDPP) showed that weight loss was the dominant predictor for decrease in T2D incidence, with T2D risk decreasing by 16% for every kilogram of BW lost in a 3-year intervention (Diabetes Prevention Program (USDPP) Research Group, 2002; Hamman et al., 2006). A modest 5kg of weight loss reduced the risk of developing T2D by 58%, hazard ratio 0.42 (0.35-0.51, P<0.001) (Hamman et al., 2006). Obesity is the number one risk factor in the current American T2D Standards of Medical Care in T2D and any weight loss (even <5%) has shown lower T2D incidence rates, via improvements in glucose metabolism, systolic blood pressure (SBP) and cholesterol levels (American Diabetes Association, 2018; Zomer et al., 2016). A behavioural modification weight loss interventions have shown that a weight loss goal of 9% achieved over 6 months resulted in a further 6% weight loss, 18 months after the intervention (Moore et al., 2000; Wadden & Stunkard, 1993; Wing et al., 2004). There is sufficient evidence around the benefits of ≥5% weight loss leading to weight loss maintenance of 6% 18 months following initial weight loss goal. However, USDPP study chose to use a weight loss goal of 7% (Diabetes Prevention Program (USDPP) Research Group, 2002). Weight loss not only prevents or delays T2D development but also treats those with T2D resulting in diabetes remission. In the DiRECT Diabetes Remission study compared a more aggressive weight loss using LED to standard care in 306 participants with T2D, resulting in a weight loss of

15kg led to over achieved diabetes remission (defined as achieving HbA_{1C} ≤48mmol/mol and no diabetes medication) in 86% of T2D participants (Lean et al., 2017; Leslie et al., 2016; McCombie et al., 2017; Taylor et al., 2017).

306 participants with T2D lost ≥15kg and established diabetes remission in 86% O/W participants, achieving HbA_{1C} ≤48mmol/mol and no diabetes medication

1.1.7 Factors increasing T2D risk

There are many non-modifiable and modifiable risk factors affecting the risk of T2D development other than excessive adiposity. Non-modifiable factors include increasing age, gender (due to fat being centrally distributed, men's 'apple-shape' is considered higher risk), family history of T2D, weight related medical conditions (such as polycystic ovarian syndrome from weight gain and IR) and previous gestational T2D (T2D during pregnancy), or giving birth to a baby weighing over 4.5kg. Also, pre-diabetes (Impaired Fasting Glucose and/or Impaired Glucose Tolerance) poses a major risk factor for the development of T2D. Modifiable risk factors include smoking and metabolic syndrome (high blood pressure, high cholesterol, impaired glucose tolerance and O/W (centrally distributed obesity), from unhealthy diet and/or physical inactivity.

Of the 3 primary risk factors - family history, age and obesity - the latter is the only modifiable cause of T2D (Ferrannini, 2014). Ethnicity and poverty are also linked with increased risk of T2D. In New Zealand, high risk ethnicities include Maori, Pacific and South Asian with at least double the risk when compared to the New Zealand Europeans (Coppell et al., 2013). In this diabetogenic and obesogenic environment, a population based T2D prevention programme is required to prevent the development in T2D in high risk groups through weight loss and its maintenance, with targeted approaches to the diverse requirements (Raben et al., 2013).

1.1.8 Effect of weight on health risk

In people with T2D, weight loss has improved glycaemia making T2D reversible, establishing diabetes remission (DiRECT) (Lean et al., 2017; Leslie et al., 2016; Taylor et al., 2017; Zhyzhneuskaya et al., 2017). In a large diabetes prevention study with 33,184 participants, Feldman et al collated information at baseline from age 30-60 years and follow-up arranged every 10 years, from 1990 and 2013 in Sweden (Feldman et al., 2017). There was a positive correlational trend of increased BMI with age and increased probability of incident T2D (Feldman et al., 2017). Using weight maintenance as the baseline, resulted in a 52% increased risk (OR 1.52) of developing T2D if any weight gain of >1.0kg/m^2. Weight loss of 1-2kg/m^2 resulted in a 28% reduced risk (OR 0.72) and larger weight loss >2kg/m^2 resulted in a lower risk with an odds ratio of 0.39, 61% (Feldman et al., 2017). In conclusion, there is a public health need to promote weight maintenance for the prevention of T2D, also to promote weight loss for those O/W (BMI ≥25kg/m^2) with targeted interventions for the high risk populations (Feldman et al., 2017). Treatment of obesity using lifestyle changes is linked to energy balance. If energy intake exceeds energy output, this will result in weight gain (McManus et al, 2001).

1.1.9 Metabolic Parameters

In the O/W and obese population, excess adipose fat increases circulating free fatty acids (FFA) to the liver, pancreas and other tissues, leading to increased triglyceride deposits, releasing adipokines, triggering an inflammatory response resulting in IR and reduced insulin sensitivity, affecting plasma insulin as excess insulin (hyperinsulinaemia) is produced to counteract the glycaemia. In 2012, the Counterbalance study was the first qualitative study exploring weight loss using commercial nutritionally complete low energy diet (LED) on T2D participants. The authors monitored patient experience and LED acceptance and found that LED was well accepted and tolerated with the weight loss result being a major motivation factor. In this study, the initial mean (SEM) BW was 98(2.6) kg and all participants lost the target of 8%, reaching 83.8(2.4) kg after 2 months of LED, Notably, 40% of the participants also reversed the T2D diagnosis, achieving a fasting glucose of under 7.0 mmol/l (Dale et al, 2009a; Dale et al., 2009b; McCombie et al., 2017; Rehackova et al., 2017). The Look AHEAD study found that it was feasible to achieve and maintain weight loss in participants with T2D and that using partial meal replacements improved diet quality over 8-year follow-up. Weight loss of 4.7% was maintained at 8 years with 50% of the participants losing at least 5% of their BW and 27% participants losing at least 10% BW (Look AHEAD Research Group & Wing, 2010). Moreover, the authors found that weight loss led to reduction of overall risk factors by improving metabolic markers, mobility, physical and sexual functioning, and health related quality of life in those O/W with T2D risk (Eckel et al., 2011; Look AHEAD Research Group & Wing, 2010).

Weight loss has a direct impact on improvement in metabolic health and glycaemic control and risk on development or worsening T2D (Chan, 2017; Eckel et al., 2011). Impaired glucose tolerance (IGT) is more prevalent than Impaired fasting glucose (IFG), in prevalence studies, ≤50% with IFG have IGT and only 20-30% with IGT also have IFG. IGT is related to the accumulation of centrally distributed fat, ectopic fat and IR showing a strong associated with cardiovascular risk factors such as hypertension and dyslipidaemia (features of the metabolic syndrome, and more common in women). Whereas, IFG is association with insulin sensitivity and is more common in men (Bourn et al., 1994; Nathan et al., 2007; Unwin et al., 2002). All of these T2D prevention trials showed reduced risk of developing T2D by up to 68% through lifestyle changes and weight reduction (Haywood et al., 2017; Nathan et al., 2007; Unwin. et al., 2002).

1.1.10 Diagnosis using Glycaemia

Diabetes is diagnosed using fasting plasma glucose (FPG) and 2-hour postprandial plasma glucose (2h-PPG) through an oral glucose tolerance test (OGTT) and Glycated Haemoglobin (HbA_{1c}) (Braatvedt et al., 2012; Coppell et al., 2013; New Zealand Guidelines Group, 2011; WHO & IDF, 2006). OGTT encompass of impaired glucose tolerance (IGT) which is associated with peripheral IR (muscle), whereas impaired fasting glucose (IFG) is associated with abnormal hepatic glucose output / insulin sensitivity (liver) (Faerch et al., 2009; Nathan et al., 2007). Table 8 summarises the diagnostic criteria for the diagnosis of IGT and T2D (American Diabetes Association, 2018; WHO & IDF, 2006). New Zealand uses the same criteria as the WHO, except for HbA_{1c}. New Zealand uses the cut-off of 50mmol/mol, which is equivalence to an HbA_{1c} of

6.8% in the old criteria, where the cut-off was 7.0% (NZSSD; 2011). To determine diagnosis of pre-diabetes, a series of fasting glucose measurements were used [mean sensitivity of 0.25 (95th confidence interval 0.19-0.32) and specificity of 0.94 (0.92-0.96)] and HbA_{1c} [0.49 (0.40-0.58) and specificity 0.79 (0.73-0.84) (Barry et al., 2017). Both parameters are used as Barry et al found in 49 studies, 47% of individuals with abnormal HbA_{1c} had no other abnormal glycaemia (Barry et al., 2017). Studies show that using OGTT results in misdiagnosis of pre-diabetes, when compared to HbA1C (Guo et al., 2014; López- López et al., 2017; Maki, 2017; New Zealand Guidelines Group, 2011; Sequeira & Poppitt, 2017; Unwin. et al., 2002). When assessed against diagnoses using FPG and 2h-PPG, HbA_{1C} had low sensitivity and high specificity for identifying T2D and pre-diabetes, varying as a function of age and race (Guo et al., 2014). Individuals who meet the impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) criteria usually have HbA_{1c} within or only just above the normal range; however this degree of glycaemia is associated with metabolic and cardiovascular abnormalities (Unwin. et al., 2002).

Pre-diabetes is defined as having impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) defined as the period prior to the onset of T2D when impaired glycaemia is identified either through raised fasting blood glucose of between 5.6-6.9mmol/l and/or raised postprandial blood glucose of between 7.8-11.0mmol/l (New Zealand Guidelines Group, 2011; WHO & IDF, 2006), or through chronically raised levels of HbA_{1c} of between 39-47mmol/mol (WHO & IDF, 2006) or 40-49mmol/mol in New Zealand (New Zealand Guidelines Group, 2011).

WHO diagnostic criteria for T2D diagnosis uses the HbA_{1c} cut-off of ≥48mmol/mol, with a cut-off ≥7.0mmol/l for FPG or ≥11.1mmol/l for 2h-PPG (WHO & IDF, 2006). In New Zealand, the cut-off for T2D diagnosis is ≥50mmol/mol (New Zealand Guidelines Group, 2011). This raised HbA_{1c} could lead to under-estimation of T2D diagnosis as the level is 2mmol/mol higher than the WHO guidelines.

For the PREVIEW study, only fasting and 2-hour postprandial glycaemia using an OGTT was used for the diagnosis of pre-diabetes. This was due to the recommendation to HbA_{1c} being recommended worldwide after the study protocol was in place.

Table 8: Diagnosis of Normal, Pre-diabetes and T2D

		ADA	WHO	New Zealand
Normal	FPG 2h-PPG	FPG ≤5.5mmol//L 2h-PPG ≤7.7mmol//L	FPG ≤6.0mmol//L 2h-PPG ≤7.7mmol//L	FPG ≤6.0mmol//L 2h-PPG ≤7.7mmol//L
	HbA_{1C}	HbA_{1C} <40mmol/mol	HbA_{1C} <40mmol/mol	HbA_{1C} <40mmol/mol
Pre-Diabetes	IFG (mmol/l) IGT (mmol/l)	FPG 5.6 to 6.9 2h-PPG 7.8-11.0	FPG 6.1 to 6.9 2h-PPG 7.8-11.0	FPG 6.1 to 6.9 2h-PPG 7.8-11.0
	HbA_{1C}	HbA_{1C} 40-47mmol/mol	HbA_{1C} 40-47mmol/mol	HbA_{1C} 40-49mmol/mol
T2D	FPG 2h-PPG HbA_{1C}	FPG >7.0mmol//L 2h-PPG >11.0mmol/l HbA_{1c} ≥48mmol/mol	FPG >7.0mmol//L 2h-PPG >11.0mmol/l HbA_{1c} ≥48mmol/mol	FPG ≥7.0mmol//L 2h-PPG >11.0mmol/l HbA_{1C} ≥50mmol/mol

FBG, Fasting blood glucose; 2h-PPG, 2-hour postprandial blood glucose; IFG, Impaired Fasting Glucose; IGT, Impaired Glucose Tolerance; T2D, Type 2 Diabetes; HbA_{1C}, Glycated Haemoglobin

1.2 Type 2 Diabetes

1.2.1 Global T2D Pandemic - Aetiology and Prevalence of T2D

T2D incidence is increasing worldwide, with total numbers multiplied at least two times in the past 2 decades and is considered one of many health conditions arising from weight gain and obesity (Alberti. & Zimmet, 2014; International Diabetes Federation, 2013; Zimmet. & Alberti, 2016). A large and growing problem, the costs of T2D to society are high and rising, with increased T2D prevalence paralleled by decreased quality of life, increased morbidity, and increased healthcare costs (Backholer et al., 2013). Previously, underrated as a global public health threat its unrelenting rise can no longer be ignored (Alberti. & Zimmet, 2014). One hundred and ten million people globally were reported with T2D in 1994, rising to 382 million in 2013, with a projected increase to 592 million by 2035 and 642 million by 2040 (Herman, 2017; International Diabetes Federation, 2013). A 6-fold increase in 40 years, with 80% from low- and middle-income countries (Guariguata et al., 2014; International Diabetes Federation, 2013). In 1980, China had a T2D prevalence of 0.9%, this has since increased to 9.6% representing to ~100 million people with T2D (International Diabetes Federation, 2013; Pan et al., 1997). In the United States, the prevalence of T2D rose from 5.1% in 1988–1994 to 7.7% in 2005–2006 (Cowie et al., 2009) and further to 10.9% in 2013 (International Diabetes Federation, 2013). Early T2D diagnosis is reported occurring in children, adolescents and young adults, reflecting on a parallel increase in overweight and obesity incidence in this population (Alberti. & Zimmet, 2014; Zimmet. & Alberti, 2016).

With the number of T2D increasing at an alarming rate, there is more emphasis and need for the development of effective screening and T2D prevention programmes to diagnose T2D early and provide appropriate treatment (International Diabetes Federation, 2013). The guidelines on T2D management focused strongly on the use of antidiabetic drugs (total of 488, excluding insulin), licensed with 70 generic compounds, with only lip service provided for diet and lifestyle advice and intervention, until the 2018 Medical Management for T2D suggesting the use of LED for weight loss followed by a supportive weight maintenance programme (American Diabetes Association, 2017; American Diabetes Association, 2018). In the Counterbalance and the DiRECT studies, using LED for weight loss of 15kg, to enable T2D remission in 86.1% of participants and improved glycaemia, resulted in a strong sense of personal achievement and empowerment (previously described in Section 1.1.6) (Lean. & Hankey, 2018; McCombie et al., 2017; Madjd et al., 2016; Rehackova et al., 2017; Taylor et al., 2017; Taylor et al., 2010). Table 9 shows the percentage incidence of T2D worldwide with an average increase of 55% (range from 22 to 109%) (Herman, 2013).

Table 9: Incidence of T2D worldwide with predicted (%) increase from 2013 to 2035 from IDF, 2013

Region	2013 (millions)	2035 (million)	Increased (%)
Africa	19.8	41.4	109.0
Middle East and North Africa	34.6	67.9	96.0
South East Asia	72.1	123.0	71.0
South and Central America	24.1	38.5	60.0
Western Pacific	138.2	201.8	46.0
North America and Caribbean	36.7	50.4	37.0
Europe	56.3	68.9	22.0
World	381.8	591.9	55.0

1.2.2 Cost Benefit Analysis

In 2015, IDF estimates that countries allocate 5-20% of total healthcare expenditure to T2D (Herman, 2017). In 2015, estimated T2D-related global health expenses equated to $673 billion, from $376 billion (12%) in 2010. From 12% in 2010 to approximately 20% of all global health expenditure. Prospective data suggests that this is just the beginning of an increase in ongoing costs linked with obesity and related factors (Alberti. & Zimmet, 2014; Herman, 2017). This cost has been projected to rise to $802 billion by 2040 (Herman, 2017). In the US alone, the estimated cost for T2D in 2012 was $245 billion, an increase of 41% since 2007, with average medical expenses of $13,700 per person per year. This is 2.3 fold higher than those without T2D (American Diabetes Association, 2016; American Diabetes Association, 2017; American Diabetes Association, 2018). Clearly, prevention and treatment of T2D is crucial for economic benefits and must become a central focus for health policy and government actions.

1.2.3 T2D in New Zealand

New Zealand is also following the same upward trend as most countries worldwide. There was an increase from 7% prevalence in 2008/09 to 11% in 2013 (Alberti. & Zimmet, 2014; Coppell et al., 2013; International Diabetes Federation, 2013). In 2015, it is estimated that 257,000 people have T2D in New Zealand (Figure 1), with 40 new diagnoses per day from 2014, which equates to 14,600 per year (Jo & Drury, 2015; Ministry of Health, 2018). Over the 5-year Ministry of Health plan, six main priorities arise, which included prevention of T2D in high risk groups, early detection to improve glycaemia and prevent complications, review and educate self-management of T2D control, improvement of overall service quality, promotion of integrated care with changes in systems and meeting the needs of people with Type 1 Diabetes (Jo & Drury, 2015; Ministry of Health, 2018).

Table 10: New Zealand T2D Prevalence Statistics across studies

	Population (n)	Age group	Prevalence of T2D NZ (%)	Specifics
Sundborn et al, 2007 (Sundborn et al., 2007)	4,049		5.2% European 7.3% Maori 6% Pacific	Highest Samoan men 26.2%, Tongan women 35.8%
Smith et al, 2008 (Smith et al, 2008)	427,400 145,300 381,500 439,600	All ages		9% CMDHB 6.4% NDHB 7.4% ADHB 5.8% WDHB
Balalla et al, 2013 (Balalla, 2013)	Auckland population	≥30 years old		9% Auckland population
Thornley et al, 2011 (Thornley et al., 2011)				9.6%
Coppell et al, 2013 (Coppell et al., 2013)	4,721 NZ Adult Nutrition Survey		7%	
Jo et al, 2015 (Jo & Drury, 2015)	198,625 VDR	All ages	4.4%	Year 2009
Warin et al, 2016 (Warin et al 2016)	63,014	≥30 years old	8.5%	Est. $1b healthcost by 2016
Ministry of Health, 2018	245,680	All ages		Year 2017

VDR, Virtual Diabetes Register, Est, estimated; 1b, 1 billion dollars

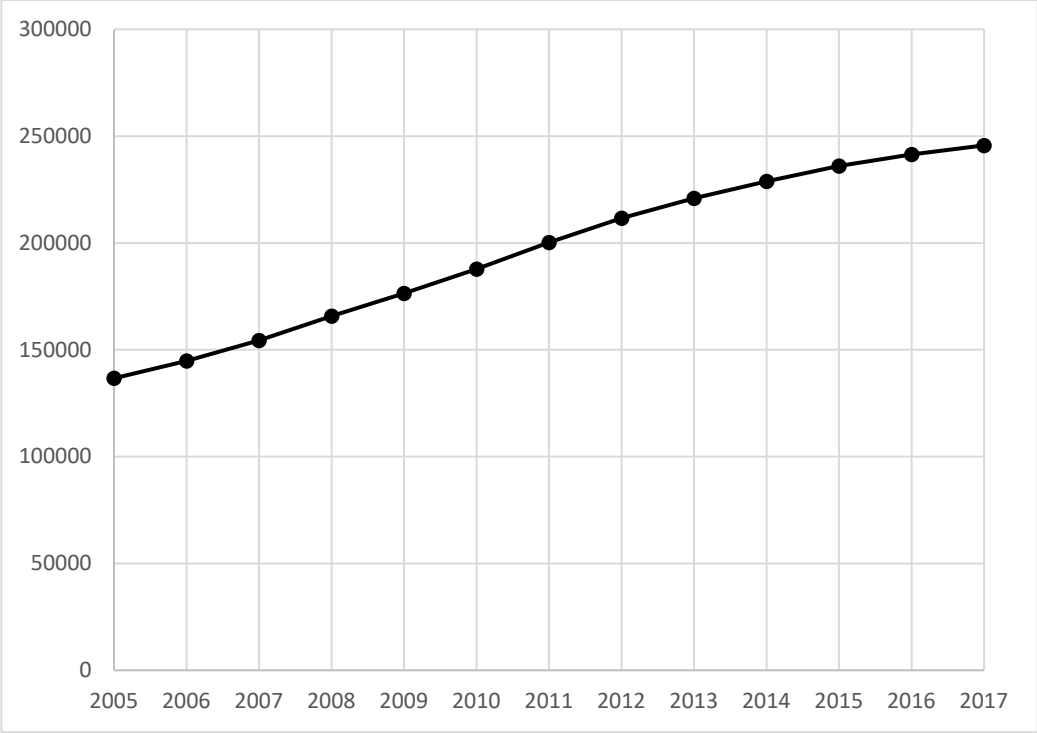


Figure 1: The number of T2D patients on the Virtual Diabetes Register from year 2005 to 2017, (Jo & Drury, 2015; Ministry of Health (2018)

Ethnicity contributes to T2D risk significantly. New Zealand has a diverse population with approx. 74% European/Caucasian, 7.4% Pacific Island, 14.9% Maori (Indigenous to New Zealand) and 11.8% Others (Sorensen et al, 2015). Sundborn et al showed that Maori population had a 2.5 times and Pacific 4 times greater risk of developing T2D when compared to European, with the highest rates found among Samoan men of 26.2% and Tongan women 35.8% (Sundborn et al.,

2007). There are an increasing number of people from the minority groups being diagnosed with T2D in the younger population. The world's highest prevalence of T2D in Tokelau - Pacific Island, where almost 40% of adults are reported to have T2D (International Diabetes Federation, 2013).

1.2.4 Prevention of T2D

1.2.4.1 Pre-Diabetes

NZSSD recommends testing the high risk population, which includes adults over 25 years of age with ischaemic heart disease, those who are obese (BMI ≥30kg/m^2, or Indo-Asian ≥27kg/m^2), of high risk ethnic group, i.e. Maori, Pacific or Asian, family history of T2D in direct family or had past diagnosis of Gestational Diabetes (New Zealand Guidelines Group, 2011). People with pre-diabetes have a higher mortality rate (Gong et al, 2016) and increased risk of developing T2D. Lindström et al has combined all the risk factors (BMI, gender, age, family history, diet and exercise and previous gestational T2D) around T2D risk and developed the Finnish Diabetes Risk Score (FDRS) to determine ones' risk of developing T2D (Lindstrom et al., 2003). This impaired glucose homeostasis and IR of pre-diabetes is directly linked to obesity and physical inactivity (Alberti. & Zimmet. 2014; Alibasic et al, 2013) and is a key target of T2D prevention. The Da Qing T2D prevention study is one of the longest T2D prevention trials with a significant reduced risk of T2D by 31-46% (Cefalu et al., 2016). At the 20- and 23-year follow-up, a continued lower reduction risk of 43% attenuated in the intervention group. As well as a reduction of T2D development, there was also a 47% reduced risk of developing diabetic retinopathy. After 23-years of follow up, there was a significantly reduced cardiovascular mortality by 41% and all-cause mortality by 29% (Gong et al., 2016; Li et al., 2008; Pan et al., 1997). Another T2D prevention study, the Finnish Diabetes Prevention Study (FDPS) showed a reduced relative risk of 58%, 43% continued reduction at 7-yr. and 38% reduced reduction after 13 yrs. (Lehtisalo et al., 2016; Lindstrom et al., 2008; Lindström et al., 2013; Nilsen et al, 2011). The USDPP study compared 3 groups (lifestyle with 7% weight loss, Metformin and control) and found a 58% reduction for the lifestyle intervention vs. a 31% reduction with Metformin when compared to the control group. Over 10 year followup, a 34% reduced reduction was shown in the lifestyle group vs. 18% for the Metformin group. After 15 years, the lifestyle group still showed a 27% reduction in risk of developing T2D (Crandall et al., 2008; Nathan et al, 2013).

All the T2D prevention trial success lies in its ability to improve glycaemia, insulin sensitivity and reduce IR through a combination of initial weight loss and weight loss maintenance, via lifestyle, metformin, support and placebo (Cefalu et al., 2016).

Group based T2D prevention programs based on lifestyle modification have been shown to provide a cost effective opportunity, where diet and/or physical activity (PA) are modified within the community in programs targeting high risk, O/W, hyperglycaemic individuals (Pan et al., 1997; Tuomilehto et al., 2001). A 37% risk reduction (95^{th} CI 28-46%) in T2D development using weight management lifestyle intervention over 3- to 6-year duration (Barry et al., 2017). This equates to 151 individual/adults diagnosed out of 1000 in the intervention, compared to 239 diagnoses in the control groups. At 20 years post intervention, this reduced RR attenuated to 20% (8-31%) in the

intervention group following the end of trial, with no further intervention after the 3- to 6-year study trials (Barry et al., 2017).

1.2.5 Weight Loss Management - Short Term Evidence

Fasting, altered macronutrient intake and restriction was suggested as an obesity treatment method with short term results from early 1900's (Evans & Strang, 1929; Folin & Denis, 1915). However, in recent years prolonged fasting for treatment of obesity and diabetes prevention was ruled out due to: problems a) poor maintenance of the initial weight loss and b) physical danger to the patients. Indeed, prolonged fasting resulted in, at least, five reported deaths by 1970, linked to ventricular fibrillation in existing cardiac patients, lactic acidosis in a hypertensive diabetic woman and small bowel infarction (Wadden et al, 1983). Less severe complications of fasting include hyperuricaemia, gout and arthritis, abdominal cramps and orthostatic hypotension (Bolinger et al, 1966; Duncan et al, 1964). Bariatric surgery provides substantial, sustained weight loss in obese individuals with T2D (Dixon et al., 2012)

Dansinger et al compared 4 popular diets (Atkins, Zone, Weight Watchers and Ornish) for weight loss and cardiac risk and found that over short term, all diets resulted in weight loss but over long-term low dietary adherence rates were reported (Dansinger et al, 2005; Gardner et al., 2007). In summary, adherence is linked to reduced risk of chronic diseases (Dansinger et al., 2005). Gardner et al conducted a 2x2 study on IR and insulin sensitive in O/W (BMI 28-40kg/m^2) participants, who were randomized to either a low fat diet (22en%protein ; 21en%fat ; 57en%CHO) or a low CHO diet (18en%protein ; 38en%fat ; 44en%CHO), both promoting high nutrient-dense quality foods. Both groups lost an average of 9% of total BW after 6 months with no substantial difference between them. The authors concluded that adherence to the diet is the key factor to achieve success (Gardner et al, 2016).

1.3 Low Energy Diet (LED)

Research on a very low energy diet was initiated in the late 1920's by physicians, Frank Evans and James Strang demonstrated that a calorie restriction of 62-67kJ per kilogram of BW results in an average weight loss of 9.9kg in 2 months in a large cohort of their patients (Evans & Strang, 1929). Evans et al provided his participants with a meal plan of 33kJ per kilogram of BW, consisting of three small meals. Participants were also given a list of acceptable vegetables which also contained guidelines to weigh and limit bread, suggestions of acceptable cooking methods for protein intake, and details on the importance of limiting fried foods, lard and butter. In this plan water was permitted, along with salt, pepper and vinegar (Evans & Strang, 1929). Reported side effects of this reduced energy intake consisted of headache, dizziness, weakness and the occasional nausea in the first 2-3 days only and a bad taste in the mouth in the first week but no longer. Weight loss resulted in clearer skin, improved sleep, improved blood pressure and correction of menstrual disorders, concluding that using the metabolic principle, a restriction of less than 33kJ per kilogram of BW is safe and recommended (Evans & Strang, 1929).

The definition for very low energy diet (VLED) or very low calorie diet (VLCD), used interchangeably in the earlier days was based on an energy content of ≤1,040kJ; However, the US Food and Drug Administration (FDA) International CODEX standardization and legislation has more recently defined VLED as total meal replacements with 1.8-3.3MJ per day (Food and Drug Administratison, 2015). Total meal replacements which are nutritionally complete and range from 3.3-5MJ per day can be defined as LED or Low calorie diet (LCD), both terms used interchangeably (Saris, 2001). Following the publication by Evan et al, Bolinger et al suggested in 1996 the use of LED over prolonged fasting as a safer option for weight management (Bolinger et al., 1996; Evans & Strang, 1929; Wadden et al., 1983). Baird et al compiled a meta-analysis on the clinical and metabolic studies using LED in the treatment of obesity. Results from this analysis sparked interest in the commercial sector to produce nutritionally complete meal replacement products with 500-1673kJ per meal (Baird et al., 1974; Howard et al, 1978). Leslie et al conducted a systematic review (n=569) on rate of weight loss using VLED (<3.3MJ/d) and LED (≥3.3MJ/d) between participants with and without T2D and found that weight loss was similar between VLED and LED groups and suggested using these diets to achieve weight loss and maintenance targets of >15-20% for people with severe and medically complicated obesity (Leslie et al., 2017).

Krietzman and Beeson reported a total weight loss of over 16,000kg in 818 patients in 25 medical practices within primary care in a weight loss study using LED at Cambridge University within the Howard Foundation Research in Cambridge, United Kingdom with a mean (SD) weight loss of 19.7(11.4) kg, from a mean (SD) BW of 97.5(19.8) kg to 79.7(16.2) kg. The average weight loss rate was 1.5(0.3) kg per week with improvements in hypertension and reduced or elimination of medication following weight loss (Kreitzman & Beeson, 1996). Many health professional raise the myth around rapid weight regain following rapid weight loss, However, Kreitzman et al only showed a small weight regain of 2.0(5.2) kg (Kreitzman & Beeson, 1996).

Saris reported that VLED and LED are shown to achieve a significant weight loss without the risk of a severe negative nitrogen balance and electrolyte imbalances associated with starvation and prolonged fasting (Saris, 2001). Baetge et al reviewed a selection of commercial weight loss programs i.e. Weight Watchers, Jenny Craig, Nutrisystems Advance; and found that all of these programs resulted in weight loss after 12 week intervention following support and leading to improvements to metabolic syndrome prevalence and cardiovascular function (Baetge et al., 2017). Traditionally, dietitians and health professionals have been taught that slow and steady weight loss is the treatment recommended for weight loss and long-term weight loss maintenance (Franz et al., 2007; Mahan et al., 2007). However, rapid weight loss using LED with psychological (motivational, perception of weight and change in behavioural) and nutritional education support is required for the weight loss and weight maintenance phase (Franz et al., 2007; Palou & Bonet, 2013).

Weight loss strategies are part of the largest commercial weight loss markets, with many varieties of commercial trends lacking sufficient long-term evidence to support their benefit. Paleo, Intermittent fasting and Atkins diets are examples of such strategies (Astrup et al, 2004;

Dansinger et al., 2005). However, some commercial companies that emphasize the importance of both dietary management and exercise i.e. Weight Watchers, Jenny Craig, etc. have been proven to be effective in promoting weight management due to the importance of the regular support, incorporated as part of their programme (Ahern et al, 2011; Dansinger et al., 2005; Tsai & Wadden, 2005, Jebb et al, 2011).

Ashley et al conducted a weight loss treatment and maintenance intervention on 113 premenopausal women randomized into three groups; dietitian-led, dietitian-led using LED meal replacement and a quick 10 min visit with physician-nurse team. All three groups achieved weight loss of 4.3(6.5)%, 9.1(8.9)% and 4.1(6.4)%, respectively after year-1 ($P<0.001$). After 2 years, weight loss was maintained in all three groups with -1.5(5.0)%, -8.5(7.0)% and -3.0(7.0)% achieved in each group, respectively (Ashley et al, 2001). Study results showed that a traditional weight loss setting using LED is an effective tool for weight loss and maintenance (Ashley et al., 2001).

Noakes et al showed that LED was an effective treatment for obesity after being administered to 66 Australian adults with features of the metabolic syndrome. In this study, both groups consumed 6MJ per day. Participants in the intervention arm received 2 nutritionally complete LED meal replacement products and a low fat evening food-based meal and was reviewed every 2-weekly with supervision and nutritional support. The control group consumed a conventional but structured weight loss diet and both groups were followed up for 3 months (Noakes et al, 2004). The LED and structured control caused weight loss of -6.6(3.4)kg / -6.3(0.8)% and -6.0(4.2)kg / -6.9(0.6)%, respectively, with reduction in plasma homocysteine levels in both groups (8% in the LED group compared to 4% in the control diet). However, the LED group reported that it was easier to follow the LED meal replacement intervention plan when dining out and was more compliance due to the convenience of plan, compared to the control group ($P<0.01$) (Noakes et al., 2004).

Adherence and compliance are key strategies for a weight loss programme, with the provision of regular support and education (Penn et al., 2013; Wing et al., 2005; Clifton et al., 2014; Dale et al., 2009a; Feldman et al., 2017; Gogebakan et al., 2011; Martens et al., 2014) . Over the past 2 decades, rapid weight loss, using a meal replacement diet with a low energy intake (or LED) has resulted in a complete reversal of pathological defects of IR, improved liver triacylglycerol, improved blood pressure and improvement in glycaemia due to improved insulin sensitivity and β-cell function, just as well as Roux-en Y Gastric Bypass (RYGB) (Hjelmesaeth. et al., 2018; Jackness et al., 2013; Leslie et al., 2017). More evidence is shown that the more weight loss using LED leads to better metabolic outcome and weight loss maintenance long-term, in par with RYGB (Anderson et al, 2001; Christensen et al., 2011; Franz, 2017; Franz et al., 2007; Hamman et al., 2006; Haywood et al., 2017; Heilbronn et al., 2001; Jackness et al., 2013; Riecke et al., 2010; Rothberg et al., 2014; Sellahewa et al., 2017; Wing & Phelan, 2005). Riissnerl et al have found that weight loss of 8-15% could be achieved in both VLED group (using <3.3 MJ per day) and LED group (with 3.3-5.5 MJ per day) (Atkinson, 1989; Riissnerl & Flatenz, 1997). Dixon et al claimed a weight loss of 15kg using bariatric surgery (laparoscopic adjustable gastric banding)

leads to 73% reduced risk of developing T2D (Dixon et al., 2008; Dixon et al., 2012). Table 11 demonstrates a list of randomised controlled trials using LED and VLED from 1- to 6-month duration, with the resulting total mean weight loss and weight loss per week (Foster et al., 1992; Ohno et al, 1989; Riissnerl & Flatenz, 1997; Saris, 2001).

Table 11: Randomised controlled trials with LED and VLED

Studies	Diet (MJ//kcal/d)	Participants (female/male)	Duration (weeks)	BW change (kg)	BW change (kg/week)
Ohno et al 1989	1 / 240	7/4	4	8.9	2.2
	1.8 / 420	6/4	4	7.6	1.4
Foster et al 1992	1.8 / 420	21/0	5	8.9	1.8
	2.8 / 660	23/0	5	8.7	1.7
	3.3 / 800	24/0	5	7.2	1.4
	1.8 / 420	21/0	24	19.5	0.8
	2.8 / 660	23/0	24	22.6	0.9
	3.3 / 800	24/0	24	90.6	0.8
Rissnerl et al 1997	1.8 / 420	20/10	6	13.4	2.2
	2.2 / 530	22/10	6	14.7	2.5
	3.7 / 880	21/10	6	12.9	2.1
	1.8 / 420	20/10	26	18.9	0.7
	2.2 / 530	22/10	26	20.2	0.8
	3.7 / 880	21/10	26	17.7	0.7

MJ, MegaJoules

Usually, there are three phases of the LED or VLED; the first phase is the intensive or exclusive 'total diet replacement' (TDR) phase with only 2-4 meal replacement sachets made up of reduced fat milk or water. Depending on the product and total energy intake, allowance includes >2 litres of water per day and 2 cups of non-starchy vegetables per day, which equates to <220kJ (Christensen et al., 2011; Gougeon, 1992; Johansson et al., 2009). Following the initial rapid weight loss during the intensive phase, there is a weaning process by introducing one small meal per day instead of one of the meal replacement sachets for approximately 3 months. This transition phase happens again over the replacement of another meal replacement with a healthy meal option, eventually the individual is placed on a healthy reduced calorie intake using a variety of dietary manipulation of macronutrients used for weight loss maintenance (Apfelbaum et al., 1999; Franz et al., 2007; Johansson et al., 2009; Joris et al., 2017; Lean. & Hankey., 2018; Saris, 2001). Due to the benefits of weight loss achieved with LED, the initial weight loss is used for many studies to investigate which intervention is beneficial for weight loss maintenance (Dale et al., 2009a; Goyenechea et al., 2011; Leslie et al., 2017; Leslie et al., 2016). Long-term weight loss maintenance is achieved through regular support through behavioural therapy and nutritional education support, with an increase in exercise to make it a long-term habit (Saris, 2001). Wing et al reported as many as 83% of participants reported a trigger for their weight loss, medical triggers were the most common (23%) and is defined as health professional advising weight loss, aim to improve medical condition e.g. T2D and/or family member having a medical event e.g.

heart attack. Other triggers include participants reported that they reached an all-time high in BW (21.3%), and seeing a picture printed or mirror reflection of themselves (12.7%) Those who said they had a medical trigger lost 36kg and were associated with less weight regain over a 2-year follow-up (Wing & Phelan, 2005; Wing et al., 2004).

The Scottish Intercollegiate Guidelines Network (SIGN) Guidelines on the Management of Obesity and the American Diabetes Association (ADA) Obesity Management Standards of Care acknowledge the benefits of -5-10% total BW but the evidence using LED and meal replacements (>3.4MJ/d) may achieve greater short term weight loss of -10-15% than intensive behavioural lifestyle intervention for the minimum of ≥5% weight loss (American Diabetes Association, 2018; Scottish Intercollegiate Guidelines Network, 2010). The most recent DiRECT trial also emphasised the importance of weight loss showing 86.1% of those who lost at least 15kg of BW went into T2D remission (Section 1.1.6 and 1.1.8) (Lean et al., 2017; Lim et al., 2011; Taylor et al., 2017). Taylor et al postulates that the 15% weight loss reduces adipose fat reverses de-differentiation of beta cells and that a supportive approach throughout the weight loss maintenance stage in routine care is required to maximise long-term benefits (Taylor et al., 2017). This summarises that weight loss through LED is an effective way to achieve health benefits with support required for long-term weight loss maintenance, where the more weight is lost over the first 8 weeks leads to successful long-term weight loss maintenance over 8-year follow-up (Unick et al., 2015).

1.4 Weight Loss Management for the Prevention of T2D - Long-term Evidence

“Slow and steady does not win the race”- (Martin & Gadde, 2014; Purcell et al., 2014). Purcell et al demonstrated that both gradual and rapid weight loss lost around 12.5% BW and then continued into a 144-week maintenance phase can be achieved. Results showed that fewer participants dropped out in the rapid weight loss group with more weight loss achieved, when compared to the gradual weight loss group (Purcell et al., 2014). There have been number of T2D prevention trials, which have investigated the long-term efficacy of diet and/or PA for BW loss in pre-diabetes populations, targeted to improve glycaemia.

Obesity is increasing at an unprecedented rate all over the world, contributes to 2.8 million deaths per year (World Health Organization, 2017). In a recent WHO report, obesity was considered to be the 5th leading cause of global mortality as it exacerbates a range of comorbidities. Nevertheless, obesity is a preventable condition (World Health Organization, 2017). The natural progression of weight gain over time is presented in Figure 2 (Lean. & Hankey, 2018).

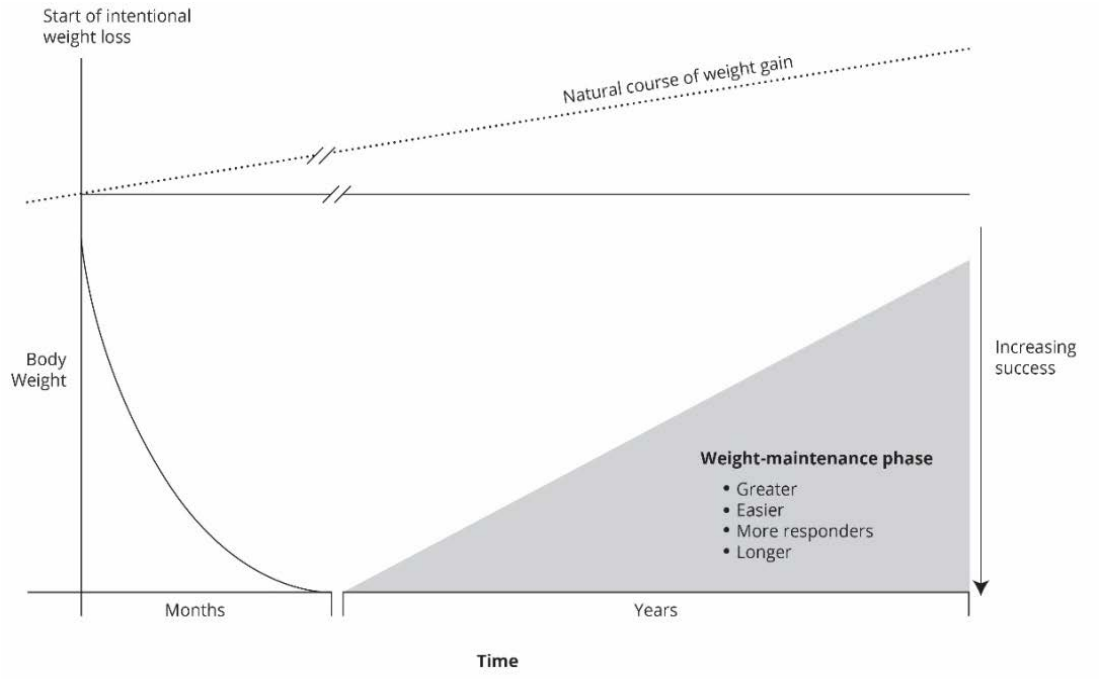


Figure 2: Obesity and the components of medical weight management (extrapolated from Lean et al, 2018, Lancet. Keeping it off: the challenge of weight loss maintenance)

Astrup and Rössner (2000) recommend rapid weight loss using non-lifestyle techniques such as LED or medication. According to the authors, a LED improves weight loss maintenance success in those who follow lifestyle recommendations over the long-run (Astrup & Rössner, 2000). Franz et al conducted a systematic review of weight loss outcomes from clinical trials with minimum of 1-year and up to 4-years of follow-up (Franz et al., 2007). The objective of this meta-analysis was to assist health professionals who see patients for weight loss on the options of weight loss methods and expected outcomes from the different interventions. Eight types of weight loss interventions were investigated – diet only, diet and exercise, exercise only, meal replacements, VLED, medication for weight loss (Orlistat and Sibutramine) and advice alone. Based on studies with a minimum of 12-months of intervention on weight management, 80 studies was reviewed, the authors showed that the VLED was the most successful in achieving the greatest weight loss after 6-months but the least successful in maintaining weight 12-months post intervention. Figure 3 showed that weight loss medication was the second most effective rapid weight loss, after VLED. Advice only was the least effective of all methods with no change in BW (Franz et al., 2007).

Successful long-term weight loss maintenance relies also on behavioural modification techniques to assist with setting SMART (specific, measurable, achievable, realistic and time bound) goals and assisting with the adherence of the lifestyle changes over the long run (Hamman et al., 2006; Smith & Wing, 2000). Behavioural techniques help with modifying lifestyle changes with problem solving techniques, motivational enhancement and relapse prevention to promote lifelong changes and adherence (Smith & Wing, 2000). The USDPP emphasized the importance of behavioural modification, alongside diet and exercise advice in group settings to achieve and maintain goals (Knowler et al., 2002).

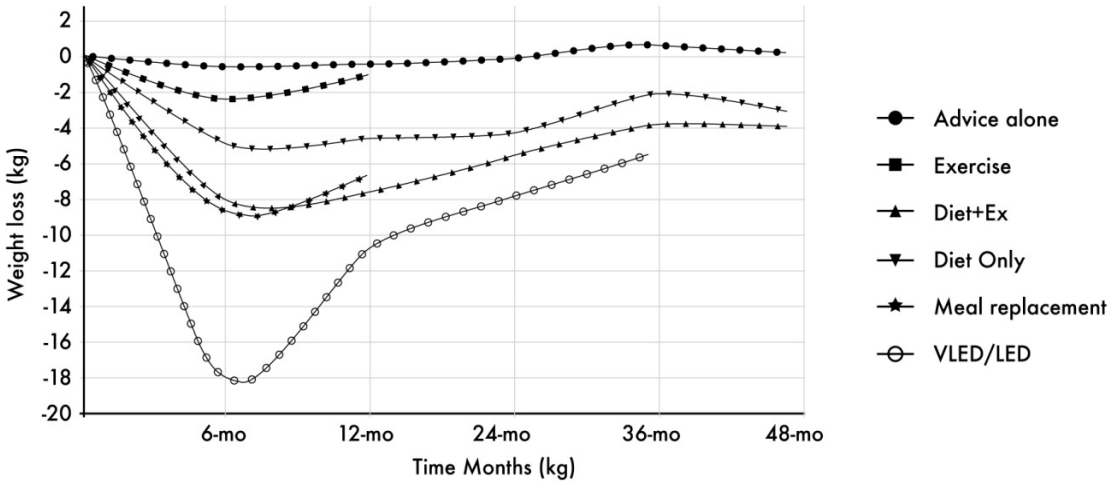


Figure 3: Analysis of weight loss achieved through different methods - a review of 80 studies (min 1 year), extrapolated from Franz et al., 2007.

Other recommendations for obesity include bariatric surgery. However, surgical risk and cost needs must be considered before surgery-based interventions. Notably, a conventional non-surgical therapy is a most cost-effective, practical population based approach for life-long lifestyle modification targeting weight loss and weight loss maintenance (Palmo, 2013). Lifestyle recommendations include nutritional education over dietary changes (low fat, calorie restricted), increased physical activity and a focus on behavioural change education (Astrup & Rössner, 2000). As previously discussed, LEDs have been known to mimic the effects of bariatric surgery, with positive effects on IR and beta cell function (Jackness et al., 2013; Sellahewa et al., 2017). Lingvay et al reported that a reduced energy diet using a LED had a greater effect in glucose homeostasis in the absence of surgery compared to after RYGB (Lingvay et al, 2013). Rapid weight loss of 7% of initial BW over 4-6 weeks through LED have shown to promote mobilization of ectopic fat from liver (effective from week-1 (Lim et al., 2011) to skeletal muscle, leading to reducing glucose, insulin, plasma γ-glutamyltransferase (GGT), triglycerides (TG) and HOMA-IR [HOMA-IR=fasting glucose (mg/dl) x fasting insulin (µU/ml)/22.5] (Xydakis et al., 2004).

In support of the benefits of lifestyle intervention, a meta-analysis instigating the effectiveness of both lifestyle and pharmacological intervention concluded that lifestyle interventions halve the risk of T2D in impaired glucose tolerant (IGT), high-risk individuals (Gillies et al., 2007). There is also evidence that lifestyle intervention is more effective in participants with a higher BMI (Diabetes Prevention Program (USDPP) Research Group, 2002; Eriksson & Lindgärde, 1991; Li et al., 2008; Lindström & Tuomilehto, 2003; Pan et al., 1997; Penn. et al, 2013; Roumen et al., 2008; Sakane, 2005), and that for each BMI unit (kg/m^2) decrease there is a parallel decrease in hazard ratio (HR) of -7.3%.

Lifestyle interventions with weight loss targets of at least 5% BW, followed by weight loss maintenance have been shown to promote a reduction in T2D relative risk (RR) from 30% to 67% over 3- to 7-years (Yamaoka & Tango, 2005).

The 3 largest T2D prevention studies - Da Qing, FDPS and USDPP - showed positive results in prevention of T2D development using lifestyle interventions, focused on moderate weight loss and increased physical activity. The early Da Qing study (n=577) encouraged the O/W study population (61%, BMI≥25kg/m^2) to reduce their BW (aiming for a BMI<23kg/m^2), followed by 105-126kJ/kg/day intake, 55-65en%CHO, 10-15en%protein with increased vegetable intake, less alcohol and less simple sugars. This lifestyle intervention resulted in a reduction in the T2D relative risk of 31-46% over 6 years (Li et al., 2008). Notably, there was a 45% reduced risk of developing T2D in the intervention group after 23-year follow-up with a delay in T2D diagnosis of 3.6 years (Gong et al., 2016; Li et al., 2008; Li et al., 2014). The FDPS and US Diabetes Prevention Programme (Nathan et al., 2013) both showed a 58% reduction in relative risk of T2D after 4-year and 3-years of active intervention, respectively. The weight loss goals were 5% in the FDPS and 7% in the USDPP, with both interventions focusing on healthy low-calorie, low-fat diets and moderate intensity physical activity, such as brisk walking, for at least 150 minutes per week (Knowler et al., 2002; Lindstrom et al., 2003; Lindstrom et al., 2008; Lindström et al., 2013). The risk of T2D development remained low after 7 years in 522 participants in the FDPS (relative risk of 43%) (Lindström et al., 2006) and after 10 years in 3150 participants in the USDPP trial (34% risk reduction at 10-year follow-up) (Diabetes Prevention Program (DPP) Research Group, 2002; Herman et al., 2012). The USDPP (Knowler et al., 2002; Knowler et al., 2009; Nathan et al., 2013) authors concluded that 1kg of BW loss is equivalent to 16% T2D risk reduction (Nathan et al., 2007). Results from these large lifestyle interventions have shown that a weight loss target of 5-10% prevents the onset of T2D in the majority of people with pre-diabetes (Knowler et al., 2002).

Another more recent study using the LED for the initial weight loss prior to maintenance is the Diet, Obesity and Genes (DioGENES) European multicentre trial. Over the 8-week weight loss phase using a 4MJ/day LED achieved an average weight loss of ~11kg. In the study, the weight loss phase was followed by a weight loss maintenance phase comparing a lower protein to a higher protein diet over 6 months and 12 months (Astrup et al, 2015; Gogebakan et al., 2011).

Physiological adaptation and persisting obesogenic environments contribute to weight regain (Greenway, 2015). However, despite popular belief, rebound regain that exceeds baseline BW is uncommon, and metabolic effects of weight loss can persist even with weight regain (Dombrowski et al, 2014). Berger et al conducted a meta-analysis on differentiating maintainers and regainers from the Look Action for Health in Diabetes (Look-AHEAD) and showed that metabolic benefits were retained in patients who regained ≤25% of the initial weight loss (Berger et al, 2017). The authors concluded that long-term metabolic benefits were clinically relevant success criteria for weight maintenance. Lean et al also postulate that a weight regain of 25% and under continues to have beneficial health effects, however, the authors emphasise the need for a well-supported weight loss maintenance programme (Lean. & Hankey, 2018).

1.4.1 Summary of risk reduction factors

The risk reduction was in development of T2D and is linked to BW, distribution and managing risk factors linked to metabolic syndrome. Maintenance of a healthy weight, particularly reducing abdominal circumference is important. This can be achieved by diet (making healthy food choices or LED) and regular physical activity. As well as maintaining weight loss, physical activity is also important for reducing blood pressure and heart rate, increasing your body's sensitivity to insulin, improving body composition, and improve general well-being (Jeon et al, 2007). Improving metabolic measures by managing blood pressure, cholesterol levels and smoking cessation will reduced risk of cardiovascular disease (Meigs et al., 2006). There is clear evidence of a link between depression and the risk of developing T2D (Knol et al., 2006). Other factors with increasing evidence includes sleep and T2D risk (Cappuccio et al, 2010; Yaggi. et al., 2006).

1.4.2 Diet and Physical Activity Lifestyle Modification Studies

Whilst many trials have investigated effects of diet on intermediary risk factors, far fewer have conducted long-term studies to determine effects of diet on incident T2D, with those studies focused primarily on CHO modification. The first two diet interventions, the Bedford study (Keen et al., 1982) and the Whitehall study (Jarrett et al, 1984) were conducted in the 1970s, and reported that whilst BW loss aided T2D prevention, intensive training in dietary CHO restriction (<120g/day) had no differential effect. Soon after, what may be the first combined lifestyle intervention for T2D prevention was conducted over 6 months in Malmo Sweden, in a non-randomised cohort of 415 middle-aged men. It comprised 4 groups of newly diagnosed T2D, IGT (intervention, IGT-I vs. control, C) and normoglycaemic (NG) healthy controls. The IGT-I group was given healthy eating advice based on Swedish guidelines (SG), regular PA advice, and encouragement to lose weight. Successful weight loss resulted in 63% and 50% relative risk (RR) reduction of incident T2D at 6- and 12-year follow-up (F/U) (Eriksson & Lindgärde, 1998), such that by 12-year F/U mortality rates were similar to NG healthy controls (Eriksson & Lindgärde, 1998).

The 6-year Chinese Da Qing T2D Prevention study was the first large lifestyle modification trial, with 577 IGT adults randomised to diet and/or PA (as described in Table 14). Diet comprised individualised advice of 55-65% energy from carbohydrates (en%CHO), 10-15en%protein, 25-30en%fat, reduced energy intake (EI), alongside PA counselling and weight loss goals for the O/W (Pan et al., 1997). The control (C) group received only general information on T2D, diet and exercise. Diet, PA and a combination lifestyle approach were all successful with a RR reduction of 33-47% by the end of the 6-year study (Pan et al., 1997). Even more encouraging was the successful RR reduction of 43% and 45% at 20- and 23-year F/U (Li et al., 2008; Li et al., 2014). Four other prevention trials rapidly followed, all of which conducted diet and PA lifestyle interventions. Wein et al., conducted a 6-year study in Australia on 200 women with IGT and a previous history of gestational T2D. The intervention group received intensive healthy diet advice compared to standard routine advice, but did not achieve significant weight loss and only a trend towards RR reduction (36%, $P<0.05$) (Wein et al. 1999).

The Japanese diabetes prevention programme (JDPP) was conducted over 4 years in 458 men with IGT, aged 30-69 years (Kosaka et al, 2005). Individualised advice and regular F/U was based on the Japanese Diabetes Society dietary guidance document of decreased EI, 55-60en%CHO, 15-20en%protein, <25en%fat and decreased SFA. At 4 years, RR for incident T2D had significantly decreased by 68% (Kosaka et al., 2005). In the UK, men with IGT were randomly allocated to the intensive higher complex CHO/fibre, lower fat diet and PA over 6-months or a no advice control. RR was not assessed in this small sample study, and whilst there were no significant effect of the intervention at 6 months, by 2-year F/U there was a significant improvement in fasting glycaemia in the intervention group (Page et al, 1992). A similar small, but uncontrolled, intervention in New Zealand with similar diet goals of 50-55en%CHO, 12-20en%protein, <30en%fat, low SFA and increased fibre resulted in improved BW, postprandial glycaemia and fasting lipid at 2 years, but in the absence of RR assessment (Bourn et al., 1994).

In 1993, the FDPS was conducted over 3 years in 522 middle-aged, O/W adults with IGT, with F/U data reported at 7- and 13 years post intervention. The goal was -5% BW loss, followed by long-term weight loss maintenance (Lindstrom et al., 2003), and diet intervention was based on lower fat and increased dietary CHO/fibre, with 30en%fat, <10en% SFA, >15g/1000kcal high fibre, in addition to increased PA. Those in the intervention group had a significant 58% RR reduction in developing T2D (Lindstrom et al., 2003). At subsequent 7- and 13-year F/U, the significant RR reduction was maintained at 43% and 38% respectively (Lehtisalo et al., 2016; Lindstrom et al., 2008).

Increased age, BMI, waist circumference (WC), fasting and postprandial blood glucose and blood pressure, as well as reduced PA and fruit/vegetable consumption were associated with T2D risk development (Lindstrom et al., 2003). To identify those at high risk of developing T2D, Lindstrom and colleagues developed a simple tool, the FDRS represented by a scale from 0 to 20, to help identify those at high risk of developing T2D (Lindstrom et al., 2003; Nilsen. et al., 2011). Following the success of the FDPS, the European T2D Prevention randomised controlled trial (RCT) was commenced where the DPS protocol was replicated in both the Netherlands (study on lifestyle-intervention and impaired glucose tolerance Maastricht, SLIM) and the UK European T2D Prevention Study-Newcastle (EDIPS-Ncl) (Penn. et al., 2013). The SLIM was a 3-year intervention, in 147 participants, aged >40-years and BMI ≥25kg/m^2 with IGT (Mensink et al. 2003).

The intervention comprised individualised recommendations based on Dutch guidelines of 30-35 en%fat, <10% SFA, increased PA, and a goal of BW loss of 5-7% whilst the control group comprised information on benefits of a healthy diet, weight loss and PA but with no individual advice (Mensink et al., 2003; Penn. et al., 2013). The lifestyle intervention again resulted in a significant 58% RR reduction (Ramachandran et al., 2006; Roumen et al., 2008), as did EDIPS-Ncl which randomised 102 O/W participants with IGT into a 3-year intervention (Penn. et al., 2009), again focused on lower fat, <30en%fat, <10en%saturated fat, and higher >50en%CHO with increased dietary fibre. Again there was a significant 58% RR reduction in the intervention group at 3-yr F/U.

These findings were replicated in the USDPP, a larger 3-year RCT conducted in 3,234 O/W adults with IGT randomised into lifestyle intervention (diet and PA), metformin therapy or placebo control. Dietary recommendations were based on a weight loss goal of >7%, using the US Department of Agriculture (USDA) Food Guide Pyramid, as a model for healthy eating, focused on lower fat, low energy substitutes and smaller portions. A goal of increased PA was also included (Knowler et al., 2002).

In the 3 years of the USDPP, T2D incidence was reduced by 58% with lifestyle intervention and by only 31% with metformin therapy, compared with control (Crandall et al., 2008). The 10-year follow-up DPP Outcome Study (DPPOS) has shown that despite incidence in the control and metformin groups falling to match that of the lifestyle group, the cumulative 10-year incidence of T2D was still reduced by 34% in the lifestyle group compared with only 18% in the metformin group confirming long-term efficacy of diet and PA (Herman et al., 2012; Knowler et al., 2002; Knowler et al., 2009). In the intervention group, there was a 4-year delay in the diagnosis of T2D in the lifestyle group over the full 10-year study (Herman et al., 2012). Recent reporting of the 15-year F/U data has shown RR reduction for lifestyle to be maintained at 27% (Nathan et al., 2013). The Indian DPP repeated the USDPP, comparing lifestyle, metformin, and control with a combined metformin and lifestyle advice in 531 middle aged O/W, adults with IGT (Ramachandran et al., 2006). The intervention focused on decreased EI, refined CHO, total fat and sugar, and increased dietary fibre. Unlike the USDPP (58% T2D risk reduction with 7% body weight loss), the Indian DPP resulted in no significant weight loss yet still reported significant RR reductions of 28.5%, 26.4% and 28.2% in lifestyle, metformin and metformin and lifestyle interventions, respectively. Since these fundamental studies, to our knowledge, 5 other T2D prevention trials have been conducted, again with similar dietary aims of replacing the lipid component of the diet with polysaccharide CHO/fibre. A number of trials have reported findings in Asian populations.

In a small study of middle aged Japanese Americans with IGT, the AHA step 2 diet significantly improved IGT parameters however RR data were not collected (Liao et al., 2002). The JDPP randomised 240 adults with IGT, where the intervention group received intensive diet and exercise advice and were encouraged to lose weight (Sakane et al., 2011) resulting in a 51% RR reduction versus a standard advice control group.

The Japanese Zensharen study was a larger study of 641 Japanese adults randomised to frequent individualised diet and PA advice, where the 3-year HR was reported as 0.56 relative to a standard advice control group (Saito et al., 2011). Finally, 2 further Chinese studies have shown diet and PA intervention to significantly decrease HR to 0.30 and 0.75 (or by 70% intervention compared to only 25% control with standard advice) respectively when compared with standard advice and education (Fang et al. 2004; Tao et al, 2004).

1.4.3 Exercise intervention

Regular exercise is an essential part of a healthy lifestyle. It has been proven to reduce glycaemia while increasing whole body and skeletal muscle oxidative capacity in obesity and T2D individuals

(Hansen et al., 2009), reversing metabolic syndrome risk factors and improving aerobic capacity. Moreover, exercise has been proven to be effective in reducing blood pressure, total body fat and BW (Astrup et al., 2004; Baecke et al., 2017; Bianchi et al., 2017; Eriksson et al., 1998; Hansen et al., 2009; Josse et al., 2011; Knowler et al., 2009; Pan et al., 1997a; Stiegler et al., 2006; Tjonna et al., 2008; Tao et al., 2004). The PREVIEW study has two exercise groups (high intensity shorter duration vs. moderate intensity longer duriation) however, this was not discussed in this thesis as the exercise group remains 'blinded' throughout the duration of the thesis.

1.4.4 Effect of Weight Loss on Anthropometric and Metabolic Parameters

It is clear that that lifestyle modification can have significant effect on the risk of developing T2D in high-risk groups, across genders and ethnicity. Commonly observed is the positive correlation between weight loss and weight maintenance with relative risk (RR) reduction. For example, Cox proportional hazards regression conducted over 3.2 years of follow-up in the USDPP trial found a 16% T2D risk reduction for every 1kg BW loss (Hamman et al., 2006). The studies with significant weight loss resulted in greater T2D risk reduction, 5% weight loss decreased risk by 43 to 55% and -7% weight loss decreased risk by -58% amongst the O/W and IGT population. Notably in all of these studies, the primary dietary focus was reduction of total and saturated fat, and an increase in total CHO with increased fibre and reduction in simple sugars (Uusitupa, 2002). There was very limited focus on protein intake and how this may affect the total diet, weight loss, weight loss maintenance and in turn the risk of development of T2D development in this high risk O/W and pre-diabetic population. To summarise, an increasing rate of obesity has resulted in a T2D pandemic worldwide. Those diagnosed with T2D is getting younger, especially as obesity drives T2D, through metabolic measures.

Weight loss doesn't always reflect intra-abdominal fat loss but studies using ectopic fat measurements showing improvements to intra-abdominal fat loss shows improvements to metabolic parameters, emphasing the importance of centrally distributed fat loss, also measured by WC (Zhyzhneuskaya et al., 2017; International Diabetes Federation., 2013). International Diabetes Federation (IDF) recommends using WC as an anthropometric measure which also has a metabolic effect on the metabolic syndrome (WHO & IDF, 2006). Lee et al compared 12-week mild calorie restriction of 300kcal/d with control and found improvements to fat intake and therefore circulating fatty acid profile, resulting in improvements to serum triglycerides, insulin and HOMA-IR (Lee. et al., 2018). Weight reduction in those who are O/W leads to benefits in metabolic and physiological markers. There is evidence supporting the fact that short term weight loss varies from changing meal sizes. A recently published study showed that having a larger meal/energy intake at lunch is favourable in weight loss in O/W women after 3 months (Madjd et al., 2016). In the same study, changes in macronutrient composition have shown that both low fat and low CHO promoted weight loss for the first 6 months. However, in both groups weight appeared to increase over the following 18 months, with participants returning to the pre-study weight (Madjd et al., 2016). What seems to be the most successful weight loss method is the LED, which is nutritionally complete with 3.4 to 4.2 MJ per day. There are so many short-term diets with a degree of short-term success. However, since obesity is a chronic condition that

affects individuals over decades, it is the long-term weight loss and maintenance that matters most.

1.4.5 Mechanisms Promoting Weight Loss and Weight Loss Maintenance

A number of mechanisms may contribute to the success of higher protein diets for weight loss and longer-term maintenance, acting both on energy intake, expenditure and utilisation. In a comparison of 15en%protein vs. 18en%protein for maintenance of weight loss, both increased satiety and decreased total energy (TE) efficiency contributed to the greater efficacy of the higher protein diet (Westerterp-Plantenga et al, 2004). Arguably satiety is the most important mechanism. Dietary protein has long been shown to have favourable effects on hunger and satiety (Anderson & Moore, 2004; Barkeling et al, 1990; Bowen et al, 2006b; Halton & Hu, 2004; Poppitt et al, 1998; Porrini et al, 1995; Veldhorst et al, 2009a; Veldhorst et al, 2009b; Weigle et al., 2005); although not all studies also find suppression of food intake when eating behaviour is assessed (Aldrich et al., 2011; Blom et al., 2006; Bowen et al, 2007; Penhoat et al., 2011).

Different protein types may have different satiating effects (Anderson et al, 2004a; Anderson et al, 2004b; Bowen et al., 2007; Burton-Freeman, 2008; Hall et al, 2003; Lang et al., 1998; Poppitt et al, 2013; Veldhorst et al., 2009); although again the mechanisms by which these compositional differences may act have yet to be defined in clinical studies. Whether individual amino acids alter satiety is also poorly understood, with much focus given to tryptophan due to its relationship with the appetite-modulating neurotransmitter 5-hydroxytryptophan (5HT, serotonin) (Veldhorst et al., 2009c). Gastrointestinal peptides such as cholecystokinin (CCK), glucagon like peptide-1 (GLP-1) and peptide YY (PYY) may also play a role (de Graaf et al, 2004; Fromentin et al., 2012; Karhunen et al, 2008), although whilst these gut peptides are certainly altered following a meal, there is limited underpinning evidence from clinical studies for direct regulation of hunger and/or eating behaviour by these ‘satiety’ peptides (Bowen et al., 2007).

In addition to effects on appetitive responses and in line with earlier findings (Westerterp-Plantenga et al., 2004), Paddon-Jones and colleagues (Paddon-Jones et al., 2008) have proposed that protein may differentially stimulate diet induced thermogenesis (DIT) noting that protein, which has a metabolic energy defined by the Atwater factor as 17kJ/g, in reality has a lower net metabolisable energy value of 13kJ/g, due to net metabolisable energy is the metabolisable energy minus heat of microbial fermentation and minus obliatory thermogenesis. Also, for dietary fibre and protein, net metabolisable energy is approximately 24-25% lower than metabolisable energy when compared to CHO, fat or alcohol. A further significant advantage of a higher protein diet is the anabolic effect on lean body mass or fat free mass (FFM), where dietary amino acids enhance muscle protein synthesis and skeletal muscle mass, and may protect against loss of lean mass during weight loss (Josse et al, 2011). As a metabolically active tissue, protection of FFM may also in turn contribute to better long-term weight maintenance.

Previous literature shows that the physiological role that these peptides play in the regulation of ingestion and eating behaviour is poorly understood, with circulating concentrations following a meal several fold lower than can be induced through direct injection of these peptides (Mars et

al., 2012). Although GLP-1 and PYY clearly suppress hunger when given exogenously at supra-physiological dosages (Astrup et al., 2009), Mars et al concluded in their comprehensive review that neither is likely to contribute individually to the satiating capacity of foods (Mars et al., 2012).

In a study from Jackness et al, LED vs bariatric surgery both achieved the same result and improved metabolic health, in particular FPG, HOMA-IR, fasting serum insulin, serum connective-peptide (C-Peptide) and beta-cell function following weight loss (Jackness et al., 2013). Incretins may have improved glucose homeostasis in the bariatric surgery group, however, non-enteral mechanisms linked to glycaemic control showed benefits in the weight loss (Jackness et al., 2013). Improved beta cell function and decreased pancreas and liver triacylglycerol was seen in the reversal of T2D Newcastle study using LED consisting of a liquid diet formula of 2.1MJ/d, 46.4en%CHO, 32.5en%protein and 20.1en%fat, vitamins, mineral and trace elements, along with allowed vegetables with a total of 2.5MJ per day. Regular telephone support was provided over the 8-week intervention (Lim et al., 2011).

1.4.6 Dietary Intervention – Higher Protein Diets for Weight Loss and T2D Prevention

There is also growing evidence that higher protein diets may improve glycaemia (Baum et al, 2006; Kushner & Doerfler, 2008; Larsen et al., 2010; Layman & Baum, 2004) with recent data showing that some proteins may have an effect on metabolic regulation independent of BW (McGregor & Poppitt, 2013). Whey protein for example, as an insulin secretagogue, may enhance glycaemic control with studies showing postprandial suppression of diet-induced hyperglycaemia by whey, decreasing glucose levels by ~20% in the 3 hours following ingestion (Jakubowicz & Froy, 2013). It also has a positive effect on the incretin system, with increased GIP, decreased GLP-1, and decreased DPP-4 activity in the small intestine (Jakubowicz & Froy, 2013).

When recommending higher protein diets for weight loss and glycaemic control, clearly the nature of the advice, increase percentage of the protein in diet rather than total protein (and TE) and the composition of the protein must both be considered. For example, various protein groups, such as dairy (McGregor & Poppitt, 2013), marine (Sofi et al, 2013) and soy (Cope et al, 2008) may have significant advantage over animal-origin protein diets. For example, the EPIC (European Prospective Investigation of Cancer and Nutrition) study with 89,432 participants from 5 countries, showed a positive association between animal-origin protein, e.g. red meat, processed meat, chicken but not fish or dairy, with greater weight gain over 6.5 years (Du et al., 2009; Halkjær et al., 2011).

This positive association between animal-origin protein and BW has been repeated in the larger EPIC-PANACEA (European Prospective Investigation into Cancer and Nutrition–Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity) study with >373,000 participants in 10 countries, where an increase in red meat, poultry and processed meat of 250g per day (e.g. a single steak, ~1.8MJ) was predicted to increase BW by 2kg over 5 years (Vergnaud et al., 2010).

Also, of concern is the association between animal-origin protein, specifically red meat, and development of T2D. Pan et al reported a strong correlation between processed red meat consumption, particularly processed red meat, and an increased risk of T2D of up to 50% (Pan. et al., 2012). Data from 3 Harvard cohorts, the Health Professionals Follow-up Study, the Nurses' Health Study and the Nurses' Health 2 study have shown that an additional 0.5 servings/day of processed red meat over 4 years is associated with an increase in T2D risk of up to 50% (Pan. et al., 2012; Pan & Hu, 2014). Processed red meat is high in SFA, nitrate, sodium and heme iron, and hypothesised to affect glucose metabolism, IR, endothelial function, glycoxidation and oxidative stress (Pan & Hu, 2014). Clearly potentially confounding effects prevent attribution of cause and effect and a micronutrient poor diet (low wholegrain, fruit and vegetable consumption), O/W and obesity, and an increase likelihood of smoking and physical inactivity may each in turn contribute (Pan & Hu, 2014).

Other issues are also associated with higher protein diets including data from NHANES III 18-year F/U showing >20en%protein of high animal-origin is associated with increased all-cause mortality and cancer from 50-65 years (Levine et al., 2014). The guidelines from the US Institute of Medicine however have concluded that there is no clear evidence that HP increases the risk of cancer or cardiovascular disease, amongst other conditions, and have set the acceptable protein range as 10-35% for adults, with recommended protein sources of low fat dairy, lean meat, fish, poultry, legumes, nuts and wholegrain with vegetables (Astrup et al., 2015) and limited processed red meat. There is clear evidence that lifestyle changes for weight loss maintenance are important for T2D prevention. Our group has recently published a systematic review looking at the different dietary recommendations and focused on the role of higher protein diets on T2D prevention (Liu et al., 2015).

Due to the vast evidence around higher protein diets, we published part of the literature review concluding that higher protein diet showed reduced TE density, aiding in appetite suppression and lean body mass preservation, resulting in successful long-term weight loss maintenance for T2D prevention (Liu et al., 2015). Diet intervention, as outlined in the studies above, has focused almost entirely on lipid and CHO content and composition. The T2D and nutrition study group within the European Association for the Study of T2D (EASD) have used this body of research to generate recommendations, focused on lower fat and moderate CHO, with suggested intake between 45-60en%CHO, based on increased vegetables, legumes, fruit and wholegrain cereals to provide foods rich in dietary fibre and with a low Glycaemic Index (GI) (Roumen et al, 2008; Roumen et al, 2011; Mensink et al, 2003; Penn et al, 2009; Penn et al, 2013; Liao et al, 2002; Sakane et al, 2005; Saito et al, 2011; Tao et al, 2004; Fang et al, 2004).

Recommended protein intake is 10-20en%protein (0.8-1.2g/kg BW), with the upper recommended range likely to be beneficial through maintenance of FFM during weight loss, and an aid to weight loss maintenance and prevention of weight regain (Layman & Baum, 2004; Mann. et al., 2007). The evidence base has as yet been insufficient to support specific recommendations for a higher protein diet for T2D prevention. There is a growing body of research, which shows that higher protein diets may provide a useful aid for short-term weight loss, although evidence is

still building in support of higher protein diets for longer-term maintenance of weight loss (Astrup, 2004; Clifton, 2012; Clifton et al, 2008; Clifton et al, 2014; Farnsworth et al., 2003; Foster et al., 2010; Gilbert et al, 2011; Kushner & Doerfler, 2008; Larsen et al., 2010; Noakes, 2008; Paddon-Jones et al., 2008) and in T2D prevention. Altering the diet in favour of a higher protein content appears likely to influence weight control (Clifton et al., 2008; Gilbert et al., 2011; Larsen et al., 2010; Noakes, 2008; Paddon-Jones et al., 2008; Te Morenga & Mann, 2012), with estimates of weight loss of ~1kg per week when higher protein diets are consumed *ad libitum* (Johnstone et al 2008; Johnstone et al., 2011).

In 2006, the pan-European Diet, Obesity and Genes (DioGENES) Study investigated higher protein diets, in association with GI, in a 6-month intervention looking at weight regain following enforced weight reduction (Halkjær et al., 2011; Larsen et al., 2010). Almost 1,000 O/W participants in 8 European countries (Denmark, Germany, Spain, Netherlands, United Kingdom, Greece, Czech Republic, Bulgaria) completed a rapid 8-week period of LED (3.3MJ/day) induced weight loss of which 773 successfully lost ≥8% BW and were randomly assigned to one of 5 diets for prevention of weight. Diets were consumed *ad lib*, with requirement to maintain the macronutrient profile where dietary fat was replaced in part by either protein or CHO. A novel approach of a higher protein (25en%protein)/low-GI (HP/L-GI) diet was compared with the traditional lower protein (13en%protein)/moderate GI (LP/M-GI) diet, and a control group which provided non-macronutrient specific diet information. Of greatest interest was the finding that the higher protein/lower GI (HP/L-GI) group had the lowest dropout and least weight regain (0.93kg less than LP/M-GI diet, P=0.003) after 6 months and this was maintained in 1 year (Astrup et al., 2015; Larsen et al., 2010). In order to have an impact on T2D prevention, it is important that higher protein diets are able to prevent the gradual weight 'creep' and long-term weight regain that is associated with most weight loss regimes.

1.4.7 Dietary Intervention - CHO Restriction for Glycaemic Control and Weight Loss

Due to the direct effect CHO has on glycaemic control, dietary CHO restriction has shown to have the greatest effect on decreasing blood glucose levels (Feinman et al., 2015) and weight loss (Bazzano et al., 2014; Foster et al., 2003; Samaha et al., 2003). Total CHO affects glycaemia due to increase in total glucose load. Early T2D prevention studies showed improved glycaemia with limited CHO intake (Feinman et al., 2015; Jarrett et al., 1979; Jarrett et al., 1984; Keen et al., 1982). Weight loss with low CHO diet and its' effect on IR was shown (Baum et al., 2006; Foster et al., 2003; Gardner et al., 2016). Current T2D related studies showed limited CHO improved glycaemia (Gardner et al., 2016; Krebs et al., 2016; Samaha et al., 2003). In these studies no difference was seen between low fat (57:21:22/CHO:Fat:Protein) vs low carb (44:38:18) diet on IR (Gardner et al., 2016; Krebs et al., 2016) – both groups lost 9% over 6 months. However, low carbohydrate diet have presented risk of nutrient insufficiency, hypoglycaemia and compliance issues (Feinman et al., 2015; Jarrett et al., 1979; Jarrett et al., 1984; Keen et al., 1982).

1.5 Dietary Intervention - GI Studies

1.5.1 Development of GI

The GI theory emerged in 1981, based on an extension of the fibre hypothesis that fibre delays the digestion rate therefore slows down the release of glucose into the blood, nature of CHO and effect on postprandial glycaemia and determined as physiological basis for CHO exchange (Jenkins. et al., 1981; Jenkins. et al., 2002). This was developed to improve glycaemia and therefore T2D related long-term complications (Jenkins. et al., 1981). The GI of foods is calculated as: GI = mean of (blood glucose response area of test food divided by the blood glucose response area of reference food taken by the same individual) x 100. The area under the glucose curve is calculated from the capillary blood glucose increments at baseline, 15 min, 30 min, 45 min, 60 min, 90 min and 120 min (Jenkins. et al., 1983; Wolever. et al., 1985). Both the amount of available CHO in the test food and the reference food (glucose or white bread) is 50 g of CHO (Wolever. et al., 1985).

The Glycaemic Index (GI) was originally developed as a mean of classifying varieties of carbohydrate-rich (>80% energy content from carbohydrates) sources according to their postprandial glycaemia, when compared to a reference control (glucose or white bread) (Arvidsson-Lenner et al., 2004; Augustin. et al., 2015; Jenkins. et al., 1981). GI is defined as the 2-hour postprandial blood glucose response to 50g of available CHO in a test food, when compared to 50g of glucose control or white bread (Augustin. et al., 2015; Foster-Powell et al., 2002). Notably this is a physiological response to the consumption of a food item, rather than a constituent of the food itself, and in turn it has long been acknowledged that there are intra-and inter-individual variations in response due to varying effects of monosaccharide glucose on small intestine absorption (Foster-Powell et al., 2002). L-GI foods are classified as being digested and absorbed slowly, whereas H-GI foods are rapidly digested and absorbed, showing a high glycaemic response (Brand-Miller et al., 2003). Glycaemic load is using GI multiplied by the amount of CHO in grams, measuring the load of glycaemia calculated with the total CHO (Salmeron. et al., 1997). It is therefore, more important to consider the total carbohydrate component of the diet, rather than the type of carbohydrate (e.g. low GI foods) in order to achieve good weight maintenance and glycaemic control.

The International Standard of GI methodology has been referenced in the Food and Agriculture Organisation (FAO) / WHO report and has defined L-GI as having a GI value of under 55 units, moderate GI (M-GI) between 56 and 69 units and H-GI above 70 units (Arvidsson-Lenner et al., 2004; Brouns et al., 2005; Wolever et al., 2003; Wolever et al., 1991). Calculations of incremental area under the 2-hour postprandial glucose curve (iAUC) are used to calculate the GI, using this calculation:

(iAUC test food / iAUC control food) x 100

The Glycaemic load (GL) may also be used to describe the glucose release of a food item, whilst considering the total amount of carbohydrates (g) and is calculated as below:

Amount of carbohydrates (g) x GI of food

1.5.2 GI and Health

Many intervention and epidemiological studies have used GI to investigate effects of health risk by looking at food biology and health effects and establishing diets of varying GI (Augustin. et al., 2015; Jenkins. et al., 1987; Jenkins. et al., 2002; Jenkins. et al., 1983; Jenkins et al., 1984; Salmeron. et al., 1997; Wolever et al., 1985). The Framingham Offspring study cohort showed a L-GI wholegrain intake is inversely associated with HOMA-IR, resulting in a lower prevalence of metabolic syndrome (McKeown et al., 2004). The GI concept has been integrated into dietary guidelines in Australia, France, Sweden, Canada and South Africa, with recommendations from FAO and WHO that dietary CHO should be L-GI and high in fibre (FAO, 1998; Ludwig, 2002). In New Zealand, the GI concept has not been integrated into dietary guidelines as the only solution. Acknowledgement of a combination in low overall energy content, high fibre, L-GI and modified macronutrient approaches is suggested as nutritional management in obesity and diabetes treatment and prevention in New Zealand (Ministry of Health, New Zealand Health Strategy, 2016; Mann et al., 2004; Mann et al., 2017). However, with the exclusion of energy-dense, high fat and high sugar, yet L-GI foods (Mann et al., 2004; Mann, 2010). Some studies indicate that a L-GI diet may have beneficial effects on obesity and obesity related conditions such as reduced risk of T2D, certain cancers (colon and breast) and cardiovascular disease (Brand-Miller et al., 2003; Hu et al, 2001; Jenkins. et al., 2002). In New Zealand, sweet potato/kumara is grown in abundance and is used as a staple CHO source. Traditionally, Maori people use sweet potato/kumara in a hangi (traditional feast steam cooked under the ground) or boiled in casseroles or ‘boilups’. Today, New Zealanders still boil or roast sweet potato/kumara, as a primary source of CHO intake. In New Zealand, there are 3 varieties of sweet potato/kumara - golden, red and purple, but no validated data available on their respective GI content. There has been some confusion with GI and sweet potato/kumara (Atkinson et al., 2008; Foo et al., 2013; Foster-Powell & Miller, 1995).

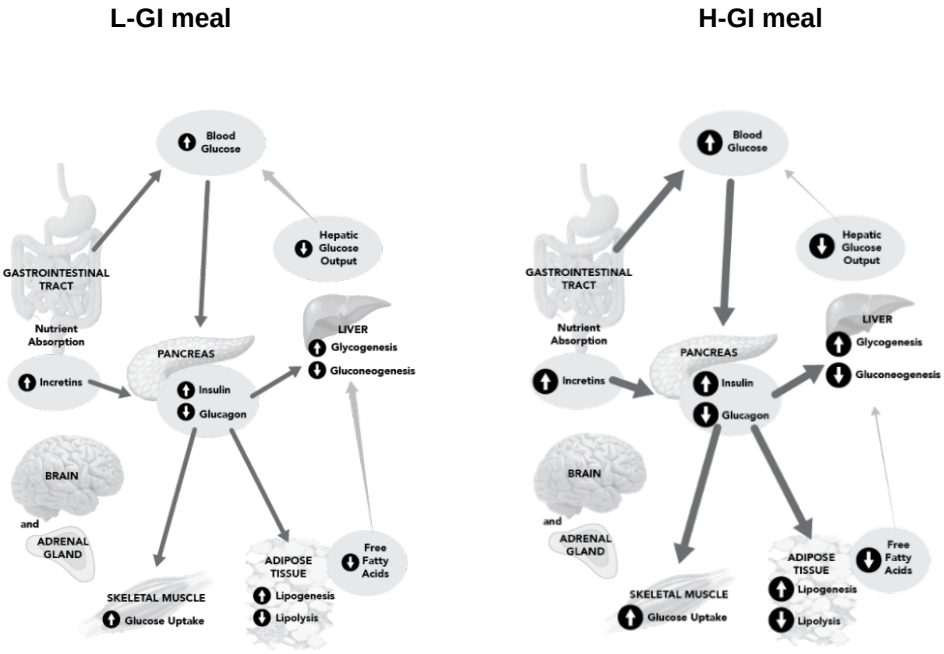


Figure 4: Physiological effects after ingestion of a L-GI meal (left) vs a H-GI meal (right) in the first 2 hours following ingestion, showing higher blood glucose following a high GI meal, extrapolated from Ludwig, 2002

1.5.3 Low GI and benefits on health

Clinical trials in healthy, diabetic and individuals with hypercholesterolaemia have shown that L-GI diets may reduce a number of adverse markers, including blood glucose concentration, insulin secretion, oxidative stress, inflammatory response and serum triglycerides (Jenkins. et al., 2002). Ludwig summarised the physiological effect of L-GI vs. H-GI in Figure 4 (Ludwig, 2002). Brouns et al also suggested that H-GI diet may lead to prolonged glucose exposure and this could potentially increase health risk and chronic disease progression (Brouns et al., 2005). Schwingshackl et al conducted a meta-analysis using 2344 participants and reported beneficial effects on CRP (-0.43mg/l, $P<0.05$) and fasting plasma insulin (-5.16mIU/L, $P<0.01$) using a low GI of (L-GI; ≤55 units), however the reported L-GI ranged from 30 to 76 units and H-GI ranged from 53 to 86 units (Schwingshackl & Hoffmann, 2013).

1.5.4 Contradicting evidence with no difference with GI

On the contrary, the use of GI values for chronic disease risk management remains controversial with a number of studies criticizing the usefulness of GI in mixed meals, suggesting no effect of the use of GI of each component of the food product on weight, glycaemia and other metabolic parameters (Augustin. et al., 2015; Barclay et al., 2008; Coulston et al., 1987; Vega-Lopez et al., 2007; Venn & Green., 2007). Salmeron et al examined the relationship between dietary fibre, glycemic load and risk of T2D in men, adjusted for age, BMI, smoking, exercise, family history of T2D, alcohol consumption, cereal fibre and TE intake and found a positive relationship between GI and total carbohydrate intake, with relative risk of T2D development of 1.37 ($P<0.05$) (Salmeron. et al., 1997). Sloth et al did not find any differences between L-GI and H-GI in weight regulation, appetite, fasting insulin and β-cell function (Sloth et al., 2004). Aston et al compared

a diet with a reduced GI in 19 O/W women (age 34-65 years, BMI: 25-47kg/m^2, fasting insulin: 49-156pmol/l) in a two consecutive 12-week study and found no effect on appetite, energy intake and BW (Aston et al., 2008). In 2005, Liese et al found no differences in GI, insulin sensitivity, insulin secretion, BMI or WC in 1,000 participants who consumed L-GI and H-GI foods (Liese et al., 2005).

1.5.5 "Should obese patients be counselled to follow a L-GI diet? No"

Raben conducted a meta-analysis on 31 short-term studies and 20 long-term studies, comparing the outcomes of high and L-GI diets and found that participants lost similar weight on either diet and participants were evenly split on whether the L-GI diet made them feel more satiated and therefore did not suggest using GI education on the O/W population (Raben, 2002). In theory, the L-GI diet have been recommended for weight management and advised as part of general nutritional guidelines. In turn many factors, ranging from the food matrix, preparation of the test food, mixed meals, and inter- and intra-individual variation, all affect the physiological measurement of GI and hence the GI value attributed to individual foods (Kataoka. et al., 2013; Matthan et al., 2016; Venn. & Green., 2007; Venn et al., 2010; Williams. et al., 2008; Wolever. et al., 1986).

1.5.6 "Should patients with T2D be counselled to follow a L-GI diet? No"

Using GI *per se* may be seen as misleading, due to the difficulties in predicting body's complex response in healthy individuals let along those with IR and T2D. Due to intra- and inter-individual variation of 25%, other epidemiological studies demonstrated that using a single GI value labeled for food items should not be used when providing nutrition guidelines due to variations affecting glycaemic response (Matthan et al., 2016; Venn. & Green, 2007). This variability will affect the health professionals ability to provide correct GI advice using single GI factors for food (when counselling a patient or the general public), and confusing due to conflicting information to the individual, due to varying glycaemic response in order to prevent high or delay the postprandial blood glucose excursions. Carels et al conducted behavioural weight loss group and monitored progress for 1 year and found GI education had no significant impact on weight loss treatment outcomes at post-treatment or at 1 year, when compared to the group with no extra GI education (Carels et al., 2005).

1.5.7 Extrinsic Factors affecting GI

Many extrinsic and intrinsic factors affect the physiological glycaemic response of individuals from consumption and absorption of a food item with set GI factor. Extrinsic factors include the changes to the environment factors that cause the composition of the food item to vary, modifying the glycaemic response and therefore GI of the food item. These factors include food variety, country of origin, soil composition and humidity, moisture, growing conditions, seasonal, ripeness, storage time, processing and cooking method. These factors associated with food variety have been shown to changing the GI of the food item, the rate of glucose absorption and subsequently glycaemia and insulinaemia (Jenkins. et al., 2002).

1.5.7.1 Food matrix – Varietal differences, growing conditions, food preparation

Food variety, country grown in, differences in soil, fertilizer used, external temperature, seasonal changes and variety (Aldughpassi et al., 2012; Nayak et al., 2014) may all contribute to variability in GI response to a food item. Composition of the standard potato (*Solanum tuberosum*) is also proven to vary according to potato varieties, maturity level, starch structure, food processing techniques, all of which may contribute to variability in the GI of the standard potato (Fernandes et al., 2005; Nayak et al., 2014). The GI for potatoes ranges from 47-70units, spreading across all three GI groups (low <50units, med 50-70units, high>70units) (Atkinson et al., 2008; Foster-Powell & Miller, 1995; Foster-Powell et al., 2002). The preparation and cooking method of the test food also affects the GI as an extreme boiling temperature modifies the starch structure (Åkerberg et al., 1998). Pasta has a GI ranging from 43 (al dente) to 61 units (boiled for 10 minutes in salted water, vs. 52 units if using unsalted water) (University of Sydney, 2017). When the food is boiled, the aqueous suspension of starch is heated causing a change in water (boiling = water is absorbed vs. roasting = water is lost). This also leads to the starch granules swelling and then a change in structure, as a fraction of the amylopectin becomes part of the substance and changes to amylose with longer cooking times (Åkerberg et al., 1998; Aldughpassi et al., 2012). Same initial cooking method but different holding time and consumption is also seen to affect GI, where cooked and consumed cold pasta compared to when consumed hot has been shown to have a lower GI due to the change in resistance starch during the cooling period (Kim et al., 2008). Despite standardization of the cooking method, different GI can occur due to different varieties of the same food producing varying results. Brand-Miller et al found that rice has a GI ranging from 64 (low amylose variety) to 93 units (other rice varieties) (Miller et al., 1992). Adding protein, fat or fibre to a higher GI-rated food item has been reported to lower the GI, also known as the mixed meal effect (Wolever & Bhaskaran, 2012).

1.5.7.2 Consuming a food item alone vs in a mixed meal

GI differs considerably when a food item is eaten alone or as a mixed meal. Adding protein, fat and fibre within a meal to the available CHO in this rice mix study I co-authored was found to lower GI (Zhang et al., 2015). In an earlier study with collaborators from Otago University, we showed in a group of T2D Asian Chinese patients that a rice mix with added nuts and seeds resulted in a lower GI response when compared to consumption of white rice alone, demonstrating the mixed meal effect where adding fat, protein or fibre reduces the GI of the food (Zhang. et al., 2015).

1.5.8 Intrinsic Factors affecting GI

Intrinsic factors includes varying absorption rate for and this may vary by the time of consumption, chewing rate, digestion and absorption rate for individuals. These differences also vary intra-individually (same person, varying result) and inter-individually (differences between different individuals) (Matthan et al., 2016).

1.5.8.1 Intra- and Inter-individual variation; sample size in GI testing studies

Williams et al reported for a food with a mean GI of 70 and standard error of 10, the estimated GI of the population would have a 95% chance of being between 50 to 90 units (Williams et al, 2008). The more participants investigated in any study, the greater the statistical power to detect the response to an intervention and the lower the variability, which also applies to GI testing (Brouns et al., 2005). Wolever et al have proposed enrolling a high number of participants in GI testing to decrease the margin of error (Wolever et al., 2003). However, the International GI Methodology has recommended a sample size of 10, in turn to reduce costs while still achieving good statistical power for classification of GI response for individual foods (Arvidsson-Lenner et al., 2004; Atkinson et al., 2008). Figure 5 showed data from an inter-laboratory study, where 47 participants were enrolled to test 5 food types, showing the difference in GI that can be detected with 80% power at $P<0.05$ (using two-tailed analysis), by the number of participants and mean GI. This resulted in a linear relationship between mean GI and the standard deviation of GI values for the 5 foods, using glucose control with a GI of 100 (Brouns et al., 2005).

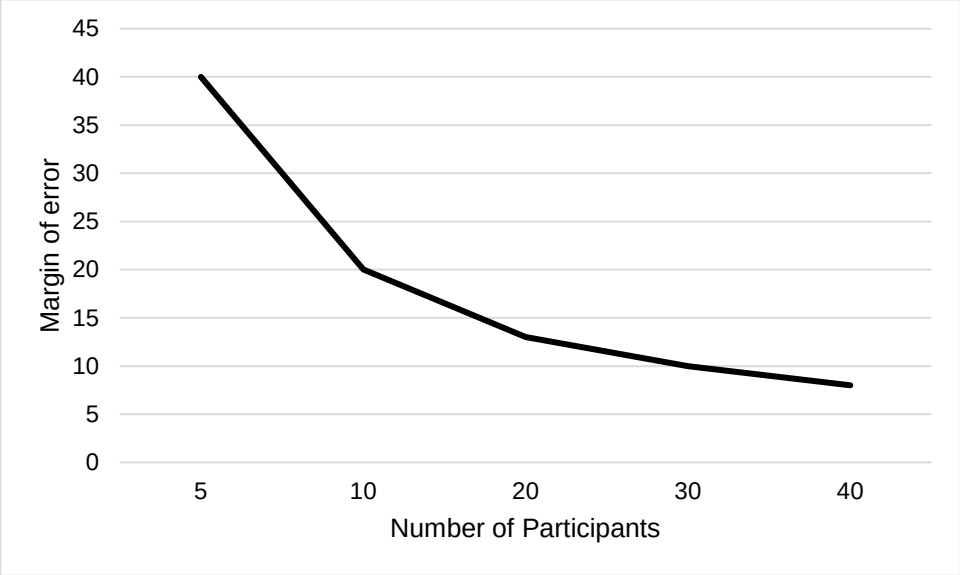


Figure 5: Estimated margin of error for 95% CI of GI values by the number of participants and mean GI for Glucose = GI 100 (extrapolated from Brouns et al, 2005)

The use of GI values for chronic disease risk management remains controversial due to inter- and intra-individual variations when testing for GI in different foods (Matthan et al., 2016). Differences in individual absorptive factors altering uptake in the small intestinal in turn affect GI, with mean intra- and inter-individual variation shown to be as high as 20% and 25%, respectively, in a recent study (Matthan et al., 2016). Ethnic differences have also shown differences in GI for the same test food is in line with growing data that shows ethnicity to be an important driver of susceptibility or resilience to hyperglycaemia and adverse metabolic health (Kataoka. et al., 2013; Venn. et al., 2010).

1.5.9 International Method of GI testing

1.5.9.1 Sample size – inclusion and exclusion criteria

In 1998, the FAO and WHO recommended the use the GI and there have been many changes during development of current International Method of GI testing (Atkinson et al., 2008; Foster-Powell & Miller, 1995; Wolever. et al., 1991). The current International GI methodology recommends at least 10 participants to obtain sufficient statistical power (Brouns et al., 2005; Mann. et al., 2007; Wolever et al., 2003). Inclusion of both sexes is acceptable, as is varying ethnicity, and body mass index (BMI) ≤29.9kg/m^2, since GI was found to be not significantly related to age, sex, BMI, ethnicity or type of blood sampling (Wolever et al., 2003). The blood sampling as recommended by the International GI methodology is using whole capillary blood as this is simple and relatively non-invasive method of collecting blood and allows for extensive screening of food (Wolever et al., 2003; Wolever. et al., 1991). The glycaemic response using capillary blood is reported to be greater than use of venous blood therefore may allow smaller differences in glycaemic responses to different foods being detected (Wolever. et al., 1991). Participants with malabsorptive disorders or chronic conditions which may affect glycaemia or IR is excluded from the study (Wolever et al., 2003).

1.5.9.2 50g Available CHO

CHO sources used for GI should be fully digestible and absorbable. The usual way for determining 'available' CHO is by subtracting dietary fibre from the total CHO. However, this may lead to an overestimation in the case of products containing indigestible CHO. GI testing requires the consumption of 50g of available CHO within the given weight of the test food, which must be consumed reasonably rapidly within a 10 minutes timeframe, as delaying the consumption of the test food can affect glucose release and glycaemic response.

1.5.9.3 Glucose Control as Reference

Numerous reference foods (glucose, bread, white bread, wholemeal barley bread, wheat chapatti, potato, rice, wheat and arepa/Mexican starchy food) have been used in the past for GI testing, although notably the majority have used monosaccharide glucose or white bread (Atkinson et al., 2008; University of Sydney, 2017; Williams. et al., 2008). The International GI method suggests using either glucose or white bread (Brouns et al, 2005; Wolever et al., 2003).

1.5.9.4 Fluid ingestion

Fluids have a strong effect on gastric emptying rate, hence the importance of standardizing the type and timing of fluid ingested when assessing GI. In the past, coffee and tea have been used as the fluid to consume with the test food. However, caffeine is known to decrease insulin sensitivity in the short term. 375mg caffeine resulted in an increase in C-peptide and insulin as well as an increase in glucose AUC by 24% (Graham et al., 2001). Therefore, fluid ingestion of 250ml standard tap water is recommended and must be consumed within the allowed 10-minute consumption window, alongside the test food or glucose control solution (Brouns et al., 2005).

1.5.9.5 Prior to test day

The evening prior to the GI test, the recommendation is to avoid unusual vigorous exercise and excessive alcohol. A 10-hour overnight fast is required with at least one day in between repeat GI assessment days. The test should take place in the morning before 10am, after an overnight fast. This fasted condition is the most stable and likely to minimize intra-individual differences due to time of the day and influence of prior meal.

1.5.9.6 Blood sampling times

Blood sampling using capillary fingerprick is recommended (as this has been shown to give the greatest sensitivity) (Brouns et al., 2005; Wolever. et al., 1991). Blood glucose should be measured at 0 min (baseline), followed by 15, 30, 45, 60, 90 and 120 min after beginning test meal consumption. The test is always terminated after 2 hours.

1.5.9.7 Calculation of GI

AUC blood glucose calculation should be based on incremental AUC (iAUC), ignoring the area under the baseline. The International GI methodology suggests calculating the mean GI by using the iAUC for n=10 individuals. Due to intra- and inter-individual variation, outliers are defined as three or more standard deviations above the mean (Knox & Ng, 1998; Leys et al, 2013). The international method notes that outlier glucose measurements can be excluded if needed due to errors such as stress or seasonal effect as participants new to the testing may experience more anxiety. This anxiety may influence glycaemic response through delayed gastric emptying or insulin antagonistic effects of stress hormones. Outliers could also be due to incorrect subject preparation (e.g. non fasting, excess exercise the night prior), not consuming all of the test food, analytical error, or errors in data calculation

The first GI test was conducted in 1981 with groups of 5 – 10 healthy volunteers, who took 62 test foods in random order after overnight fasting, and compared these results with the glucose control. GI is a physiological response of blood glucose to a food, and is defined as the area under the curve (AUC) of circulating blood glucose after the test food (equivalent to 50 g CHO, or 25 g if unable to tolerate excessive volume i.e. broad beans, beetroot, carrot, parsnip and swede) is eaten. L-GI is defined as a rating of 55 units or below; H-GI is defined as above 70 units, as shown in Table 12. Another area with some evidence of effect on obesity is using the GI of foods where the lower the GI, the more satiety one experiences, promoting a reduction in overall food intake and resulting in weight loss or assist with weight loss maintenance. Jenkins et al found an inverse relationship between fat and GI but no relationship was seen between fibre or sugar and GI (Jenkins. et al., 1981; Jenkins et al., 1984; Jenkins. et al., 1988), which was surprising as one of the purposes of formulating the GI was to see how this was affected by fibre.

$$GI = \frac{\text{Blood glucose area of test food}}{\text{Blood glucose area of reference food taken by the same individual}} \times 100$$

Table 12: GI Classification

	L-GI	Moderate GI	H-GI
GI (units)	≤ 55	56-70	> 70

GI, Glycaemic Index; L-GI, low glycaemic Index; H-GI, high glycaemic index

An interesting finding from the initial GI testing showed that the high CHO foods with the lowest GI were those eaten commonly by the poor people living in Western countries, Africa and Asia, these include oatmeal porridge (GI 49 units), sweet potato/kumara (GI 48 units), spaghetti (GI 42 units), buckwheat (GI 51 units), yam (GI 51 units) and legumes (GI 29-40 units) (Foster-Powell & Miller, 1995). Following this study, 3-years later Jenkins et al conducted a report using 5 studies who also found discrepancies in the GI levels using normal and diabetic volunteers, demonstrating variations within individuals (Table 13) (Jenkins. et al., 1984).

Table 13: Mean GI of foods

	Jenkins et al 1981 (N) - GI	Jenkins et al 1984 (N+DM) - GI
Porridge	49	85
Muesli	66	96
Sweet potato/kumara	48	70
Potato	70	81
Spaghetti	42	66
Buckwheat	51	74
Yam	51	74
Legumes	29-40	20-60
Apple	39	53
Banana	62	79

Gi, Glycaemic Index; n = healthy volunteers; DM = volunteers with T2D; data extrapolated from Crapo et al., 1977; Jenkins et al., 1981; Jenkins et al., 1983

The International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC) have shown the health benefits on GI and glycemic load (GL). Consequently, in this publication, authors have suggested the importance of implementing GI and GL in national dietary guidelines, food composition tables and food labeling, in order to best educate the public and prevent their risk of developing chronic diseases (Augustin. et al., 2015). In 5 large epidemiological studies, a L-GI diet has shown many beneficial effects on obesity and obesity related conditions such as reduced risk of T2D, certain cancers (colon and breast) and cardiovascular disease (Brand-Miller et al., 2003; Hu et al., 2001; Jenkins. et al., 2002; Larsen et al., 2010; Williams. et al., 2008). Clinical trials in healthy, diabetic and individuals with hypercholesterolaemia have shown that L-GI diets may reduce a number of adverse markers, including blood glucose concentration, insulin secretion, oxidative stress, inflammatory response and serum triglycerides. Physiological testing is required to assign a GI value to each individual food item, and there is contradictory data for some items, including sweet potato/kumara, which is widely eaten in NZ. In the 1995 International Table of GI, sweet potato/kumara was assigned a GI of 48 (Foster-Powell & Miller, 1995), whereas in 2002 it was assigned a GI of 77 (Foster-

Powell et al., 2002), Jenkins et al 1984 assigned GI of 70 (Jenkins. et al., 1984); both using a reference standard of 50g glucose/white bread. The recommendations suggest using glucose over white bread, due to intraindividual variation with white bread, as white bread requires an average of three control test results to to variations compared to one sample using glucose (Wolever et al., 1985). The international resource 'Glycaemicindex.com,' which is widely used in dietary trials and clinical practice, assigns sweet potato/kumara a GI of 50 units (Wolever et al., 1985).

Wolever et al reported that there was an inverse association between protein and fat on GI, where increase in protein and fat would reduce the GI in mixed meals (Jenkins. et al., 1983; Wolever. et al., 1985). There is also growing evidence supporting the hypothesis that higher protein diets may improve glycaemia (Baum et al., 2006; Kushner & Doerfler, 2008; Larsen et al., 2010; Layman & Baum, 2004) with recent data showing that some proteins may have an effect on metabolic regulation independent of BW (McGregor & Poppitt, 2013). Whey protein for example, as an insulin secretagogue, may enhance glycaemic control with studies showing postprandial suppression of diet-induced hyperglycaemia by whey, decreasing glucose levels by ~20% in the 3 hours following ingestion (Jakubowicz & Froy, 2013). It also has a positive effect on the incretin system, with increased GIP, decreased GLP-1, and decreased DPP-4 activity in the small intestine (Jakubowicz & Froy, 2013).

1.6 Prevention of T2D in Europe and Around the World (PREVIEW) study

Development of T2D even in high-risk groups is not inevitable. Diet and PA lifestyle modification has long been shown to delay the progression from pre-diabetes, but the lifestyle strategy chosen may be of considerable importance. T2D prevention studies such as China Da Qing (Pan et al., 1997), Finnish Diabetes Prevention Study (FDPS) (Lindstrom et al., 2003) and USDPP (Diabetes Prevention Program (USDPP) Research Group, 2002) amongst others have shown a lower fat, higher complex CHO diet to be effective in decreasing risk of progression to disease. In the international PREVIEW study, it is hypothesized that a higher protein, lower GI diet may further improve dietary adherence, promote maintenance of weight loss longer term and so further prevent disease progression. Lower GI enhanced the effect of the higher protein diet, suggesting that protein content whilst clearly important was unlikely to be the only driver of intake in this study. This is also hypothesised in my thesis investigating the PREVIEW:NZ cohort in Auckland, New Zealand. Certainly lower fat, higher protein diets look to be efficacious in shorter-term studies, with increased satiety, thermogenesis and FFM, decreased FM and enhanced glycaemic control. There has been a need for longer-term RCTs, investigating the role that higher protein diets can play in T2D prevention, particularly in O/W groups at heightened risk (as summarised in Table 14).

The success of the DioGENES trial, as previously described, led to considerable interest in higher protein diets for longer-term maintenance and, in turn, amelioration of T2D risk (Larsen et al., 2010). Hence, the implementation from July 2013 of a large, global, 3-year *ad lib* diet and

exercise intervention, PREVIEW (PREVention of T2D through lifestyle intervention in Europe and Worldwide, NCT01777893 (Fogelholm et al., 2017) in New Zealand, Australia and 6 European countries. The aim was to investigate whether a low fat, higher protein and L-GI diet was also successful for longer-term control of glycaemic and prevention of T2D, when compared with current best practice of low fat, higher CHO diet.

Two thousand five hundred high-risk O/W and dysglycaemic adults and children were randomised into the international PREVIEW trial, with primary endpoint incidence of T2D at 3 years, and findings expected at the end of 2018. The PREVIEW International trial used a 2x2 factorial with 2 diets (higher protein/low fat/L-GI (HP/L-GI) intervention diet vs. higher CHO/low fat/moderate GI (LP/M-GI) control diet) and 2 exercise (high intensity/short duration intervention vs. moderate intensity/moderate duration control) strategies for the prevention of T2D, using diagnosis of T2D as the main outcome (Fogelholm et al., 2017).

This thesis is based on 2 years of the 3-year international PREVIEW T2D prevention RCT investigating the response of T2D biomarkers following dietary intervention, in the Auckland cohort of 321 participants (Silvestre et al., 2014). Group education was formatted using objectives set for each group session and conducted according to the protocol and individualised for the New Zealand population. We aimed to investigate the interaction of the two diets (higher protein vs. higher CHO) for prevention of worsening glucose control and other markers associated with T2D. Measures included anthropometric and biochemical measures, diet compliancy and attendance to group education sessions.

This PhD thesis aims to investigate factors that are important for T2D prevention over a 2-year weight loss maintenance follow-up through dietary factors with anthropometric and metabolic markers as the end point. Due to the ethnic diversity of Auckland, New Zealand, this thesis aims to look for ethnic differences and the risk of developing T2D with the diverse ethnic groups within New Zealand. The first results chapter is the LED Chapter 3, with the goal of ≥8% BW loss in 2 months, and investigates between anthropometric and metabolic measures in this population. Chapter 4, then investigates the weight loss maintenance during the higher protein lifestyle intervention over the 2-year period and again presents data on the anthropometric and metabolic measures. The final results chapter for this thesis, Chapter 5, presents a substudy investigating GI of three New Zealand varieties of sweet potato/kumara. The results from this sweet potato/kumara and GI substudy were used to inform PREVIEW:NZ participants on the GI value of an important and widely consumed NZ food, the sweet potato/kumara, from which they in turn would be able to modify their dietary intake accordingly.

1.7 Aims, Objectives and Hypothesis

The main aim of this thesis was to investigate the benefits of short term acute LED-induced weight loss and longer term lifestyle-induced weight change (loss, gain or no change) on metabolic parameters associated with risk of T2D in Caucasian, Maori/Pacific and Other ethnicity subgroups within the Auckland sub-set of PREVIEW:NZ. The aim of the substudy on

GI was to analyse the GI of kumara to be able to make diet recommendations in the lifestyle intervention weight maintenance phase.

1.7.1 PREVIEW-NZ primary objectives

1.7.2 The main objectives for this thesis were:

- To investigate changes in BW, body composition and metabolic markers during LED-induced weight loss and 2-year higher protein lifestyle intervention weight maintenance follow up in overweight New Zealand cohort with pre-diabetes.
- To investigate the role of ethnicity and gender on weight loss, weight loss maintenance and metabolic health.

1.7.3 PREVIEW-NZ secondary objectives

- To investigate the GI of the commonly eaten CHO staple, sweet potato/kumara in a subgroup of healthy adults

1.7.4 The main hypotheses for this thesis are:

- An 8-week LED (4MJ/day) will lead to ≥8% BW loss and improve in metabolic markers associated with T2D.
- An *ad libitum* low fat, higher protein, lower GI diet will improve weight loss maintenance and associated metabolic markers when compared to a low fat, higher CHO, moderate GI diet.
- Baseline BW will predict absolute BW and FM loss during LED in all ethnicities, and markers of metabolic health may be ethnicity dependent (Caucasian, Maori, Pacific Island and other cohorts within the Auckland subset of PREVIEW:NZ)
- Continued weight loss and/or maintenance of BW during lifestyle intervention will result in improved metabolic health; and that changes in markers of metabolic health may be gender and ethnicity dependent.

Table 14: Lifestyle Intervention Studies for T2D Prevention

Trial, Duration, Year	Population	Intervention	Effect on BW/BMI	Effect on T2D risk	F/U – T2D risk
Bedford study UK (Keen, Jarrett, Ward, & Fuller, 1973; Keen et al., 1982) 10 yrs (5 + 5) 1962-72	n=241 49% F middle aged O/W, IGT	2 x 2 factorial: tolbutamide vs. placebo; trained to restrict CHO intake (<120g/d) C: advice on table sugar	ns effect of treatments; -2kg BW loss across all cohorts at 5yrs	No evidence that CHO restriction reduces T2D risk at 5 or 10yr	10 yr: baseline glycaemia major predictor of T2D; BMI predicts T2D only at 5-10yr (9.8% vs. 0.9%), P<0.05
Whitehall study UK (Jarrett et al., 1984) 10 yrs (5 + 5) 1967-1980	n=204, M 48-65 yrs. H, O/W IGT	2 x 2 factorial: phenformin vs. placebo; trained to restrict CHO intake (<120g/d) C: advice on table sugar	-5kg BW loss in CHO restricted group at 5yrs	No evidence that CHO restriction reduces T2D risk at 5 or 10 yr	10 yr: baseline glycaemia major predictor of T2D; BMI does not predict T2D at 5 or 10yr
Malmö study Sweden (Eriksson & Lindgärde, 1991; Eriksson & Lindgärde, 1998) 6 yrs, 1974-1992	n=415, M 47-49 yrs. H, O/W: T2D, IGT-D+PA, IGT-C, NG;	nonrandomised D+PA: 10-15en%protein, <30en%fat, 55en%CHO, high fibre; +increase PA C: std advice+increase PA	significant -2.0 to 3.3kg BW loss in IGT-D+PA vs. +0.2 to 2.0kg gain in IGT-C (P<0.01)	significant 63% RR reduction for IGT-D+PA vs. IGT- C at 6yr, P<0.003	N/A; significantly lower mortality for IGT-D+PA (6.5 per 1000 person yrs. at risk) vs. IGT- C (14.0) at 12yr F/U
Da Qing, China (Li et al., 2008; Li et al., 2014; Pan et al., 1997) 6 yrs 1986-1992	n=577 47% F >25 yrs H + O/W IGT	D only: 10-15en%protein, 25-30en%fat, 55-65en%CHO,; if O/W, also decrease EI for BW loss of 0.5-1kg/wk PA only:increase leisure PA D+PA: as above C: general information, no counselling	+0.93kg BW gain in D only and +0.71kg in PA only; -1.77kg BW loss in D+PA; vs. +0.27kg BW gain in C	significant 33% reduction in incident T2D for D only, 47% for PA only, 38% for D+PA; 51% for 3 combined lifestyle groups	20 yr : 43% lower incidence for combined lifestyle gps 23 yr: 45% lower incidence for combined lifestyle gps
Mercy Hospital Australia (Wein et al., 1999) 6 yrs 1989-1997	n=200, F >36yrs previous GD H, O/W, IGT	Intensive D advice – healthy diet + PA; regular compliance follow up C: routine advice – healthy diet + PA, no follow-up	BMI increased in both intensive D (+0.8kg/m^2) and C (+0.6kg/m^2)	ns 36.6% RR reduction (P>0.05)	N/A
Japan DPS (Kosaka et al., 2005) 4 yrs 1990-1996	n=458, M 30-69 yrs H, O/W, IGT	Intensive: D+PA - restrict EI, aim BMI <22kg/m^2, 52-18-20en%protein, 21-28en%fat (low SFA) 61en%CHO, C: standard (S): D+PA - aim BMI <24kg/m^2	significant -2.18kg BW loss in D+PA vs. -0.39kg BW loss in C	significant 67.4% RR reduction	N/A

Trial, Duration, Year	Population	Intervention	Effect on BW/BMI	Effect on T2D risk	F/U – T2D risk
Oxford, UK (Page et al., 1992) 6 mths <1990	n=31 29% F 18-60 yrs H, O/W IGT	D+PA: decrease EI, 15en%protein, <30en%fat, 55en%CHO, limit SFA, fibre 20g/1000kcal C: no D or PA advice	ns change from baseline & ns difference in BW	RR not reported; ns change from baseline & ns difference in FPG	2 yr: significant FPG increase in D+PA; ns change in C
New Zealand (Bourn et al., 1994) 2 yrs 1988-1992	n=52 52% F 18-79 yrs H, O/W T2D, IGT	D+PA:15-20en%protein,<30en%fat,50-55en%CHO,fibre 20g/1000kcal, limit SFA and sugars; C: no Control group	-0.6kg BW loss in IGT group No C group	RR not reported; 40% of IGT with normal 2 hr glucose at OGTT No C group	N/A
FDPS (Lindstrom et al., 2003; Lindstrom et al., 2008; Uusitupa et al., 2003) 3.2 yrs 1993-1998	n=522 67% F 40-64 yrs O/W, IGT	D+PA - individualised advice 30en%fat, <10en%SFA, >15g/1000kcal fibre, incr PA. Goal 5% BW loss. C: general advice, not individual, decr BW, incr PA	significant -3.5kg (4%) BW loss in D+PA vs. -0.9kg (1%) loss in C	significant 58% RR reduction	7 yr : significant 43% RR reduction 13 yr : significant 32% RR reduction
USDPP (Crandall et al., 2008; Knowler et al., 2009; Nathan et al., 2013) 3 yrs 1996-2001	n=3234 27 centres 68% F 25-85 yrs H, O/W, IGT	3 groups; MF + standard advice; Lifestyle intensive D+PA goals, 7% BW loss, low EI, <25en%fat, PA 150min/wk, individualised C: placebo + standard advice	significant -5.6g BW loss [7% BW goal achieved by 49% at 6m, 37% at 3yr] in Lifestyle vs. -2.1kg in MF vs. -0.1kg in C	significant 58% RR reduction for Lifestyle; 31% RR reduction for MF	10 yr, 34% RR reduction for Lifestyle; 18% RR reduction for MF 15 yr, RR reduction 27% for lifestyle
Indian DPP (Ramachandran et al., 2006) 3 yrs 2001-2005	n=531 21% F 35-55 yrs H, O/W IGT	4 groups; MF; D+PA:lowEI/refinedCHO/fat, increase fibre, regular PA;MF+D+PA; C: usual care, no individual advice	ns change in BW	significant 28.5% RR reduction in D+PA; 26.4% in MF; 28.2% in MF+ D+PA	N/A
SLIM NL (Mensink et al., 2003; Roumen et al., 2008) 3 yrs 1999-2005	n=147 49% F >40 yrs O/W, IGT	Dutch guidelines, individualised D+PA advice, 30-35en%fat, <10en% SFA,150 min/wk C: healthy eating plus PA, no individualised advice	significant -1.1kg BW loss for D+PA vs. +0.2kg BW gain for C	significant 58% RR reduction for D+PA vs. C	N/A

Trial, Duration, Year	Population	Intervention	Effect on BW/BMI	Effect on T2D risk	F/U – T2D risk
EDIPS-Ncl (Penn. et al, 2013 ; Penn. et al, 2009) 3 yrs 2000-2007	n=102 59% F >40 yrs O/W, IGT	D: >50%enCHO, <30%enfat, <10% SFA, high fibre, BW loss goal BMI <25kg/m^2 C: health promotion advice	significant -2.3kg BW loss in D vs. +0.01kg BW gain in C	significant 55% RR reduction in D vs. C	N/A
USA (Liao et al., 2002) Japanese Ethnicity 2 yrs 2002-2005	n=74 55% F 42-66 yrs H, O/W IGT	AHA Step 2 intensive D <30en%fat, <7en%SFA, 55en%CHO, endurance PA C: AHA Step 1 D <30en%fat, 10en%SFA, 50en%CHO, stretching PA	significant -1.8kg BW loss in Step 1 vs. +0.7kg BW gain in Step 2 C	RR not reported; significant improvement in IGT for AHA Step 2 vs. Step 1 C	N/A
JDPP (Sakane, 2005) (Sakane, 2005) 3 yrs 1999-2006	n=304 50% F 30-60 yrs H, O/W, IGT	Lifestyle intensive D+PA goals -5% BW and increase leisure PA (+700kcal/wk), <25en%fat, limit alcohol, C: healthy lifestyle advise at baseline only	significantly greater BW loss in D+PA at yr 1 (P<0.05); ns difference at yr 3	ns 51% RR reduction in D+PA vs. C (P>0.05) at yr 3	N/A
Zensharen (Saito et al., 2011) Japan 3 yrs 2004-2009	n=641 28.5% F 30-60 yrs H, O/W BMI>24kg/m^2 IGT	Freq individualised FINT: low EI, 20-25en%fat, 55-60en%CHO, high fibre, increase PA, goal -5% BW C: same advice, less freq	significant -2.5kg BW loss in FINT vs. -1.1kg BW loss in C	HR 0.56 in FINT vs. C	N/A
China (Tao et al., 2004) N/A	n=60 43% F 34-65 yrs O/W, IGT	D+PA: D advice with moderate PA C: D advice only	N/A	HR 0.30 in D+PA vs. C	N/A
China (Fang et al., 2004) 5 yrs	n=178 45% F 34-65 yrs IGT	4 groups: acarbose; flumamine; D+PA education and monitoring C: education	N/A	HR 0.75 in D+PA vs. C	N/A

Footnotes: AHA, American heart association; BMI, body mass index; BW, body weight; CHO, CHO; C, control; D, diet; D+PA, diet plus physical activity; DPS, T2D prevention study; EDIPS, European T2D prevention study; EI, energy intake; FPG, fasting plasma glucose; F, female; F/U, follow-up; GD, gestational T2D; H, healthy (BMI<25kg/m^2); HR, hazard ratio; IGT, impaired glucose tolerance; JDPP, Japanese T2D prevention program; L, lifestyle; M, male; MF, Metformin; mths, months; N/A, not available; Ncl, Newcastle; NL, Netherlands; ns, not statistically significant; NG, normoglycaemia; OGTT, oral glucose tolerance test; O/W, overweight (BMI ≥25kg/m^2); PA, physical activity;%en, percentage of energy; RR, relative risk; SFA, saturated fatty acids; SLIM, study on lifestyle intervention and impaired glucose tolerance Maastricht; std, standard; T2D, T2D; TE, total energy; USDPP, US T2D prevention program; wk, week; yr, year; yrs, years, O/W, overweight

Chapter 2 Common Methodologies

2.1 Overview: The PREVIEW Trial

The International PREVIEW trial aimed to recruit 2,500 O/W, pre-diabetic participants (2,300 adults and 200 children) into a 3-year (36-month) intervention. It was a multi-national, randomized, clinical intervention study in 8 sites in 6 EU countries: Bulgaria, Denmark, Finland, Spain, the Netherlands, United Kingdom, and in Australia and New Zealand. The primary outcome for this large study was the diagnosis of T2D. The adult intervention was performed in all the 8 intervention sites. PREVIEW:NZ was conducted at the Human Nutrition Unit, University of Auckland, New Zealand from July 2013 till the end of study in May 2018. PREVIEW comprised of 2 phases. Phase 1 was an 8-week LED-weight loss period, and Phase 2 was a 3-year weight maintenance period where participants were randomised to a lifestyle (diet and exercise) intervention. This thesis presents data from the first 2 years of the study conducted in New Zealand (PREVIEW:NZ).

2.1.1 Ethics Approval

Human ethical approval for the PREVIEW:NZ trial was obtained from the New Zealand National Health and Disabilities Ethics Committee (HDEC) Northern X Regional Ethics Committee; Ethics number 13/NTB/41/AM02. All participants completed written consent before any measurements were undertaken. Participants were informed that their input was voluntary and that they had the right to withdraw from the study at any time without providing a reason. They were also informed that this was an intention to treat (ITT) study and that all aspects of the study would analysed. Complete withdrawal from the study was recorded and an end of trial termination form was then completed. The Clinical Trial Registration number for the international PREVIEW study is NCT01777893.

2.2 Recruitment

2.2.1 Advertising and Recruitment Process

Recruitment for PREVIEW-NZ commenced in July 2013. A one-page advertisement was circulated via email among University staff, Hospital staff members, social media, local newspapers, radio advertisements posters in supermarkets, around the university and throughout the Auckland region. Respondents contacted the Human Nutrition Unit (HNU) research team.

2.2.2 Study Participants

For PREVIEW-NZ, 1654 adult participants were pre-screened using the telephone and an internet survey tool (SurveyMonkey™, Sydney, Australia). After pre-screening for eligibility, 584 participants were invited for in clinic screening using an OGTT at the Human Nutrition Unit. Following screening, 321 participants were found to be eligible and enrolled for PREVIEW-NZ.

2.2.3 Pre-Screening

Interested participants were invited to contact the research team by email or phone. They were then asked to complete a short survey via phone or using an online tool i.e. SurveyMonkey using the questions raised as risk factors in the FDRS (Saaristo et al., 2005). Those with a FDRS ≥12 points were contacted to progress to the second stage of the screening process, the clinic information meeting where the study was explained in person, participant information sheet provided and questions answered. The pre-screening questions included physical characteristics such as weight, height, medical history including prior surgery, glycaemia related disorders and monitored lifestyle patterns such as fruit and vegetable intake and exercise frequency.

2.2.4 Screening

The screening process was conducted in clinic and involved anthropometric and laboratory assessments, in addition to questionnaires. The anthropometric measurements involved weight, height, resting BP and HR, plus an electrocardiogram (ECG) was required for those aged over 55 years of age. An OGTT was conducted to assess glycaemic status. This was a simplified 2 sample test, with blood samples collected fasted and at 120 minutes after the oral glucose load. Safety tests were also conducted including for liver and kidney function. Blood samples were analysed locally at the Human Nutrition Unit using a Roche Reflotron benchtop analyser. A series of questions to confirm each individual's eligibility criteria were asked at the screening visit. Questions included age, ethnicity, medical history, recent weight change and behavioural patterns.

2.2.5 Inclusion and Exclusion Criteria

2.2.5.1 Inclusion Criteria

Inclusion criteria included being aged between 25-70 years of age, O/W with BMI ≥25kg/m^2. Pre-diabetic using the WHO/IDF criteria, of fasting glucose concentration between 5.6-6.9mmol/l and/or 2-hour glucose concentration between 7.8-11mmol/l following 75g oral glucose bolus. Smokers were included in the trial, provided there was no change in smoking habit over the past month. Motivated participants had to be willing to be undertake the weight loss study using LED and understand that they may be randomized to follow to one of two diets and one of two exercise groups for the weight loss maintenance phase. Lastly, participants had to attend the clinical investigation days (CID) at the Human Nutrition Unit during normal working hours or at the weekends (see Table 15).

2.2.5.2 Exclusion Criteria

Exclusion criteria included both normoglycaemia and T2D at screen. Also other significant cardiovascular disease within the past 6 months, significant hypertension or unstable treated hypertension. A range of other medical exclusions are listed in Table 15. Participants were also excluded for >5% BW change in the previous 2 months, current active weight loss diets (e.g. Atkins diet or similar), eating disorders and severe food intolerance. Previous bariatric surgery was also an exclusion (see Table 15).

Table 15: Summary of Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Aged 18 and over	Diagnosed with T2D. Other Medical conditions as reported by participant
BMI ≥25kg/m2	Had a significant cardiovascular disease (e.g. current angina, myocardial infarction or stroke) within the past 6 months.
PreT2D according to WHO/IDF	Heart failure or with symptomatic peripheral vascular disease.
IFG: Fasting venous plasma glucose level of 5.6-6.9mmol/l OR	Systolic blood pressure above 160mmHg and/or diastolic blood pressure above 100mmHg (with or without hypertension treatment).
IGT: Venous plasma glucose concentration 7.8-11mmol/l 2 hr after 75g glucose solution following OGTT criteria, with fasting glucose <7mmol/l	If treated for hypertension, no change in drug treatment within last 3 months to be included in the study.
Read Participant Information Sheet and signed Consent Form	Advanced chronic renal impairment
No change in smoking habit over the past 1 month (smoking allowed but no change)	Significant liver disease e.g. cirrhosis (fatty liver disease allowed)
Agreed to partake in the LED and randomized intervention group	Active cancer/malignancy or in remission for less than five years after last treatment
Agree to attend the clinical investigation days (CID) during normal working hours	Active inflammatory bowel disease
	Coeliac disease
	Chronic pancreatitis
	Other malabsorptive disorders
	Previous bariatric surgery
	Chronic respiratory
	Neurological, musculoskeletal or other disorders where participants would have unacceptable risk or difficulty in complying with the protocol (e.g. physical activity program).
	With transmissible blood-borne diseases e.g. hepatitis B, HIV
	Psychiatric illness (e.g. major depression, bipolar disorder) are also excluded.
	Certain medication taken within the past three months with a potential of affecting BW or glucose control e.g. glucocorticoids (allowed inhaled and topical steroids or bronchodilators), psychoactive medication, epileptic medication or weight loss prescriptive, over the counter or herbal medication is also excluded.
	Other factors:
	Engaging in competitive sports
	Reported weight change, >5% weight change within two months of screening is also excluded.
	On a special diets (e.g. Atkins, vegan)
	Drink more than 21 standard alcohol drinks per week or men or more than 14 standard drinks for women
	Drug users in the past 12 months
	Suffer from severe food intolerance
	Reported eating disorders
	Pregnant or lactating or plans to become pregnant in the next 36 months
	Limited or no access to either phone or internet
	Inadequate understanding of English language
	Suffer from psychological or behavioural problems making it difficult to comply with the protocol
	Donated blood/blood transfusion in the past one months from baseline
	Laboratory – if venous plasma glucose fits the eligibility criteria
	Haemoglobin concentration below local reference values i.e. anaemia
	Creatinine >1.5 times upper limit of normal local reference value
	Abnormal Electrocardiography (ECG) – only required for age 55-70 yrs
	After LED phase at CID2/Post LED - Failure to reach 8% weight loss from initial BW

BW, body weight; BMI, Body Mass Index; T2D, Type 2 Diabetes; OGTT, Oral glucose tolerance test; IFG, Impaired Fasting Glucose; IGT, Impaired Glucose Tolerance; ECG, Electrocardiography; Clinical Investigation Day 2, Post LED at 8 weeks

2.3 Study Design

The PREVIEW study design is shown in Figure 6. Phase 1 of the study was the 8-week weight loss LED intervention intended to achieve ≥8% BW loss. Participants attended the clinic every 2-weekly, where BW was measured and they received group counselling sessions intended to promote compliance to the diet. Phase 2 of the study was a randomized 3-year weight loss maintenance intervention intended to prevent weight re-gain, from which this thesis presents data for years 1 and 2. Participants attended a further 13 group counselling sessions, with months between sessions increasing as the intervention progressed in a fading visit design. Eight weight loss maintenance group education sessions were conducted in the first year, only 3 in the second year and 2 in the third year. Figure 6 represents PREVIEW International study of 3 years with a total of 7 CID visits and 13 group sessions. In order to meet the recruitment target, 44-48 participants per cohort was recruited. Table 16 represents PREVIEW:NZ study of 2 years with a total of 6 CID visits and 11 group sessions, as presented in this thesis.

CIDs were conducted throughout the trial, where participants underwent anthropometric and laboratory assessment.

CID1 - Baseline, pre LED, 0months (CID1/Baseline)

CID2 - Post LED/2 months (CID2/Post LED)

CID3 – 6 months (CID3/6m)

CID4 – 12 months (CID4/12m)

CID5 – 18 months (CID5/18m)

CID6 – 24 months (CID6/24m)

CID7 - 36 months [data not presented in this thesis]

Details of both phases of the intervention are provided in following sections of this Chapter. Table 16 presents the timing of the endpoint measures conducted throughout the 2-year study. In summary, primary end points of BW and FPG were measured at all CIDs; an OGTT was conducted at all CIDs other than CID2/Post LED (end of LED); body composition was measured at all CIDs other than CID5/18m (18 months). Adverse events were reviewed throughout the intervention at all CIDs, as were changes in medications. Medical diagnosis of progression to T2D, either during PREVIEW assessment at CIDs or by a healthcare practitioner, was an exclusion criterion for the study, hence the intervention was terminated and the participant referred for appropriate medical treatment.

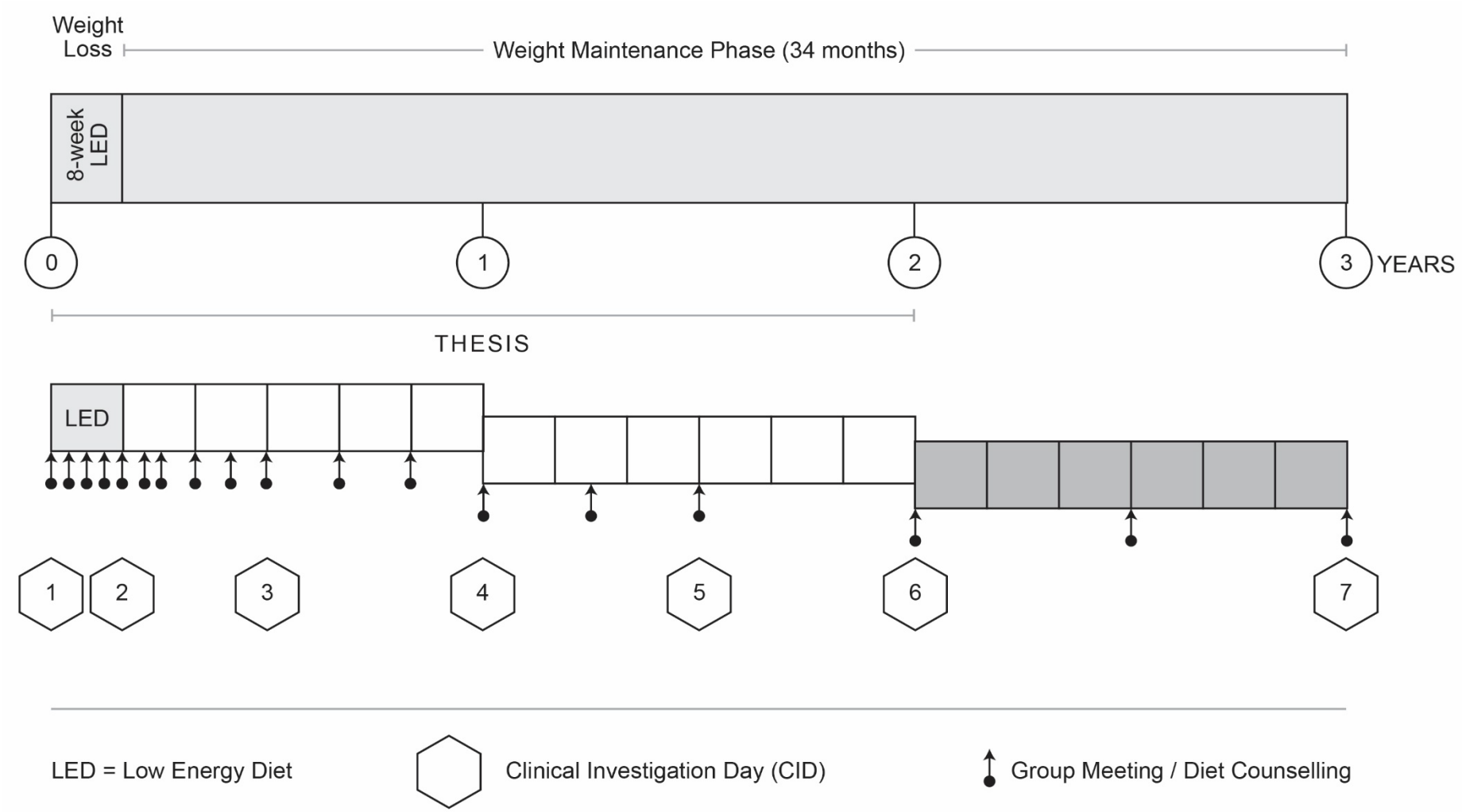


Figure 6: PREVIEW Study Diagram

Table 16: PREVIEW:NZ Study Design

	Screen Baseline		Weight Reduction (LED)								Weight loss Maintenance Intervention						
Visit	1	2 CID1	3	4	5	6 CID2	7	8	9	10	11 CID3	12	13	14 CID4	15	16 CID5	17 CID6
Time (months)		0				2		3	4	5	6	8	10	12	15	18	24
Time (weeks)		0	2	4	6	8	10	12	16	20	26	32	44	52	64	78	104
Group meeting		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BW (kg)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (m)	X																
WC (cm)		X				X					X			X		X	X
Body composition (DXA)		X				X					X			X			X
Blood pressure, ECG (55-70 y)	X	X				X					X			X		X	X
Fasting blood samples	X	X				X					X			X		X	X
OGTT (0, 30, 60, 90, 120 min)	0+120min	X									X			X			X
Food diary collection 4-day food record		X									X			X			X
Adverse event and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

X, measurements conducted; CID, Clinical Investigation Day; BW, Body weight; WC, waist circumference; DXA, Dual Energy X-ray Absorptiometry; ECG, Electrocardiogram; OGTT, Oral glucose tolerance test

2.3.1 CID1/Baseline visit for eligible participants

Following screening, 321 participants were enrolled for PREVIEW:NZ and invited for a CID1/Baseline visit. Parameters measured at CID1/Baseline are shown in Table 17. This was a 3-hour clinic visit and included anthropometry, collection of a fasting blood sample (glucose method, via THL (commercial analytical commercial company) collaborator in Helsinki using hexokinase enzymatic method), a repeat multi-sample OGTT, and a DXA, GE Lunar iDXA (GE Healthcare, Waukesha, WI) body composition scan, all described in detail later in this Chapter.

Upon enrolment, and prior to both CID1/Baseline and the commencement of the 8-week LED, eligible participants were asked to complete a 4-day self reported food diary as 'homework'. This completed data was brought by the participant to CID1/Baseline visit.

Once participants had completed CID1/Baseline they began Phase 1 of the intervention, the 8-week weight loss LED. Meal replacement sachets were dispensed, information on use of the meal sachets was provided, and an LED 2 week appointment was booked. Details of the LED are described in detail later in this Chapter.

Table 17: PREVIEW:NZ - Parameters measured at Clinical Investigation Days (CIDs)

	CID#	Parameters Measured
	Screening	Weight, Height 2-sample OGTT, incl fasting and 2 hr glucose Safety tests, incl liver function BP, HR, ECG (55-70y)
Weight loss 8-week LED	CID1/Baseline 0 week	Weight, WC Fasting glucose, multi-sample OGTT, Insulin, C-Peptide, HbA_{1c}, Lipids, CRP BP, HR Body Composition DXA Food record diary
	CID2/Post LED 2 month	Weight, WC Fasting glucose, Insulin, C-Peptide, HbA_{1c}, Lipids, CRP BP, HR Body Composition DXA
Weight Loss Maintenance	CID3/6m	Weight, WC Fasting glucose, OGTT, Insulin, C-Peptide, HbA_{1c}, Lipids, CRP BP, HR Body Composition DXA Food record diary
	CID5/18m	Weight, WC Fasting glucose, Insulin, C-Peptide, HbA_{1c}, Lipids, CRP BP, HR
	CID6/24m	Weight, WC Fasting glucose, OGTT, Insulin, C-Peptide, HbA_{1c}, Lipids, CRP BP, HR Body Composition DXA Food diary record

CID, Clinical Investigation Day; LED, Low Energy Diet; OGTT, Oral Glucose Tolerance Test; HbA1C, Glycosylated Haemoglobin; CRP, C-Reactive Protein; C-Peptide, serum connecting peptide; BP, Blood Pressure; ECG, Echocardiogram; DXA, Dual Energy X-ray Absorptiometry

2.4 Phase 1 - LED

2.4.1 Initial ≥8% weight loss using LED

Weight loss was achieved using the LED, consisting of 4 sachets of the energy-controlled meal replacements using milk shakes, porridge and soup, from the Cambridge weight loss programme (Cambridge Weight Plan, Corby, United Kingdom). Each meal replacement sachet was reconstituted using 250ml trim milk (3/day) and tap water (1/day). In addition 2 cups of non-starchy vegetables and 2 litres of water were allowed per day. These products contained all of the macronutrients, vitamins and minerals required, whilst limiting TE intake to 4MJ per day to achieve the weight loss goal of ≥8%. Side effects from the sudden decrease of energy intake may occur including headaches dizziness, tiredness, nausea and constipation. Sensitivity to the cold, dry skin, bad breath and increased risk of hair loss may also occur when on a LED. Extra fibre using psyllium husk was provided to prevent bowel discomfort. During the 8-week LED, no vigorous exercise was recommended. Fluids allowed included water, black tea/coffee and sugar-free diet carbonated drinks/cordial only. No energy containing drinks were allowed, including

alcohol, fruit juice, sugar sweetened drinks or full cream milk. (Appendix A: Full preparation and instructions on the LED)

During the LED phase, participants attended the HNU every 2 weeks for a period of 8 weeks. At each visit they were weighed (non-fasted, often evening measurements) to encourage compliance to the diet. Participants calculated their own goal weight and total weight loss required to meet the 8% weight loss goal using the calculations below:

_____ **kg x 0.92 =** _____**kg**

(current weight) (goal weight)

_____**kg –** _____ **kg =** _____**kg**

(current weight) (goal weight) (amount of weight to lose)

2.4.2 Group counselling/education sessions

Group sessions were held every 2 weeks during the 8-week weight loss LED phase, as described above. At each session participants were provided with dietary counselling as a group of ~8 participants, with particular focus on completion of the LED phase and compliance to the strict diet. Behavioural training was a key part of each session, as described below.

2.4.3 Behavioural Education

Behavioural training in the group setting was also conducted throughout the LED phase at each 2-weekly session, using the PREVIEW behavior modification intervention toolbox (PREMIT) paradigm (Huttunen-Lenz. et al., 2018; Kahlert et al., 2016). The group counselling sessions were aimed for ~8 participants, lasted about 120 minutes, and were delivered by members of staff trained in using the PREMIT methods such as persuasive communication and action planning. The baseline session in Phase I included information about the LED designed to facilitate the loss of ≥8% BW. The second and third sessions highlighted for participants the recommended behavioural changes that they would be required to following in Phase 2, and also and promoted self-efficacy. The fourth session promoted willingness to follow the recommended diet in Phase 2, and also reinforced positive outcome expectancies. The fifth session continued to reinforce self-efficacy and provided support in setting behavioural goals and defining an action plan for Phase 2 weight loss maintenance. Details of the PREVIEW PREMIT group program can be found in the recent publication of (Huttunen-Lenz. et al., 2018; Kahlert et al., 2016).

2.5 Phase 2 – Weight Loss Maintenance

2.5.1 Phase 2, weight loss maintenance

In the PREVIEW International study, after the ≥8% weight loss goal was achieved, participants entered into the second phase of the study, a 148-wk randomised weight-maintenance intervention. This was a 2x2 factorial which included both diet and exercise arms. The diet intervention, intended to promote long-term weight loss maintenance, is shown in Table 18. It comprised: A higher protein (HP, 25 en%protein), moderate CHO (MC) (45en%CHO), L-GI (GI

<50), low fat (<30en%fat) (HP/L-GI) diet vs. lower protein (LP, 15en%protein), higher CHO (HC) (55en%CHO), M-GI (GI>56), low fat diet (<30en%fat) (LP/M-GI) diet.

Table 18: Dietary Intervention: HP/L-GI vs. LP/M-GI

	HP, MC, L-GI	LP, HC, M-GI
CHO	45en%CHO	55en%CHO
Protein	25en%protein	15en%protein
Fat	<30en%fat	<30en%fat
GI	L-GI	M-GI

HP, Higher Protein; LP, Lower Protein; MC, Moderate Carbohydrate; HC, High Carbohydrate, L-GI, Low Glycaemic Index; M-GI, Moderate Glycaemic Index; CHO, Carbohydrates; en %, percentage of TE

In addition participants were counselled to undertake a fixed exercise program which was either with high intensity (HI) for short duration of 75min/week with 76-90% of maximal heart rate, or moderate intensity (MI) exercise with maximal heart rate of 60-75% for longer duration of 150min/week. Table 19 summarises the two exercise intervention conducted in the PREVIEW trial. Healthy exercise recommendation is based around 150 min per week of moderate intensity (Hansen et al., 2009; McLean et al., 2009; Pan et al., 1997; Tjonna et al., 2008), a ~3 to 6 metabolic equivalence with maximal heart rate of 60-75%, compared to the experimental group of shorter duration of 75 min per week of high intensity, >6 MET at 76-90% maximal heart rate.

Table 19: Exercise Intervention: High Intensity vs. Moderate Intensity

	HI	MI
MET	>6 MET	3-6 MET
Maximal HR	76-90%	60-75%
Exercise per week (min/wk)	75min/week	150min/week

MET, Metabolic Equivalent for Task; HR, heart rate; HI, High Intensity; MI, Moderate Intensity

Although physical activity/exercise was also a factorial within the international PREVIEW trial, this was not included in the analysis of PREVIEW:NZ and again the data remains locked until the end of 2018. Hence the data presented in the chapter thesis is for diet only.

2.5.2 Group counselling/education sessions

Again, group education sessions were based on the PREMIT programme (Section 2.4.3) with set objectives set for each group visit. The group visit was conducted by myself or the dietitian research assistant (Fogelholm et al., 2017; Huttunen-Lenz. et al., 2018; Kahlert et al., 2016).

2.5.3 Behavioural Education Based on Health Psychology Theory

Behavioural change education was also emphasised during the group meetings for Phase 2 of the intervention. The main concept of behavioural change is based on health psychology theories; social cognition theory, trans-theoretical model and self-determination theory around motivational interviewing and setting SMART goals (Huttunen-Lenz. et al., 2018; Kahlert et al., 2016). Specified PREMIT education (Section 2.4.3) was provided by the central PREVIEW

Stuttgard group based in Germany for the group educators, which focused on setting SMART goals, fear appeal, mental contrasting and asking open ended questions within the group (Huttunen-Lenz. et al., 2018; Kahlert et al., 2016).

2.6 Statistical Analysis

Statistical analyses are presented in detail in each individual data Chapter within the thesis.

2.7 PREVIEW:NZ Contribution and PhD Thesis

As lead Dietitian and for this thesis, I investigated the effect of LED and lifestyle intervention during the first 2 years of PREVIEW:NZ. From July 2013, I have been involved with the recruitment of the study participants, planned the objectives according to the protocol and amended this for the New Zealand population, led and conducted the group counselling session and monitored the progress of participants, whilst gathering data from years 1 and 2 of the study. I also trained another dietitian research assistant using the PREMIT behavioural education (Section 2.4.3) for the weight loss maintenance phase over 3 years for the two dietary groups. I reviewed and created all the dietary handouts and materials used for the New Zealand population, whilst considering New Zealand foods, measuring metrics and economical food options for budgeting purposes.

2.7.1 Pre-screening, Screening, Informed Consent

Initially, I was involved in the design of the pre-screening questionnaire and formation of the "surveymonkey" online questionnaire to allow for easier assessment for eligibility into the study using questions from the FDRS. Eligible participants were contacted by phone and suitable times were arranged for screening at the HNU. At screening visits, explanation was provided on the PREVIEW study, including the 8-week weight loss phase using the LED, the 4-randomized streams, CID visits, group sessions and tasks required e.g. food diary, 7-day physical activity record, accelerometer and urine samples required, stool sample was also required for some participants, after signing off the informed consent form. The physical activity data, urine samples and faecal samples were not used in the PREVIEW:NZ thesis.

2.7.2 Clinical Investigation Days – Measurement

As part of my thesis, I collected anthropometric data collected at the clinical investigation (CID) visits by filling in the Clinical Record Forms (CRF). During the clinic visits, the 4-day food diaries was collected, checked and further questions may be asked if the food diary was incomplete or needed clarification on the type and/or amount consumed. During the CID visit, medical history, medication and adverse event was checked and documented. During the CID, BW and anthropometric measures was collected and documented on the CRF. The clinic nurse collected the blood samples at the different time points as per protocol. Following the blood sample, participants had their DXA (GE Healthcare, Waukesha, WI) body composition scan. When the participant left, all the anthropometric data collected was entered on the online database,

OpenClinica (version 3.1.4.1, OpenClinica, LLC, USA). The 4-day food diary was entered onto a local food analysis database, Foodworks (Xyris 8.0 Professional, Australia).

2.7.3 Blood Sample Collection and Plasma Glucose Sample

During the early stages of the study, I was involved in assisting in the collection of blood sample during screening and CIDs 1, 2 and 3. This included laboratory handling and separation of the blood samples analysis using the Reflotron Plus desktop analyser, segregated blood sample into aliquot, labelled for interim storage at the Auckland site. I also participated in preparing and arranging transportation for the samples to the central laboratory in Helsinki, Finland.

2.7.4 Group Meeting Conduction and Education to Other PREVIEW Educators

The conduct of group counselling/education sessions was a major part of the PREVIEW protocol. As a dietitian, I have been trained to conduct consultations and group sessions using motivational interviewing and asking open questions. The PREVIEW consortium had prepared a group education training schedule involving techniques such as setting SMART goals, use of fear factor to motivate participants, asking open ended questionnaire and technique and mental contrasting skills. From these education sessions, each centre had to formulate lesson plans using the education assigned by the PREVIEW consortium. I led and conducted the group education for 2 years with the PREVIEW:NZ participants, and also trained another dietitian research assistant using the PREMIT behavioural education (Section 2.4.3) while meeting study objectives (Huttunen-Lenz. et al., 2018; Kahlert et al., 2016).

2.8 Anthropometric Measures

CID measurement time points for anthropometric outcomes are as described previously and shown on Table 16. Details of each measurement procedure are presented below.

2.8.1 Weight and height

BW was measured with an empty bladder, in the fasted state with participants dressed in light clothing and without shoes. BW was measured on a digital scale (SECA, Germany). Two measurements were taken to the nearest 0.1kg. The average of these two BW measurements was used for the final reading. Height was measured using a wall-mounted stadiometer (SECA, Germany) with participants without shoes and standing in a straight position (heels, buttock and upper back touching the wall mounted stadiometer and measured to the nearest 0.5kg. The average of these two height measurements was used for the final reading.

2.8.2 WC

Waist was measured twice to the nearest 0.5kg using a non-stretch measuring tape with the fasted subject standing with an empty bladder. The mean of the 2 measurements was also used. Waist measurement was taken at the midway between the end of the lower rib and the iliac crest as per study protocol.

2.8.3 Body composition

Body composition was measured via dual-energy X-ray absorptiometry (DXA) scan using a GE Lunar iDXA (GE Healthcare, Waukesha, WI) at Auckland city hospital. DXA measurements take less than 15 minutes, are non-invasive, have low rates of error with inter-operator variability, and provide both total body and regional (trunk, arms, legs, pelvis, android, and gynoid) distribution with automated analysis from a single whole-body scan (Hind et al., 2010). Parameters calculated included FM, and FFM. Total body precision for FM and FFM were 0.5%, 1.0%, and 0.5% coefficient of variation (CV), respectively.

2.8.4 Blood pressure

Systolic and diastolic blood pressure (SBP, DBP) were measured using a validated automatic device (Dinamap, V100, Carescape, GE Medical Systems Information Technologies, Wisconsin, USA) on the right arm while seated in a resting position. The measurement was taken three times with a minutes rest between, measured to the nearest 1mmHg, and the mean of the three values was used.

2.9 Metabolic Measures

CID measurement time points for metabolic outcomes are shown in Table 16, as described previously. Details of each measurement procedure are presented below. All laboratory measurements were conducted at the PREVIEW central laboratory hub in Helsinki, Finland by the National Institute for Health and Welfare. Samples were frozen at -20°C immediately after collection in Auckland, and stored at -80°C until air couriered to Finland where they were batch analysed by the central laboratory hub in Helsinki.

2.9.1 OGTT

A standardised WHO OGTT was conducted where a baseline fasted venous blood sample was collected, after which 75g glucose bolus was consumed. Repeat venous blood samples were collected over the following 2 hours. Participants had an indwelling venous cannula inserted to aid collection of repeat samples. At the screening visit, a short 2 sample test was conducted, with collection of fasting (0min) and 2-hour (120min) samples only. At CID visits a multi sample test was conducted, with collection of fasting (0min) and 15, 30, 45, 60, 90 and 120 minute samples. OGTT was conducted at screening, CID1/Baseline, CID3/6m, CID4/12m and CID6/24m.

2.9.2 Fasting blood samples

The fasting blood sample was also analysed for Insulin, HbA_{1c}, C-peptide, hs-CRP and lipids - total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglyceride (TG) and total cholesterol to HDL-C ratio (TC:HDL ratio). Glucose measurements were conducted using an enzymatic hexokinase method, Architect ci8200 from Abbott Laboratories. Fasting blood samples were collected at screening, CID1/Baseline, CID2/Post LED (8-wk), CID3/6m, CID4/12m, CID5/18m, CID6/24 months.

2.10 Dietary composition, nutrient intake and GI assessment

Dietary assessment was conducted using a 4-day reported food diary. The diary was completed in hard copy, where 3 consecutive week days and 1 weekend day were analysed for total food intake and nutrient composition. Participants were asked to record everything that they ate and drank during the diet record days. Accuracy was important so participants were asked to use measuring cups, spoons and measuring scales to maximise accuracy. Individual weighing scales were not provided, but participants were encouraged to use their home scales if available. Food diaries were checked at relevant CIDs and clarification of the food diaries was completed through discussion with the participant, and corrected, if required. Food diaries were then manually entered into the Australian/New Zealand food analysis programme, Foodworks (Xyris 8.0 Professional, Australia). Nutrient analysis included TE, en%protein, en%fat, en%CHO and GI.

2.11 Physical activity assessment

A subjective self-administered Baecke questionnaire (22 questions measuring habitual physical activity in work, sport and leisure activities) (Baecke et al, 1982) and 7-day accelerometer data was collected throughout the trial. However access to this data was not available until the end of 2018.

2.12 Adverse events

Adverse events (AEs) and serious adverse events (SAEs) were reported and recorded. PREVIEW:NZ was monitored by an independent diabetes clinician based at Greenlane Hospital, Auckland who reviewed all side/adverse effect reports throughout the trial.

2.13 Online data management

All data were both collected in a participant clinical trial file held at the Human Nutrition Unit and also reported online to the PREVIEW co-ordinating centre in Copenhagen, Denmark using an electronic case record form (eCRF) using the data capture system OpenClinica (version 3.1.4.1, OpenClinica, LLC, USA).

2.14 Glycaemic Index

PREVIEW:NZ substudy on Kumara and GI: The GI protocol using the International GI methodology with 10 subjects on the test food, two types of kumara with varying preparation and standard potato. The control was 50g glucose solution, not white bread due to increased individual variation and suggested the need to do each control three times, as suggested by Wolever et al (Wolever et al., 1991) University of Auckland Human Ethical Approval was obtained. To ensure consistency with protocol compliance, SOPs was developed prior to recruitment of participants. The study investigating Kumara and GI was conducted as per international protocol. Data was analysed following each of the kumara and GI study.

Chapter 3 PREVIEW:New Zealand – Acute weight loss via an 8-week low energy diet (LED)

Obesity is prevalent worldwide and is linked to adverse metabolic health and increased risk of chronic conditions, hence, any weight loss in the O/W and obese population is expected to improve metabolic health (Taylor, 2018; World Health Organisation, 2013; World Health Organization, 2000; Zimmet. & Baba, 1990). There is strong evidence showing that a BW loss of 5-10% prevents the onset of T2D in those with pre-diabetes, by improving glycaemic control, BP, lipids and microvascular damage. In the USDPP, a modest weight loss of 5kg in a cohort of O/W adults provided a clinically significant 58% reduction in the risk of T2D over 3.2 years (Diabetes Prevention Program Research Group, 2002). The more recent DiRECT study showed remission of T2D with 10% weight loss (Lean et al., 2017). For those with a BMI >35kg/m^2 or alternatively 30kg/m^2 but classified as obese with a serious medical complication (such as T2D), a higher target BW loss of 15-20% is recommended (Logue et al., 2010; Stegenga et al, 2014).

Weight loss can be achieved slowly or rapidly with some considerable debate as to which is most efficacious (Affuso et al., 2014; Anderson et al., 2001; Astrup, 2004; Dunkley et al., 2014; Foster et al., 1992; Franz, 2017; Franz et al., 2007; Madjd et al., 2016; McManus et al., 2001; Moore et al., 2000; Thom & Lean, 2017). One approach that has been effective for approaching rapid weight loss is the use of an LED, with energy content between 2.5-6MJ/day (Alibasic et al., 2013; Anderson et al., 2001; Apfelbaum et al, 1987; Apfelbaum et al., 1999; Atkinson, 1989; Chan, 2017; Christensen et al., 2012; Christensen et al., 2011; Clifton et al., 2014; Franz, 2017; Haywood et al., 2017; Howard et al., 1978; Larsen et al., 2010; Leslie et al., 2017; Leslie et al., 2016; McCombie et al., 2017). Leslie et al conducted a systematic review and meta-analysis on 5 weight loss interventions using LED (n=569, mean BMI 35.5-42.6kg/m^2), comparing TE intake >3.3MJ LED with energy intake <3.3MJ/day (VLED) in O/W patients with and without T2D. The authors found that both diets (LED and VLED) successfully led to the weight loss target of 15-20% in those who were severely obese (Leslie et al., 2017). In 2010, the European multicentre DioGENES study, a dietary intervention for weight loss and its maintenance in O/W adults, used a commercial LED (4MJ/day) to promote a weight loss goal of ≥8% BW. At the end of the 8-week LED, 83% of the participants successfully met the weight loss goal (Goyenechea et al., 2011; Halkjær et al., 2011; Rudovich et al., 2016).

It has been suggested that rapid weight loss may be unfavourable due to both (i) large loss of lean/muscle mass, and (ii) equally rapid weight re-gain. In 2007, Franz et al. conducted a systematic review and meta-analysis of weight loss investigating the different types of weight loss in 80 clinical trials (n=26,455) with at least 1-year follow-up. The authors concluded that an intervention using an LED containing ≤4.0MJ/day was the most effective weight loss method, with both greatest weight loss at 6 months and substantial weight loss maintenance after 36months (Franz et al., 2007). Moreover, Christensen et al compared an LED (3.3-5MJ/day) with a VLED (1.8-2.3MJ/day) in 192 obese and sedentary participants in a randomised controlled trial over 4 months, with a good completion rate of 91%. The authors found that both LED and VLED were

equally successful in weight loss (-10.7kg (0.5) vs. -11.4kg (0.5), respectively) (Christensen et al., 2011). However, there was a significantly greater loss of lean tissue (-2.1kg (0.2) vs. -1.2kg (0.4), P<0.05) and more frequent adverse effects (bad breath (35% vs 22%), intolerance to cold (41% vs 18%) and flatulence (45% vs 29%)) in the VLED group, when compared to the LED group (Christensen et al., 2011).

Diabetes prevention studies and weight loss systematic reviews confirm that rapid weight loss does not cause (i) unfavourable lean muscle mass loss; and (ii) faster weight regain when compared to traditional weight loss methods. The DioGENES study confirmed the use of rapid weight loss using a LED and maintaining weight loss at 6 months and 12 months post study (Fogelholm et al., 2017).

Consequently, LEDs may have prolonged benefits to metabolic health (Franz et al., 2007; Hamman et al., 2006; Lindstrom et al., 2008; Uusitupa et al., 2003). The LOOK-AHEAD trial (n=2,290) showed that rapid weight loss using LED in a population with early T2D provided the strongest predictor for long-term weight loss success (Unick et al., 2015). Anderson conducted a meta-analysis with 29 studies (n=1,026) comparing an LED of 3.3 MJ/day to a conventional diet matched for energy intake and also found that the LED achieved more weight loss at 5-years (Anderson et al., 2001).

The Effects of an LED on Metabolism

A recent systematic review of 17 studies assessing the metabolic effects of a nutritionally complete VLED and LEDs (ranging from 1.8-3.3MJ/day) showed that a significant mean weight loss of -13.2kg (BW loss of -4.1 to -24.0kg) caused a significant improvement in glycaemic control. In this review, HbA_{1c} was also reduced by -15mmol/mol (reduction by -1 to -31mmol/mol) after the weight loss intervention. Notably, in the systematic review, the dropout rate of 4.7 to 33% was reported and evidence of continued metabolic benefits was seen for 5-years (Sellahewa et al., 2017). Other groups have reported improved metabolic health following LED-related weight loss. Riecke et al reported a reduction or withdrawal in antihypertensive and antidiabetic medication following 4 months of 1.7MJ/day (VLED) and 3.4MJ/day (LED) followed by 5MJ food based diet in T2D (Riecke et al., 2010). Moreover, In the Newcastle Counterpoint study (UK) researchers were able to reproduce the metabolic benefits of bariatric surgery by conducting an LED intervention in a group of O/W, with mean (SD) BMI of 33.6 (1.2) kg/m^2 in 11 participants with newly diagnosed T2D (Lim et al., 2011). In this study, beta cell failure and IR were reversed by rapid weight loss using 2.5MJ/day, over 2 months (Lim et al., 2011). After 1 week on the LED, fasting mean (SD) plasma glucose normalised from 9.2 (0.4) mmol/l to 5.9 (0.4) mmol/l (P<0.05). By week 8, mean (SD) hepatic triacylglycerol reduced from 12.9 (2.4) % to 2.9 (0.2) % (P<0.05) and mean (SD) insulin response continued to improve from week 1, 4 and 8, from 0.19 (0.002), 0.46 (0.07) and 0.62 (0.15) nmol min^{-1} m^{-2}, respectively (Lim et al., 2011). A significant body of evidence supports the use of LED for successful weight loss and consequent improvements in anthropometric and metabolic outcomes (Leslie et al., 2017; Leslie et al., 2016; Roberts et al.,

2017; Sellahewa et al., 2017; Taylor et al., 2017). Advantages with respect to the efficacy of this type of diet include good adherence and compliance, making it an easy strategy to achieve the targeted results.

In PREVIEW:NZ, participants underwent an 8-week LED in order to achieve the required minimum of 8% BW loss and enter the randomised long-term maintenance phase. The LED regime was selected on the basis of the evidence presented above which showed that a high proportion of those who commenced the meal replacement LED regime were likely to successfully achieve the weight loss target. In addition, no evidence was found to support better outcomes from a VLED versus an LED. Nor was there enough evidence to show that rapid weight loss achieved through LED would drive rapid weight re-gain and hence compromise maintenance during the randomised phase of the intervention.

3.1 Aim and Hypotheses

The aim of this thesis chapter was to investigate the effects of the 8-week LED on anthropometric and metabolic changes within the Auckland cohort of the PREVIEW study

The primary hypothesis was that an 8-week LED would result in ≥8% BW and improvement in glucose metabolism in the PREVIEW:NZ cohort.

The secondary hypotheses were that:

(i) baseline BW would predict BW (kg) and FM (kg) loss during LED; and that this may differ between genders (men vs. women) and ethnicity (Caucasian, Maori/Pacific, Other)
(ii) improvements in glucose and other markers of metabolic health during LED may also differ between genders (men vs. women) and ethnicity (Caucasian, Maori/Pacific, Other)

3.2 Methods

3.2.1 Study participants

Participants were recruited to the PREVIEW-NZ study using the inclusion and exclusion criteria described in detail on Chapter 2.2.5. Participants were recruited via newspaper adverts, followed by telephone and online pre-screening questionnaires, with 1,654 candidates completing the pre-screening assessments, based on the FDRS (Lindstrom et al., 2003; Lindstrom et al., 2008). 584 potentially eligible candidates (35%), who scored ≥12 points in the FDRS were then screened in clinic, at the Human Nutrition Unit to assess objective eligibility. The eligibility criteria are outlined in Chapter 2.2.5. Of those who were screened, 263 (45%) participants were found to be ineligible due to normoglycaemia, T2D, abnormal ECG or personal reasons. 321 eligible participants (55%) who met all the inclusion criteria (O/W, pre-diabetes assessed through an OGTT), were enrolled in the trial, randomised into 1 of 4 diet/exercise groups and invited to attend CID1/Baseline. A further 16 were then excluded due to personal reasons, pregnancy, screening duplication or failure to attend the CID1/Baseline visit. The participant flowchart is shown in Figure 7.

At CID1/Baseline, a total of 305 participants commenced the study and began the LED weight loss phase. A total of 38 participants were further excluded or withdrew during the 8-week intervention prior to CID2/Post LED visit. Reasons included withdrawal due to personal reasons such as sickness and family deaths, difficulties in following the LED protocol, and failure to comply and attend the CID2/Post LED. At CID2/Post LED, 267 participants attended the clinic visit, of which 249 (79%) met ≥ 8% weight loss goal. Three ethnic groups were defined as, Caucasian European, Maori/Pacific and Other. Caucasians were the largest ethnic group; followed by Maori/Pacific (Samoan, Tongan, Niuean, Cook Island Maori or Fijian), followed by Other - classified as any other ethnic group, e.g. Indian, Chinese, Korean. Multi-ethnicities were classified as stated in the New Zealand Census, based on a whole assignment bridging method with the higher health risk ethnic group identified as the main ethnicity, in this order of highest risk - Maori/Pacific, Other and lastly Caucasian (Kukutai & Callister, 2009; Liebler & Halpern-Manners, 2008). BW and height were used to calculate BMI, using the WHO BMI classification (O/W 25-29.9kg/m^2, obesity class I 30-34.9kg/m^2, class II 35-39.9kg/m^2, class III being ≥40kg/m^2).

3.2.2 Clinical Assessments

Methods for assessing BW, height, calculated BMI, FM, Android fat, FFM, WC and BP were described in detail in Chapter 2.8.

3.2.3 Blood samples

FPG, 2h-PPG, Area under the glucose curve from time 0 to 120 min ($AUC_{GlucoseT0\text{-}120m}$), HbA_{1c}, Insulin, HOMA-IR, C-Peptide, hs-CRP and lipids were assessed from plasma/serum samples. These samples were taken at all the CID as specified on Table 17. A detailed description of the analytical methods can be found in Chapter 2.9.

3.2.4 Low energy diet (LED)

The weight loss phase is an 8-week weight loss phase using a formula LED (3.4MJ/day) intended to induce weight loss of ≥8% in order to qualify for the weight loss maintenance phase. The LED was implemented by using a range of Cambridge Weight Plan (Corby, United Kingdom) products and provided to the participants with no charge and consisted of soups, shakes and porridges. All participants were instructed to consume 4 sachets (4x40g) per day. Of these, 3 sachets were to be dissolved with low fat (≤0.5g/100ml fat and ≤170kJ/100ml TE) milk (3 x 250ml = total 750ml per day) and 1 sachet made with 250ml water. Participants with a BMI ≥40kg/m^2 were encouraged to dissolve all 4 sachets in milk in order to increase the protein intake. In total, the LED provided an estimated 3.4MJ/day, 85g protein, 5g of essential fatty acids and the daily requirement of vitamins and minerals (Full LED instruction preparation: Appendix A). The macronutrient composition was as follows: 43.7en%protein, 41.2en%CHO and 15.5en%fat. The fibre content was relatively low at 13.3g/day and participants were encouraged to use extra fibre i.e. psyllium fibres and to drink adequate amounts of water to remain hydrated. In addition to the sachets and milk, the participants were permitted to consume 2 cups of 375g low starchy

vegetables, such as tomato, lettuce and cucumber per day, as described in Chapter 2.4 (Full LED nutritional composition: Appendix B and C).

3.3 Statistical Analysis

Baseline characteristics at CID1/Baseline are summarised as mean and SD and differences between gender and ethnic subgroups were analysed. Data was analysed in 2 approaches: (i) The ITT population defined as participants who completed CID1/Baseline and entered the LED (n=305), and (ii) The Completers population defined as participants who completed CID2/Post LED (n=267). For the ITT-population (n=305), data analyses were carried out using imputation for missing data based on the last-value-carried-forward (LVCF) imputation method for those who baseline visit (CID1/Baseline) but did not attend a visit at week-8 (CID2/Post LED). For the Completers-population (n=267), analyses were undertaken as complete case analyses with no imputation for missing data during the LED weight loss phase from CID1/Baseline to CID2/Post LED (see methods Chapter 2.4). Changes were calculated by subtracting the baseline (CID1/Baseline) from the 8-week follow-up (CID2/Post LED). The mean change between CID1/Baseline and CID2/Post LED was calculated using paired t-test and is presented as mean and SEM. Changes between gender and ethnic subgroups from CID1/Baseline to CID2/Post LED were analysed with independent sample t-test and one-way ANOVA, respectively. Tukey's *post hoc* analysis was used to compare the different ethnic groups. Interaction between subgroups (gender and ethnicity) and changes over time was achieved with Two-way-ANOVA and the P value is shown in the graphs. P value for *post hoc* analysis is described in the footnotes of each graph. Mean and SEM were used to present efficacy data. Correlation between baseline BW and outcome variables was also conducted as shown as the Pearson correlation coefficient (r^2, P value).

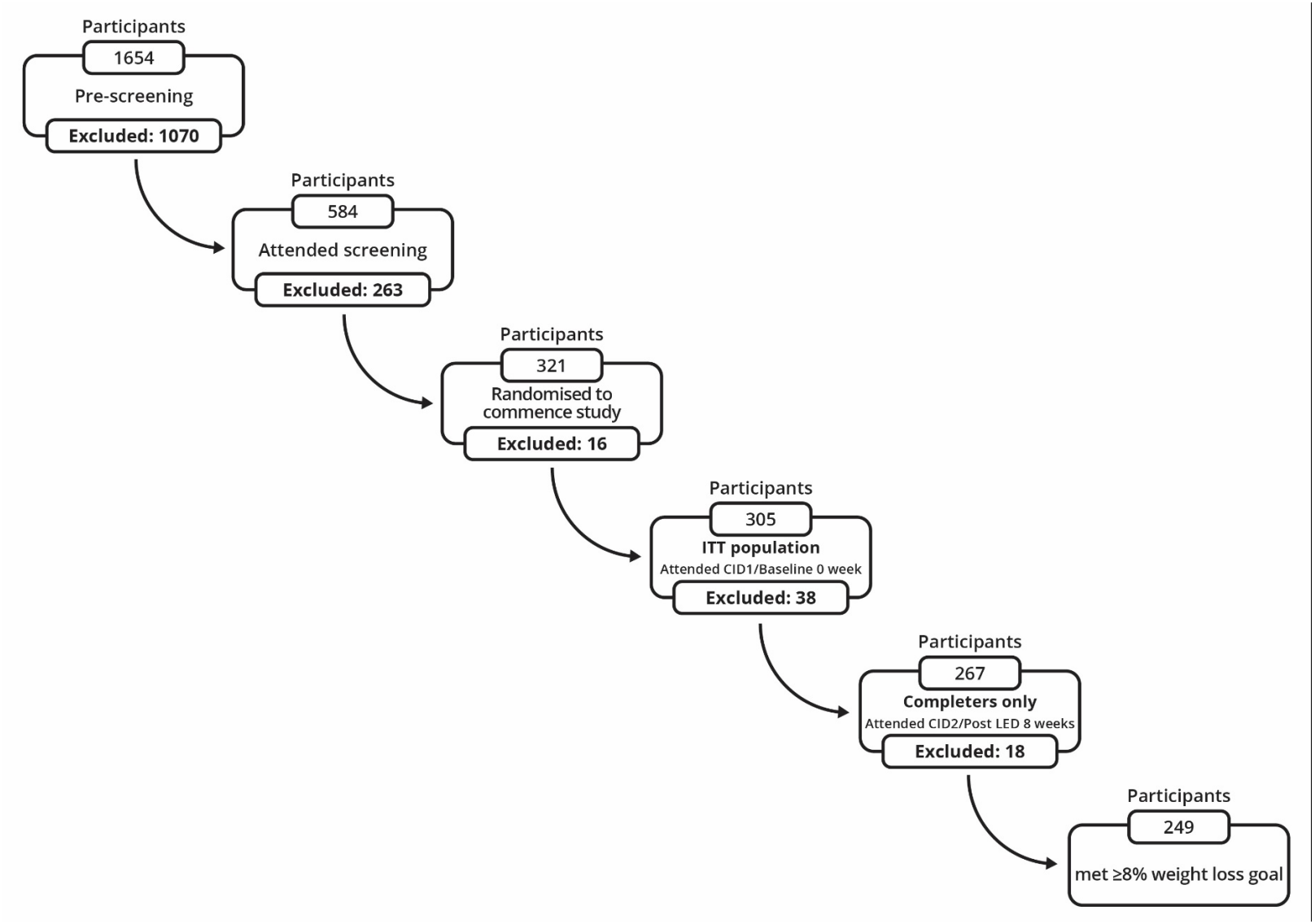


Figure 7: Flowchart from pre-screening, screening in clinic, CID1/Baseline and completion of CID2/Post LED

3.4 Results

3.4.1 ITT population (n=305) baseline characteristics (CID1/Baseline)

3.4.1.1 Baseline BW and BMI

The baseline characteristics of the 305 participants who started the LED and defined as the ITT population are shown in Table 20. The mean (SD) age of the population were 47(11) years. The age group distribution at CID1/Baseline showed that only 5% of the study participants were aged 20-29 years, 20% were aged 30-39 years, 38% were aged 40-49 years, 21% aged 50-59 years and 16% in the older group, aged 60-70 years. The mean (SD) BMI at CID1/Baseline was 38.6 (7.5) kg/m^2, which is classified as morbidly obese. The majority of the population were of Caucasian ethnicity (n=163, 53%), followed by 37% Maori/Pacific (n=112) and 10% Other (n=30). At CID1/Baseline, Maori/Pacific had the highest mean (SD) BW and BMI of 120.5 (26.9) kg and 42.5 (8.5) kg/m^2 respectively. Caucasian were the second ethnic group with the highest BW and BMI of 103.3 (19.7) kg and 36.8 (5.9) kg, respectively. The last ethnic group, Other (as specified in Chapter 2.2.2 and 3.2.1) had the lowest BW and BMI of 95.7 (15.2) kg and 34.8 (4.5) kg/m^2. Differences between BW and BMI across ethnicities were significant (P<0.001 for both variables).

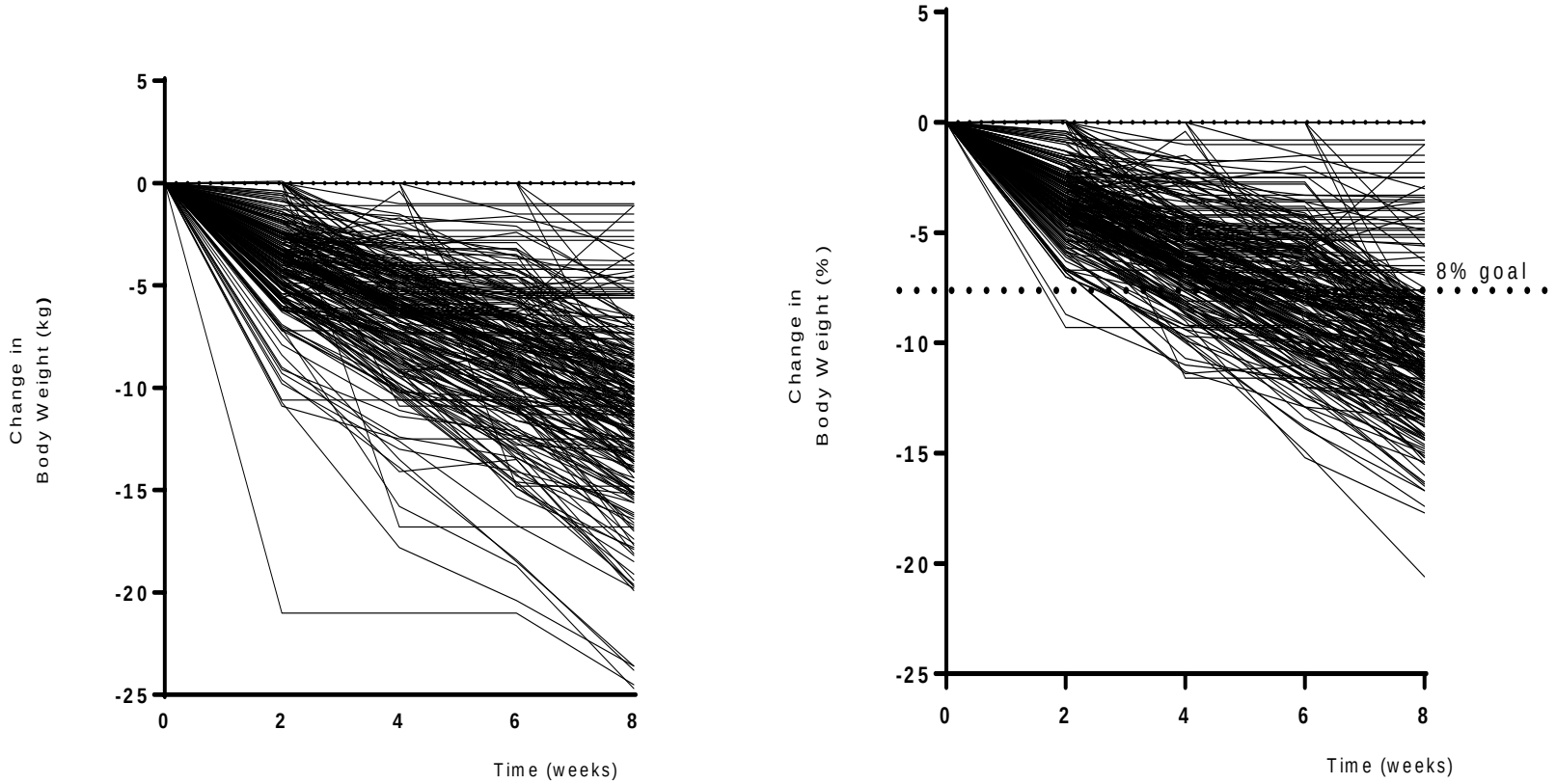
3.4.1.2 Post LED BW and BMI

The CID1/Baseline mean (SD) BW decreased significantly from 108.9 (24.0) kg to 98.2 (22.6) kg (-10.7 (0.3) kg or -9.9 (0.2) %, P<0.001), during the 8-week LED. Change in BW varied considerably between individuals, ranging from -0.5 to -24.7kg (Figure 8). In the first 2 weeks, the mean (SEM) weight loss was -3.7 (0.1) kg, followed by -6.1 (0.2) kg at week 4, -8.1 (0.2) kg at week 6 and total weight loss at week-8 was -10.7 (0.3) kg (Chapter 2.8.1). Males lost more weight by week-8 (-12.8 (0.6) kg), when compared to females (-10.0 (0.3) kg P<0.001). No significant differences were seen when comparing the changes in BMI between male (-4.1 (0.2) kg/m^2), and female (-3.7 (0.1) kg/m^2). BW changes were different across ethnic groups. Caucasians lost the most weight (-11.0 (0.3) kg or -10.7 (0.2) %), compared to Maori/Pacific (-10.5 (0.5) kg or -8.7 (0.4) %, P<0.001) and Other (-9.6 (0.8) kg or -9.9 (0.7) %, P<0.001). These differences were statistically significant, when comparing percentage of weight loss (%), but not when comparing changes in absolute weight loss (kg). No significant differences between ethnicities were seen for changes in BMI.

Table 20: CID1/Baseline Characteristics ITT (n=305) – Anthropometric and Metabolic outcomes

ITT population, n=305	Mean ± SD
Age (years)	47.0 ± 11.0
Female	232 (76%)
FDRS	15.0 ± 3.0
BW (kg)	108.9 ± 24.6
Height (m)	1.7 ± 0.1
BMI (kg/m^2)	38.7 ± 7.4
WC (cm)	111.8 ± 16.0
FM (kg)	49.4 ± 15.1
FM (%)	46.8 ± 6.7
Android fat (kg)	4.9 ± 1.7
FFM (kg)	57.7 ± 12.2
FFM (%)	54.1 ± 6.9
SBP (mmHg)	121.9 ± 16.7
DBP (mmHg)	67.1 ± 9.5
FPG (mmol/l)	5.8 ± 0.6
30 min glucose (mmol/l)	8.9 ± 1.6
60 min glucose (mmol/l)	9.4 ± 2.3
90 min glucose (mmol/l)	8.6 ± 2.2
2h-PPG (mmol/l)	7.4 ± 1.8
$AUC_{GlucoseT0\text{-}120m}$	1007.3 ± 193.2
HbA_{1C} (mmol/mol)	36.6 ± 3.5
Insulin (mU/l)	13.8 ± 8.4
HOMA-IR	3.6 ± 2.3
C-Peptide (pmol/l)	873.2 ± 335.3
hs-CRP (mg/l)	5.5 ± 5.9
TC (mmol/l)	5.3 ± 1.1
HDL-C (mmol/l)	1.3 ± 0.3
LDL-C (mmol/l)	3.3 ± 0.9
Triglyceride (mmol/l)	1.5 ± 0.8
TC:HDL ratio	4.2 ± 1.0

Mean±SD. FDRS, Finnish Diabetes Risk Score; BW, Body weight; BMI, Body Mass Index; WC, waist circumference; FM, Fat Mass; FFM, Fat Free Mass; FPG, Fasting Plasma Glucose; 2h-PPG, 2-hour Postprandial Plasma Glucose; $AUC_{GlucoseT0\text{-}120m}$, Area under the glucose curve time 0-120 min; HbA_{1c}, Glycated Haemoglobin; Insulin, Fasting serum insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; C-Peptide, serum connecting peptide; hs-CRP, high sensitivity C-reactive protein; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; TC:HDL ratio, Total cholesterol:high density lipoprotein ratio



a) b)

Figure 8: Changes in BW: a) in kg and b) in % - between CID1/Baseline (week 0) and CID2/Post LED (week 8) for individual participants (n=305)

3.4.2 Comparison of BW and BMI between ITT population and Completers only

Of the 305 individuals who started the study at CID1/Baseline (ITT population), only 267 (88%) individuals completed CID2/Post LED (Completers only population). Following the ITT population data analysis, this group was then compared to the Completers only population (Table 21). There was no difference between ITT population and Completers only in terms of baseline BW (Figure 9). However, changes in mean (SEM) BW following LED were different between the groups, as expected, with ITT population losing -10.7 (0.3) kg and Completers only losing -11.5 (0.3) kg, (P<0.05) (Table 21).

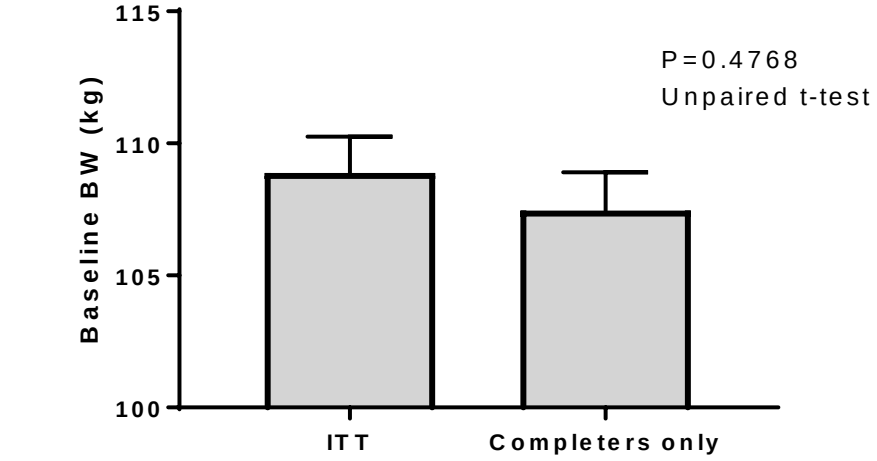
Table 21: CID1/Baseline ITT (n=305) vs. Completers only (n=267)

ITT population, n=305				
	CID1/Baseline	CID2/Post LED	Change (kg)	Change (%)
BW (kg)	108.9±1.4	98.2±1.3**	-10.7±0.3*	-9.9±0.2***
BMI(kg/m^2)	38.7±0.4	34.9±0.4**	-3.8±0.1	

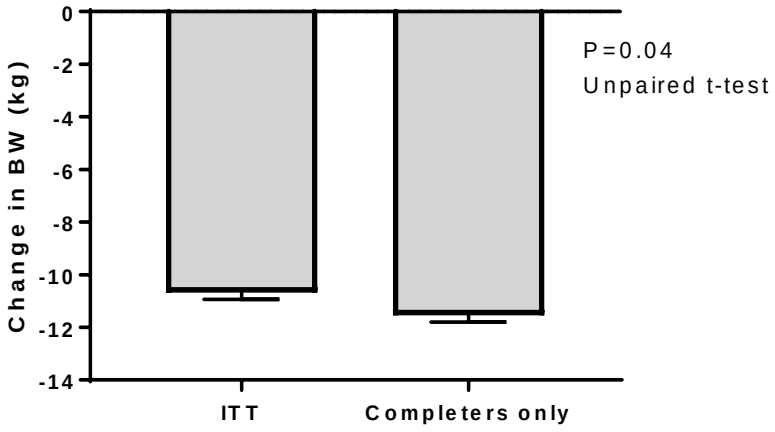
Completers only, n=267				
	CID1/Baseline	CID2/Post LED	Change (kg)	Change (%)
BW (kg)	107.5±1.4	95.9±1.3***	-11.5±0.3***	-10.7±0.3***
BMI(kg/m^2)	38.3±0.4	34.4±0.4**	-3.9±0.1	

ITT population, n=305 vs Completers only, n=267			
	ITT population Change (kg)	Completers only Change (kg)	P value
BW (kg)	-10.7±0.3*	-11.5±0.3***	P<0.05
BMI(kg/m^2)	-3.8±0.1	-3.9±0.1	ns

Mean±SEM, BW, Body weight; BMI, Body Mass Index, ***P<0.001; ** P<0.01; *P<0.05



a)



b)

Figure 9: Baseline BW a) ITT population (n=305) and Completers only (n=267), ns; b) Change in BW during 8-week LED, P<0.05. Mean (SEM)

The remainder of this chapter presents outcomes from the Completers only population, as those who did not complete the 8-week LED or who did not attend CID2/Post LED were excluded from the PREVIEW:NZ study.

3.4.3 Completers only population (n=267) baseline characteristics (CID1/Baseline)

3.4.3.1 Baseline BW and BMI

The baseline characteristics of 267 participants who were defined as the Completers only population (Table 22). The mean (SD) BW was 107.5 (23.6) kg, with a mean (SD) BMI of 38.3 (7.3) kg/m^2, which is classified as morbidly obese. Males (n=65, 24%) were significantly heavier 120.0 (28.9) kg but had a lower BMI of 37.9 (8.7) kg/m^2 when compared to females (n=202, 76%, 103.4 (20.0) kg (P<0.001) and BMI of 38.4 (6.8) kg/m^2 (P<0.001), respectively (Figure 10). As for the ITT group, the majority of the population was ethnically Caucasian (n=154, 58%), followed by 33% Maori/Pacific

(n=83) and 9% Other (n=24). There was a significant effect of ethnicity on baseline BW (P<0.001). Maori/Pacific were the heaviest with a BW and BMI of 119.1 (27.9) kg and 42.0 (8.6) kg/m^2, respectively, followed by Caucasian (102.5 (19.1) kg and 36.7 (5.9) kg/m^2) and Other (96.4 (13.7) kg and 35.0 (4.3) kg/m^2) (Figure 10). *Post hoc* analysis showed that Maori/Pacific were significantly heavier than Caucasians (P<0.001) and then Other (P<0.05) in both absolute BW and BMI. When comparing to gender differences between ethnic groups, all groups were proportional. There were 76% female (n=202) and 24% male (n=65) in total. There were 59% Caucasian female (n=120), 34% Maori/Pacific female (n=68) and 7% Other female (n=14). For males, 52% Caucasian (n=34), 32% Maori/Pacific (n=21) and 7% Others (n=14).

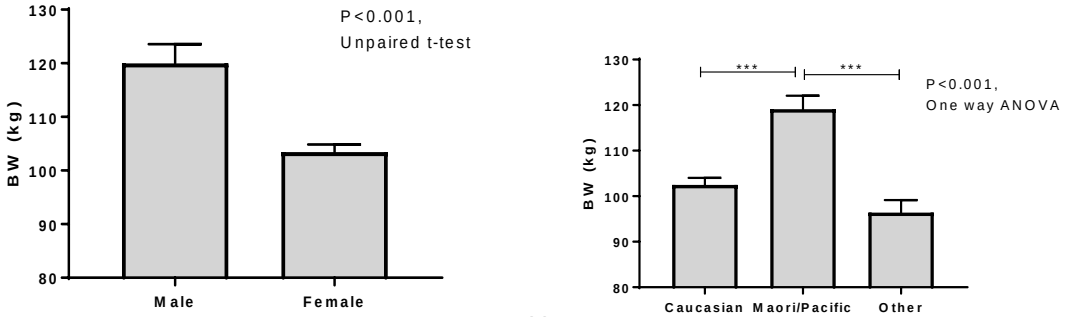


Figure 10: Baseline BW. Comparison between: a) Gender and b) Ethnicity, Mean(SEM; Statistically significant results following Tukey's *post hoc* analysis are marked with *** P<0.01 and **P<0.05

Table 22: CID1/Baseline Characteristics – Gender and Ethnicity

	N (%)	BW (kg)	BMI (kg/m^2)	FM (kg and %)	FFM (kg and %)	WC (cm)	FPG (mmol/l)	2h-PPG (mmol/l)	$AUC_{GlucoseT0\text{-}120m}$ (mmol/l * min)	HbA_{1c} (mmol/mol)
All	267 (100)	107.5±23.6	38.3±7.3	49.4±15.1kg 46.8±6.7%	57.7±12.2kg 54.1±6.9%	111.8±16.0	5.8±0.6	7.3±1.8	996.2±197.4	36.4±3.4
Gender										
Male	65 (24)	[1]120.0±28.9	[ns]37.9±8.7	47.6±19.5kg [1]39.8±6.7%	[1]71.5±11.6kg [1]60.9±6.9%	[1]119.3±18.8	[ns]5.9±0.6	[ns]7.5±2.0	[ns]1036±174.9	[ns]36.3±3.4
Female	202(76)	103.4±20.0	38.4±6.8	49.9±13.4kg 49.0±5.0%	53.2±8.5kg 52.0±5.4%	109.4±14.3	5.8±0.6	7.3±1.8	983.2±202.8	36.6±3.3
Ethnicity										
Caucasian	154(58)	[2a]102.5±19.1	[2a]36.7±5.9	[2]47.5±13.5kg [2c]47.3±6.8%	[2a]54.1±9.4kg [2c]53.4±6.9%	[2a]109.4±13.6	[ns]5.9±0.6	[ns]7.5±1.9	[ns]1011±206.4	[ns]36.0±3.1
Maori/Pacific	89(33)	[b]119.1±27.9	[b]42.0±8.6	[b]54.9±17.2kg 46.8±6.3%	[d]64.3±13.8kg 54.4±6.8%	[d]117.5±19.4	5.8±0.5	7.0±1.7	976.8±192.8	36.9±3.5
Other	24(9)	96.4±13.7	35.0±4.3	40.4±8.3kg 43.3±7.0%	55.8±11.6kg 57.5±7.1%	106.1±9.5	6.0±0.8	7.4±1.7	972.9±146.5	36.5±4.5

Mean±SD; BMI, Body mass index; FM, Fat Mass; FFM, Fat Free Mass; WC, waist circumference; FPG, Fasting plasma glucose; 2h-PPG, 2 hr postprandial glucose; $AUC_{GlucoseT0\text{-}120m}$, Area under the glucose curve time 0 to 120min; HbA_{1c}, Glycated haemoglobin; [1]gender differences using unpaired t-test (P<0.001); [2]ethnic differences using one way ANOVA (P<0.001), [a]compared to Maori/Pacific (P<0.001); [b]compared to Other (P<0.001); [c]compared to Other (P<0.01), [d]compared to Other (P<0.05); ns, not significant

	N (%)	Insulin (mU/l)	HOMA-IR (mU/L)	C-Peptide (pmol/l)	hs-CRP (mg/l)	TC (mmol/l)	HDL-C (mmol/l)	LDL-C (mmol/l)	TG (mmol/l)	TC:HDL ratio
All	267 (100)	12.9±7.3	3.4±2.0	844.6±311.1	5.5±6.2	5.3±1.0	1.3±0.3	3.4±0.9	1.5±0.9	4.2±1.0
Gender										
Male	65 (24)	[ns]12.7±7.2	[ns]3.6±2.2	[3]922.1±355.0	[ns]6.1±8.3	[ns]5.2±1.1	[1]1.2±0.2	[1]2.6±0.8	[ns]1.6±0.7	[2]4.5±1.2
Female	202 (76)	13.7±7.9	3.4±1.8	819.7±292.2	5.4±5.4	5.4±1.0	1.3±0.3	3.4±0.9	1.5±0.8	4.1±0.9
Ethnicity										
Caucasian	154 (58)	[5ad]11.0±5.9	[4b]2.9±1.7	[5b]791.0±279.0	[ns]5.3±6.3	[4a]5.6±1.0	[5b]1.4±0.3	[5b]3.5±0.9	[ns]1.5±0.6	[ns]4.2±1.0
Maori/Pacific	89 (33)	15.6±8.7	[c]4.1±2.5	927.5±332.8	6.1±6.5	5.0±1.0	1.2±0.3	3.1±0.8	1.4±0.9	4.2±1.0
Other	24 (9)	15.2±6.5	4.0±1.8	880.9±361.0	4.7±4.4	5.1±1.0	1.2±0.3	3.2±0.9	1.7±1.0	4.3±1.2

Mean±SD; Insulin, Fasting serum insulin; C-Peptide, serum connecting peptide; HOMA-IR, Homeostatic model assessment for insulin resistance; hs-CRP, high sensitivity C-Reactive Protein; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; TC:HDL ratio, Total cholesterol: High density lipoprotein cholesterol ratio; [1]gender differences using unpaired t-test (P<0.001); [2]gender differences using unpaired t-test (P<0.01); [3]gender differences using unpaired t-test (P<0.05); [4]ethnic differences using one way ANOVA (P<0.001); [5]ethnic differences using one way ANOVA (P<0.01); [a]compared to Maori/Pacific (P<0.001); [b]compared to Maori/Pacific (P<0.001), [c]compared to Other (P<0.01); [d]compared to Other (P<0.05); ns, not significant

3.4.3.2 Body composition

There were clear and consistent differences between men and women and also between ethnicities at baseline. The 267 participants who completed the LED had a baseline FM of 49.4 (15.1) kg or 46.8 (6.7) %. Whilst females tended to have greater FM (kg) (Figure 11), this only became significant when normalised as % FM (49.0 (5.0) % vs. 39.8 (6.7) %, P<0.001 (Figure 12). Maori/Pacific had the highest absolute FM of 54.9 (17.2) kg, compared to both Caucasians 47.5 (13.5) kg (P<0.001) and to Other 40.4 (8.3) kg (P<0.001) (Figure 11). However, when normalised Caucasians tended to have the highest % FM, followed by Maori/Pacific (ns) and by Other (P<0.05) (Figure 12).

In all participants, baseline mean (SD) FFM was 57.7 (12.2) kg or 54.1 (6.9) %. Males had greater FFM of 71.5 (11.6) kg or 60.9 (6.9) %, when compared to females (53.2 (8.5) kg or 52.0 (5.4) %, (P<0.001) (Figure 13). Maori/Pacific had the highest absolute FFM of 64.3 (13.8) kg, significantly greater than Caucasians 54.1 (9.4) kg (P<0.001) and Other (55.8 (11.6) kg (P<0.05) (Figure 13). Interestingly, when normalising FFM, Other had the highest FFM percentage of 57.5 (7.1) % statistically different from Caucasians 53.4 (6.9) % (P<0.05) (Figure 14).

3.4.3.3 WC

WC was used as a marker of central adiposity, hence it is not surprising that it followed a similar pattern to absolute FM (kg). At baseline, participants had a mean (SD) WC of 111.8 (16.0) cm. Male had a significantly greater WC of 119.3 (18.8) cm, when compared to female (109.4 (14.3) cm, P<0.001). Maori/Pacific had the highest WC 117.5 (19.4) cm when compared to both Caucasians (109.4 (13.6) cm, P<0.001) and Other (106.1 (9.5) cm, P<0.05) (Figure 15).

3.4.3.4 Food diary record

Food records calculated as an average of the 4-day food diary were collected at CID1/Baseline. Outcome parameters were: Total energy (TE), percentage energy from protein (en%protein), percentage energy from fat (en%fat), percentage energy from carbohydrates (en%CHO) and GI. The CID1/Baseline dietary composition was summarised on Table 23. The mean en%protein of 18.6% was used to define the 2 diet groups – LP vs. HP – analysed in Chapter 4 of this thesis.

Table 23: CID1/Baseline Diet Records (all, n=267)

TE (kJ/d)	en%protein	en%fat	en%CHO	GI (units)
10361(3974)	18.6(3.7)	37.4(6.5)	40.8(6.1)	55.5(4.5)

Mean (SD), TE, total energy; en%protein, total energy percentage protein; en%fat, total energy percentage fat; en%CHO, total energy percentage carbohydrates; GI, Glycaemic Index

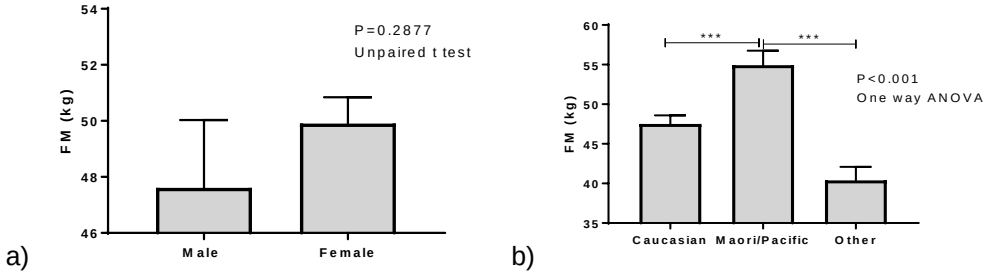


Figure 11: Baseline absolute FM. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

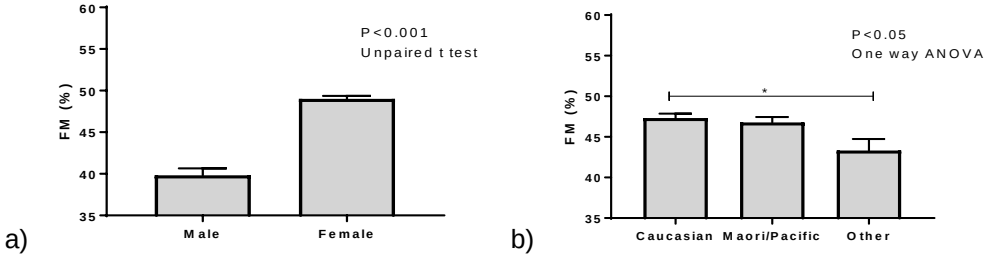


Figure 12: Baseline percentage FM. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

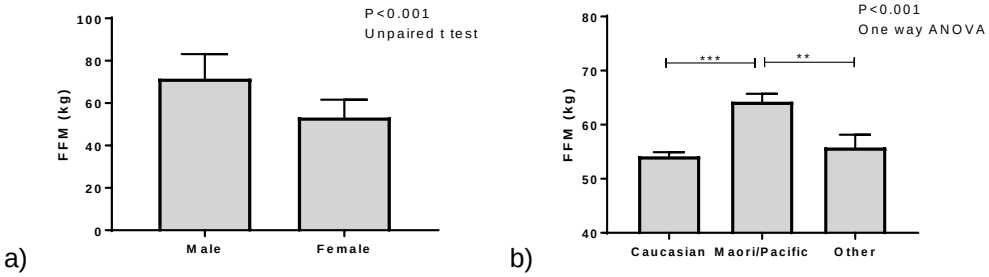


Figure 13: Baseline absolute FFM. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

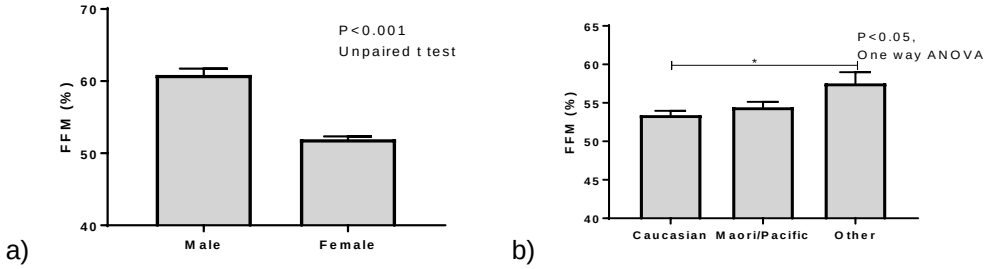


Figure 14: Baseline percentage FFM. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

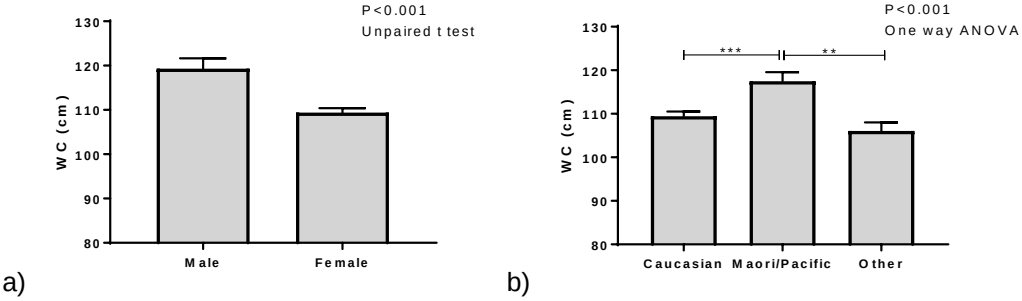


Figure 15: Baseline WC. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

3.4.3.5 Glycaemia

According to the PREVIEW protocol, all the participants at screening (American Diabetes Association, 2017; American Diabetes Association, 2018; WHO & IDF, 2006) were identified as pre-diabetic using the ADA cut off values for plasma glucose, based on either impaired IFG, IGT or both. However, 70 of the 267 participants (26%) had reverted to normoglycaemic at the time they attended CID1/Baseline visit, which is unexpected but possible, considering that there was a 2 to 12-week period between screening and baseline (Table 24). At CID2/Post LED, 164 participants or 61% of all participants reverted to normoglycaemia. From the 197 individuals who were still pre-diabetic at CID1/Baseline, only 58 (29%) were defined as having pre-diabetes using the HbA_{1c} cut-off ≥40mmol/mol (Table 25).

Table 24: Normoglycaemic (Completers only, n=267)

	Screening		CID1/Baseline		CID2/Post LED	
Participant (n, %)	0	0%	70	26%	164	61%

CID, Clinical Investigation Day; LED, Low Energy Diet

Table 25: Proportion of participants (n=267) characterised with different types of dysglycaemia at CID1/Baseline-; IFG, IGT and HbA_{1c}

Completers only, n=267	n (%)	HbA_{1C} (normal / pre diabetes ≥40mmol/mol)
Neither / Normoglycaemia (FPG<5.6mmol/l, 2h-PPG<7.8mmol/l)	70 (26%)	Normal: 68 (97%) Pre-diabetes: 2 (3%)
IFG (≥5.6mmol/l)	166 (62%)	Normal: 83 (82%) Pre-diabetes: 18 (18%)
IGT (≥7.8mmol/l)	88 (35%)	Normal: 1 (6%) Pre-diabetes: 17 (94%)
both	71 (27%)	Normal: 55 (71%) Pre-diabetes: 23 (29%)

n (%); IFG, impaired fasting plasma glucose; IGT, impaired glucose tolerance; FPG, Fasting plasma glucose; 2h-PPG;, 2h Postprandial plasma glucose; HbA_{1c}, Glycated Haemoglobin

In all participants FPG which was within the pre-diabetic range at baseline (5.84 (0.6) mmol/l) had improved significantly with the weight loss. With a change of -0.31 (0.03) mmol/l (P<0.001), mean FPG decreased to 5.5mmol/l, which was under the cut-off of normoglycaemia at CID2/Post LED (Table 24). No gender specific or ethnic specific differences were seen for decrease in FPG after the weight loss period, with improvement in glycaemic control observed in both men and women, Caucasian, Maori/Pacific and Other, as shown on Figure 16. A number of factors were associated with the improvement in FPG from CID1/Baseline to CID2/Post LED. A greater decrease absolute in BW (kg) (r^2 = 0.1493, P<0.05) and percentage BW (r^2 = 0.06906, P<0.001), reduction of absolute FM (r^2 = 0.2118, P<0.001) and a greater percentage decrease in FM (r^2 = 0.05147, P<0.001).

Both genders had a similarly high baseline FPG of 5.9 (0.6) mmol/l and 5.8 (0.6) mmol/l, respectively with no significant gender differences between them. Moreover, there were also no significant difference between ethnicities, with all 3 groups sitting within the ADA pre-diabetic range of 5.9 (0.6) mmol/l, 5.8 (0.5) mmol/l. and 6.0(0.8) mmol/l for Caucasians, Maori/Pacific and

Other, respectively (Figure 16). The 2h-PPG (Figure 17) following the OGTT (Figure 18) was, however, below the ADA cut-off for pre-diabetes was (7.3 (1.8) mmol/l), with only 7% of the cohort having IGT. No differences were seen for gender and ethnicities in terms of glucose tolerance, assessed by the $AUC_{GlucoseT0\text{-}120m}$, although there was a trend for men to have worse glucose response (P=0.059) (Figure 19). In all participants, baseline mean (SD) HbA_{1C} was 36.4 (3.4) mmol/mol with no significant gender or ethnic differences (Figure 20). This was an unexpectedly low HbA_{1c} but in line with the full cohort of n=305.

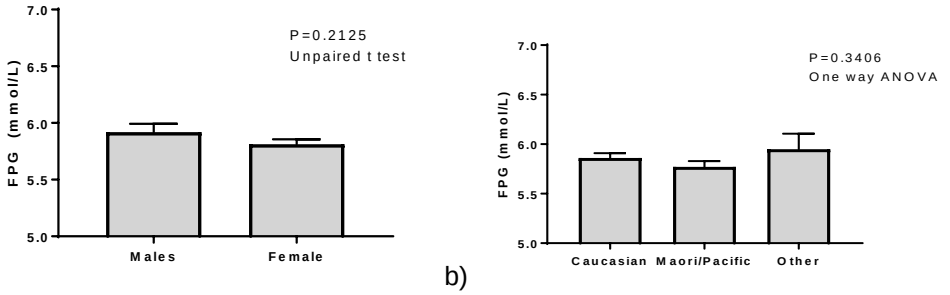


Figure 16: Baseline FPG. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

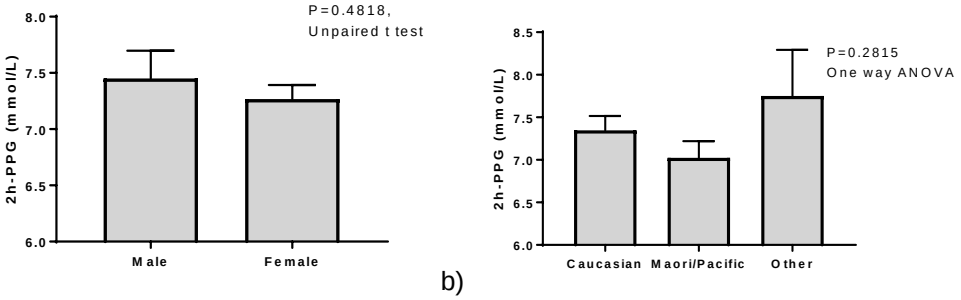


Figure 17: Baseline 2h-PPG. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

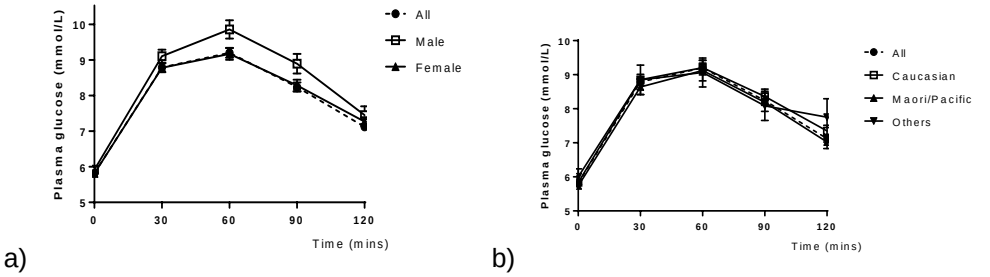


Figure 18: Baseline OGTT. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

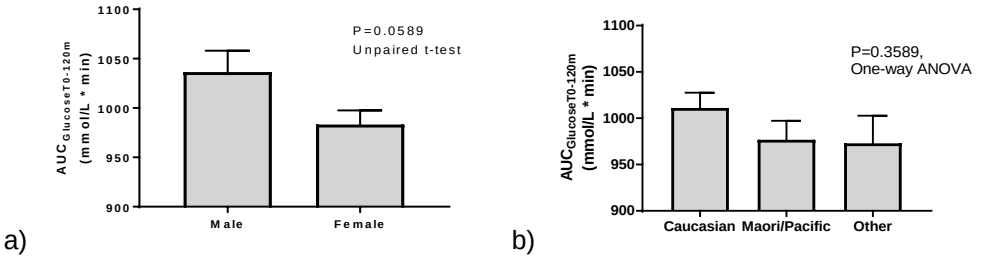


Figure 19: Baseline $AUC_{GlucoseT0\text{-}120m}$ curve. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

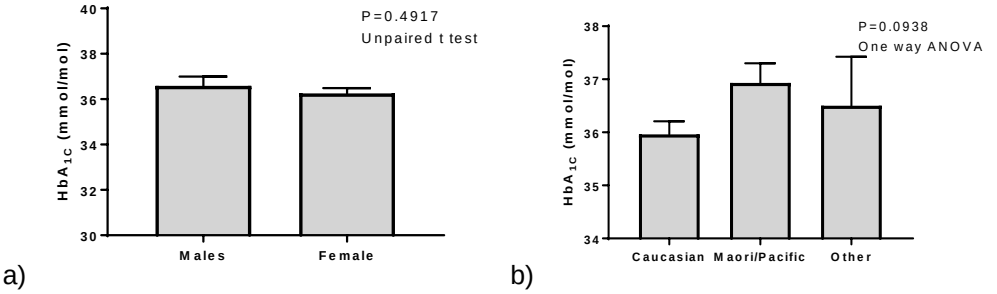


Figure 20: Baseline HbA_{1c}. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

At CID1/Baseline, there were no significant correlations between change in BW and FPG for all participants, or between gender and ethnicity (ns) (Figure 21). However, there was trend between baseline BW and 2h-PPG in female may show an increase in 2h-PPG with an increasing baseline BW (r^2 = 0.0199, P=0.0531). There was also no significance between FPG and percentage FM (ns) (Figure 22).

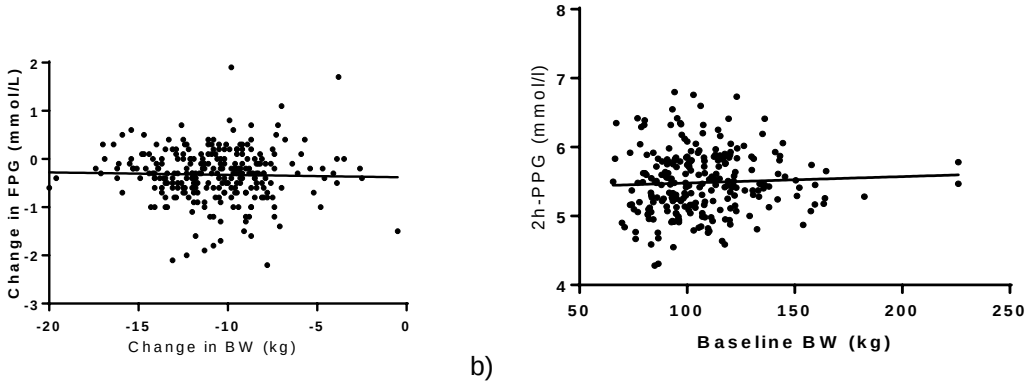


Figure 21: Correlation between FPG and 2h-PPG and baseline BW a) Gender b) Ethnicity.

a) All participants r^2=0.000774, P=0.6509; Male, r^2=0.0001, P=0.8785; Female, r^2=0.0018, P=0.5521; Caucasian, r^2=0.0007, P=0.9210; Maori/Pacific, r^2=0.01355, P=0.2744; Other, r^2=0.0006, P=0.9061

b) All participants r^2=0.002377, P=0.4437; Male, r^2=0.0345, P=0.1515; Female, r^2=0.0019, P=0.0531; Caucasian, r^2=0.0370, P=0.0179; Maori/Pacific, r^2=0.0647, P=0.0256; Other, r^2=0.0398, P=0.3857

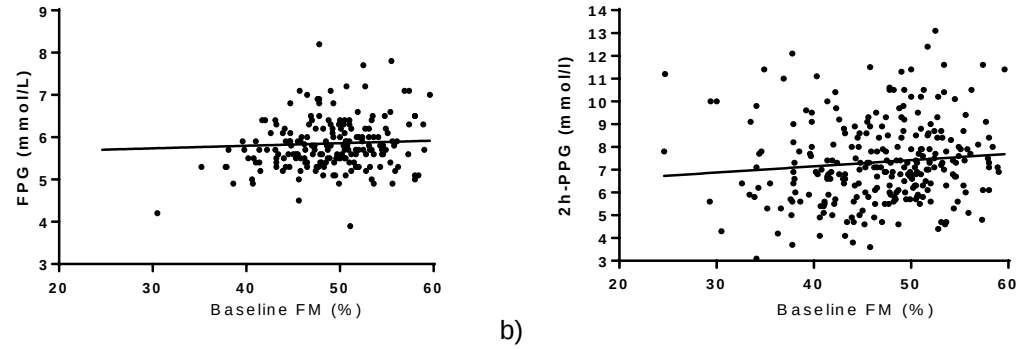


Figure 22: Correlation between FPG and 2h-PPG and Baseline FM (%) a) r^2=0.00461, P=0.2690; b) r^2=0.01012, P=0.1009

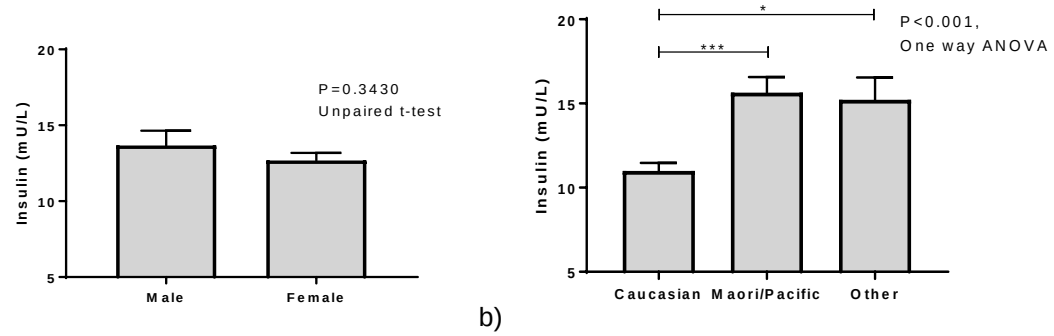


Figure 23: Baseline Insulin. Comparison between a) Gender and b) Ethnicity, Mean (SEM); a) P=0.3430; b) P<0.001

3.4.3.6 Fasting Serum Insulin

In all participants, baseline mean (SD) Insulin was 12.9 (7.3) mU/L. No gender differences were found. Caucasians had mean (SD) Insulin of 11.0 (5.9) mU/L, which was significantly lower than Maori/Pacific (15.6 (8.7) mU/L, P<0.001) and Other (15.2 (6.5) mU/L P<0.05). *Post hoc* analysis showed Maori/Pacific and Other to be significantly higher than Caucasian (P<0.05), indicating worse IR (Figure 23).

3.4.3.7 Homeostatic Model Assessment – IR

In all participants, baseline mean (SD) HOMA-IR was 3.4 (2.0) mU/L, which can be classified as moderate IR (HOMA-IR score 3-5). No gender difference was found. Maori/Pacific had the highest HOMA-IR of 4.1 (2.5) mU/L, which was similar to Other (4.0 (1.8) mU/L), P<0.001. Both groups were significantly more IR than Caucasians (HOMA-IR of 2.9 (1.7) mU/L, P<0.001 vs. Maori/Pacific and P<0.05 vs Other) (Figure 24).

3.4.3.8 Fasting serum C-Peptide

In all participants, baseline mean (SD) C-Peptide was 844.6 (311.1) pmol/L, with men having a higher concentration of C-Peptide (922.1 (355.0) pmol/L) than female (819.7 (292.2) pmol/L, (P<0.05). Maori/Pacific had the highest C-Peptide of 927.5 (332.8) pmol/L, which was similar to Other 880.9 (361.0) pmol/L but higher than Caucasians 791.0 (279.0) pmol/L (P<0.01) (Figure 25).

3.4.3.9 High-sensitivity C-Reactive Protein

In all participants, baseline mean (SD) hs-CRP was 5.5(6.2)mg/l, with no differences between gender nor ethnicities. Notably, the results were highly variable among participants (Figure 26).

3.4.3.10 Lipid profile

In all participants, baseline mean (SD) TC was 5.3 (1.0) mmol/l. Women had higher HDL-C 1.35 (0.29) mmol/l (P<0.001) and LDL-C 3.4 (0.9) mmol/l (P<0.001) when compared to men. Men had a significantly higher TC:HDL ratio 4.5 (1.2) (P<0.01). Caucasian had a significantly higher TC 5.6 (1.0) mmol/l (P<0.001), HDL-C 1.36 (0.29) mmol/l (P<0.01) and LDL-C 3.5 (0.9) mmol/l (P<0.01) than Maori/Pacific (P<0.01). (Figure 27).

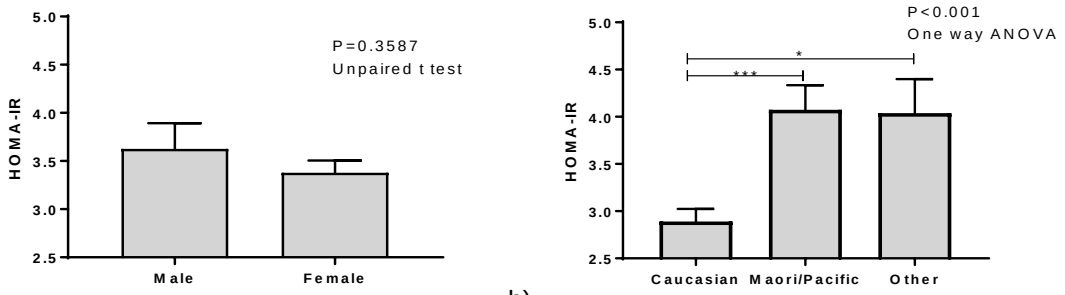


Figure 24: Baseline HOMA-IR. Comparison between a) Gender and b) Ethnicity, Mean (SEM)

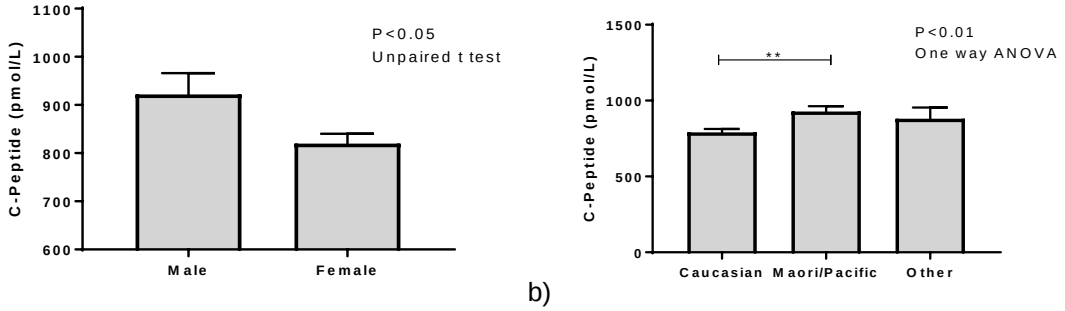


Figure 25: Baseline C-Peptide. Comparison between a) Gender and b) Ethnicity. Mean (SEM)

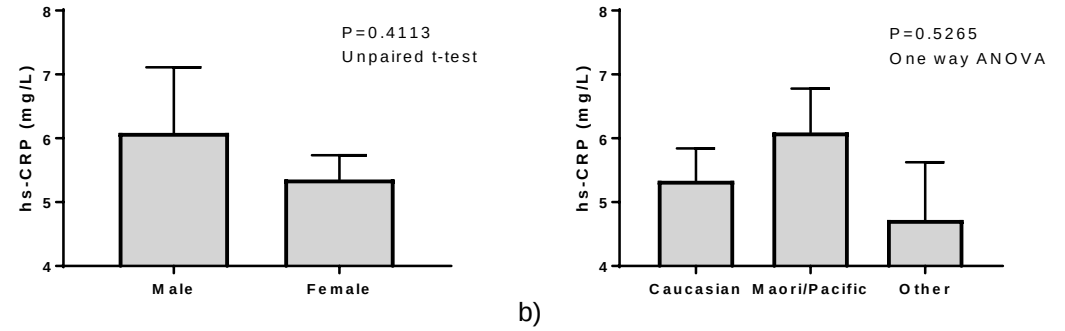


Figure 26: Baseline hs-CRP. Comparison between a) Gender and b) Ethnicity. Mean (SEM)

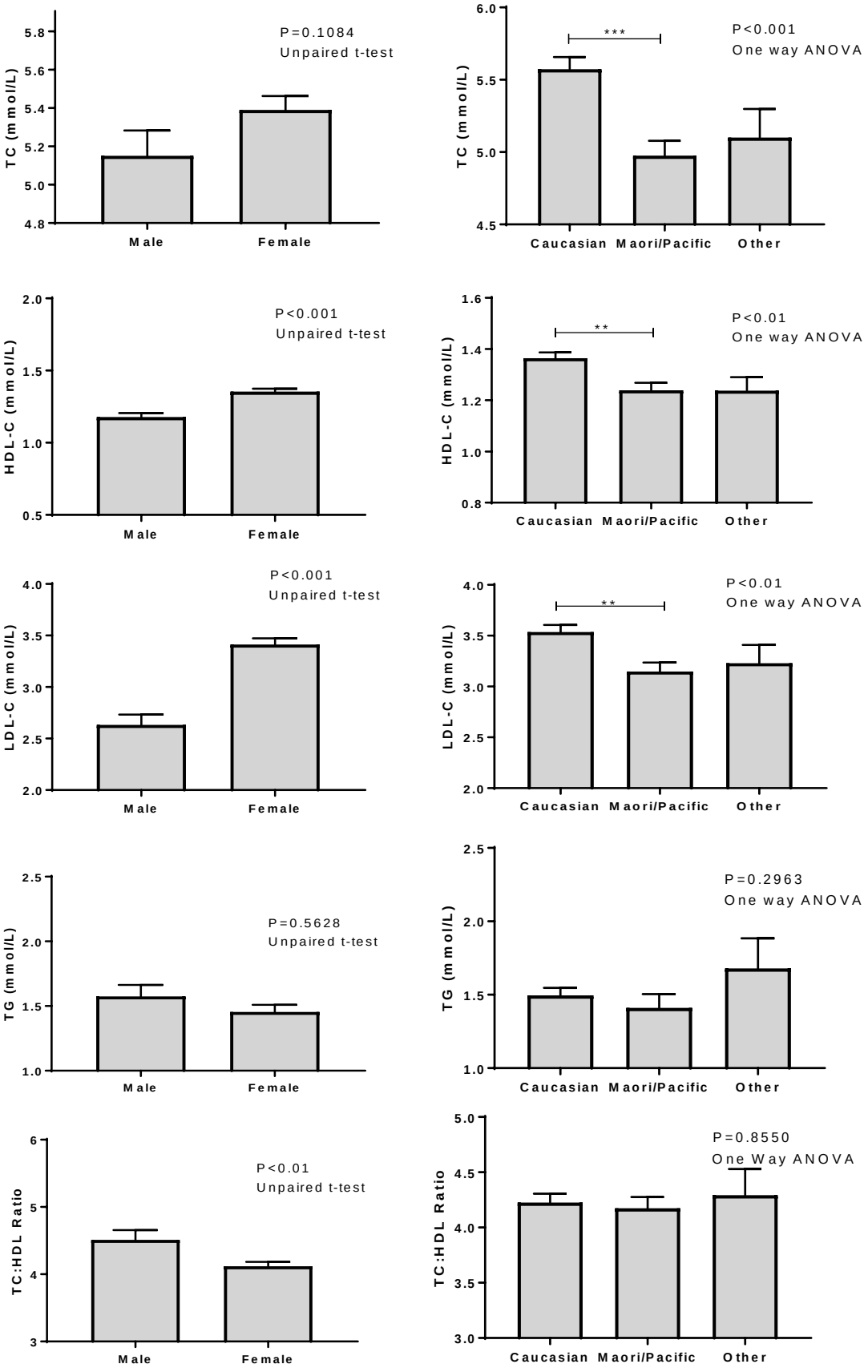


Figure 27: Lipid profile showing gender and ethnicity differences at CID1/Baseline, Mean (SEM)

3.4.4 Completers only population (n=267) 8-week post LED (CID2/Post LED)

3.4.4.1 BW and BMI

For the Completers only population, BW loss varied between individuals during the 8-week LED phase. All participants lost weight, ranging from -0.5kg to -26.4kg equivalent to -0.5 to -20% BW loss (Figure 28). From the 267 participants who attended CID2/Post LED, 249 individuals met the ≥8% weight loss goal. In the first 2 weeks, mean (SEM) weight loss was -3.3 (0.1) %. At week 4, mean(SEM) weight loss was -5.6(0.1)%, at week 6 mean(SEM) weight loss was -7.4 (0.2) % and at the 2-month CID2/Post LED clinic visit, mean(SEM) BW loss was -11.5 (0.3) kg or -10.7 (0.2) % (P<0.001). There was a significant positive correlation between CID1/Baseline BW and BW loss during LED (P<0.001), where participants who had highest baseline BW lost the greatest absolute BW over 2 months, as expected on a fixed intake LED (Table 26). However no significance was found in the percentage change in BW (ns) (Figure 29). There was a high rate of success in the Completers only (n=267) cohort; which 249 achieving the weight loss goal of ≥8% BW and continuing into the weight maintenance phase. Of 65 males, 4 (6%) did not achieve the ≥8% weight loss goal, a success rate of 89%, compared to 202 females, where 14 (5%) did not achieve the ≥8% weight loss goal, a success rate of 93%. As expected, males lost more BW than females with mean (SEM) weight loss of -13.9 (0.6) kg (-11.8 (0.4) %) vs. -10.7 (0.3) kg (-10.4 (0.2) %) at CID2/Post LED (P<0.001) (Figure 30). Again, CID1/Baseline BW correlated significantly with BW loss (kg) (P<0.001) but not percentage BW change in both male and female (ns) (Figure 29).

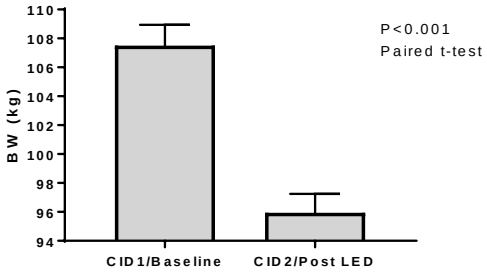


Figure 28: BW at CID1/Baseline and CID2/Post LED in all participants, n=267 (mean, SEM)

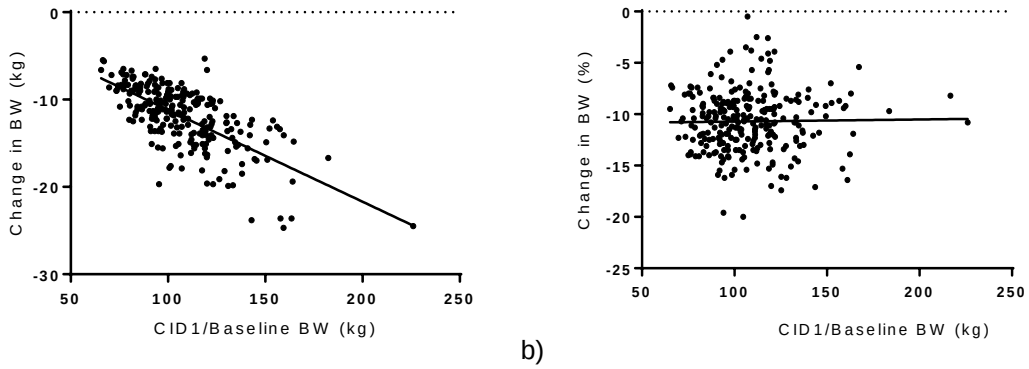


Figure 29: Correlation between baseline BW and weight loss during the 8-week LED in all participants (n=267) - gender differences. *** indicates P<0.001; ns, no significance p≥0.05

a) All participants r^2=0.03481, P<0.001; Male, r^2=0.2645, P<0.001; Female, r^2=0.3129, P<0.001

b) All participants r^2=0.000264, P=0.7915; Male, r^2=0.03953, P=0.1123; Female, r^2=0.0004355, P=0.7682

Table 26: BW between CID1/Baseline and CID2/Post LED: Gender and Ethnicity Differences

n = 267 BW (kg)	n (%)	CID1/Baseline BW (kg) Mean±SEM (range)	P value	CID2/Post LED BW (kg) Mean±SEM (range)	Change in BW (kg) Mean±SEM (range)	P value	Change in BW (%) Mean±SEM (range)	P value
All	267(100)	107.5±1.4 (65.2 to 226.0)		95.9±1.3 (59.0 to 201.5)	-11.5±0.3 (-0.5 to -26.4)	P<0.001	-10.7±0.2 (-20.0 to 3.4)	P<0.001
Male	65 (24)	[1]120.0±3.6 (75.9 to 232)	[1]P<0.001	[1]106.1±3.3 (68.2 to 201.5)	-13.9±0.6 (-26.4 to -5.3)	[1]P<0.001	[1]-11.8±0.4 (-24.7 to -5.3)	[1]P<0.001
Female	202 (76)	103.4±1.4 (65.2 to 167.3)		92.7±1.3 (59.0 to 158.3)	-10.7±0.3 (-24.5 to -0.5)		-10.4±0.2 (-16.7 to 0.0)	
Caucasian	154 (58)	[2a]102.5±1.5 (65.2 to 162.9)	[2]P<0.001	[2a]91.0±1.4 (59.0 to 149.8)	-11.5±0.3 (-22.5 to -4.7)	[2]ns	[2a]-11.3±0.2 (-22.5 to -4.7)	[2]P<0.01
Maori/Pacific	89 (33)	[b]119.1±2.9 (66.4 to 226.0)		[b]107.3±2.7 (61.5 to 201.5)	-11.8±0.5 (-26.4±-0.5)		-9.9±0.4 (-26.4±-0.5)	
Other	24 (9)	96.4±2.8 (13.7) (71.3 to 128.1)		85.9±2.5 (63.7 to 113.5)	-10.5±0.8 (-20.8 to -3.8)		-10.8±0.7 (-20.8 to -3.8)	

n (%); Mean±SEM; BW, body weight; [1]gender differences using unpaired t-test, [2]ethnicity differences using one way ANOVA, [a]compared to Maori/Pacific, P<0.001; [b]compared to Other, P<0.001

In all participants, there was a significant correlation in baseline BW and absolute change in mean (SD) BW (kg) Caucasian and Maori/Pacific lost more BW than Other (Figure 31), Change in BW was -11.5 (0.3) kg, -11.8 (0.5) kg and -10.5 (0.8) kg respectively (Figure 32). However, significance was lost when comparing percentage BW change (Figure 33). In all participants, CID2/Post LED, mean (SD) BMI was 34.2 (6.7) kg/m^2. BMI decreased by -4.1 (1.3) kg/m^2 (P<0.001). There were no gender or ethnicity differences (ns) (Figure 34).

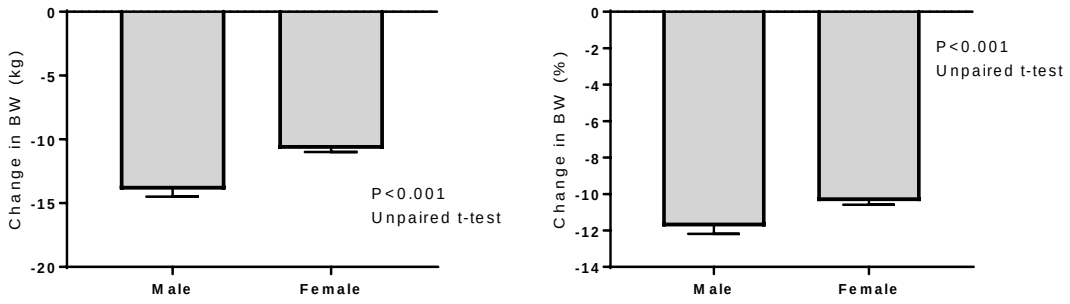
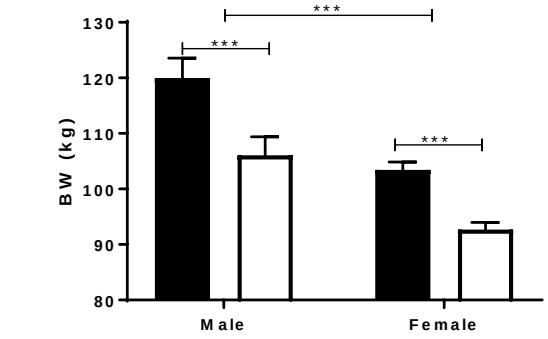
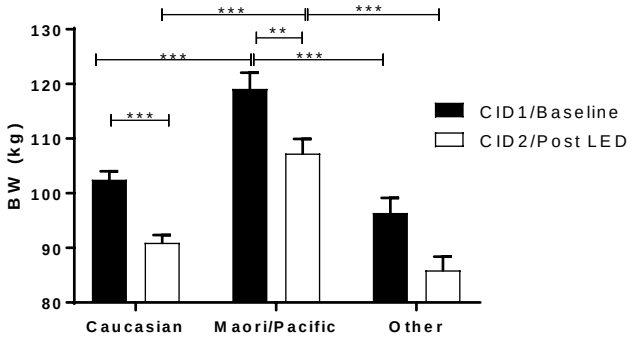


Figure 30: Change in BW showing gender differences in BW at CID1/Baseline and CID2/Post LED, n=267; (Two-way ANOVA, P<0.001) Mean (SEM)

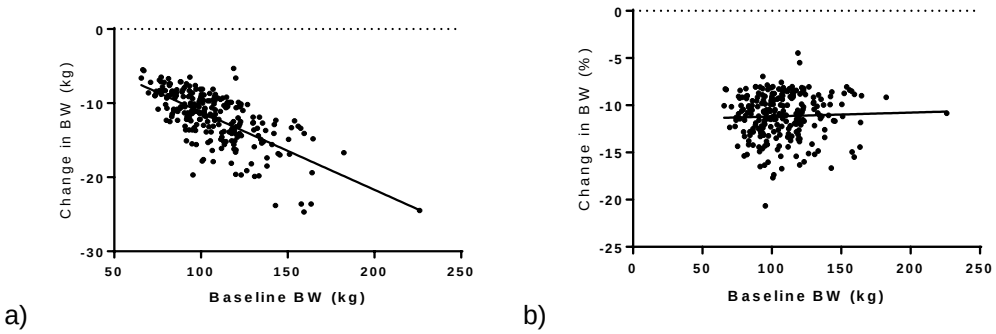


a)



b)

Figure 31: BW at CID1/Baseline and CID2/Post LED for a) gender; b) ethnicity, n=267; Two-way ANOVA (P<0.001; **, P<0.01), Mean (SEM); a) Gender; P<0.001; b) Ethnicity, Interaction P=0.9811 (ns), Groups P<0.001, CID(time): P<0.001



a) b)

Figure 32: Correlation between baseline BW and weight loss during the 8-week LED in all participants (n=267) - ethnic differences; a) absolute and b) percentage weight loss during the 8-week LED

a) All participants r^2=0.4542, P<0.001; Male, r^2=0.2802, P<0.001; Female, r^2=0.4955, P<0.001; Caucasian, r^2=0.4424, P<0.001; Maori/Pacific, r^2=0.4764, P<0.001; Other, r^2=0.2803, P<0.05

b) All participants r^2=0.001557, P=0.5354; Male, r^2=0.0552, P=0.0683; Female, r^2=0.0002, P=0.9830; Caucasian, r^2=0.0013, P=0.6530; Maori/Pacific, r^2=0.0006, P=09480; Other, r^2=0.0169, P=0.5737

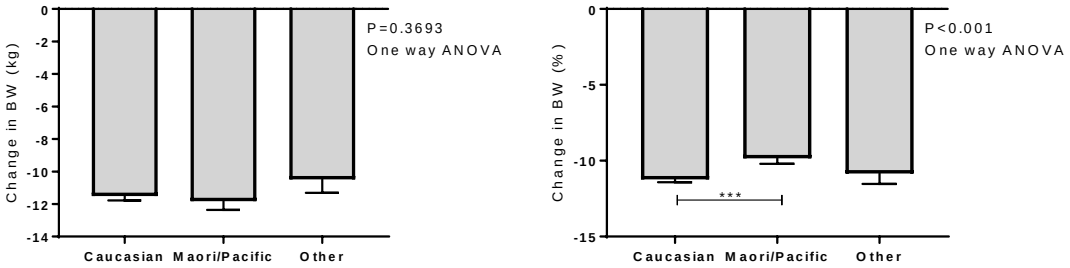
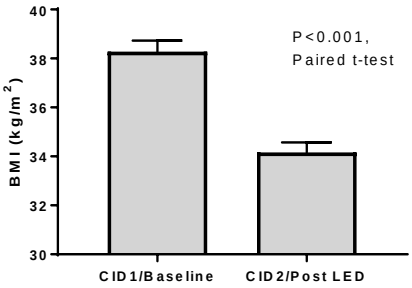
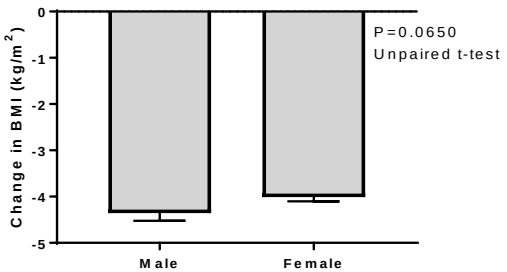


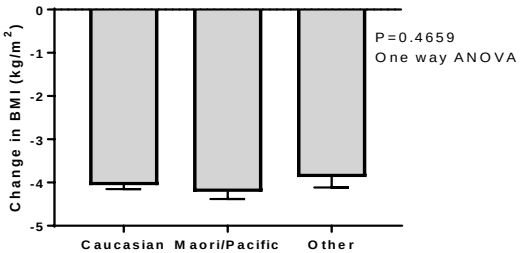
Figure 33: Change in BW showing ethnic differences from CID1/Baseline to CID2/Post LED, Mean (SEM)



a)



b)



c)

Figure 34: BMI a) CID1/Baseline and CID2/Post LED, n=267, b) change in BMI, Mean (SEM); a) P<0.001; b) P=0.0650; c) P=0.4659

Table 27 shows the changes in BMI between CID1/Baseline and CID2/Post LED with gender and ethnic differences. Table 28 showed changes to anthropometric measures between CID1/Baseline to CID2/Post LED. In response to the LED-induced weight loss, all anthropometric parameters significantly improved in response to the ≥8% LED-induced weight loss (P<0.05).

Table 27: Gender and Ethnicity Differences in BMI between CID1/Baseline and CID2/Post LED

n = 267 BMI(kg/m^2)	N (%)	CID1/Baseline	P value	CID2/ Post LED	P value	Change in	P value
All	267(100)	38.3±7.3		34.4±6.7	P<0.001	-4.1±1.3	P<0.001
Male	65 (24)	[1]37.9±8.3	[1]P<0.001	[1]33.6±8.2	P<0.001	-4.4±1.3	[1]ns
Female	202 (78)	38.3±6.8	[2]P<0.001	34.4±6.2	P<0.001	-4.0±1.2	
Caucasian	154 (58)	[2a]36.8±5.9		[2a]32.6±5.3	P<0.001	-4.1±1.2	[2]P<0.001
Maori/Pacific	89 (33)	[b]42.0±8.6		[b]37.8±7.8	P<0.001	-4.2±1.6	
Other	24 (9)	34.8±4.3		31.1±4.2	P<0.001	-3.9±1.2	

Mean±SEM; BMI, Body mass index; [1]gender differences using unpaired t-test, [2]ethnic differences using one way ANOVA, [a]compared to Maori/Pacific, P<0.001; [b]compared to Other, P<0.001

Table 28: Anthropometric measures during LED, between CID1/Baseline and CID2/Post LED, in Completers only (n=267)

n = 267	CID1/Baseline	CID2/Post LED	Change in	P value
SBP(mmHg)	121.9±1.0	114.8±0.9	-7.0±0.8	P<0.001
DBP(mmHg)	67.1±0.6	66.0±0.5	-1.1±0.5	P<0.05
WC(cm)	111.8±1.0	101.1±0.9	-10.7±0.4	P<0.001
FM (kg)	49.4±0.9	41.6±0.9	-7.8±0.2	P<0.001
FM (%)	46.8±0.4	43.7±0.5	-3.0±0.1	P<0.001
FFM (kg)	57.7±0.7	54.8±0.7	-2.9±0.1	P<0.001
FFM (%)	54.1±0.4	51.1±0.4	-2.6±0.1	P<0.001

Mean±SEM; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; WC, waist circumference; FM, Fat Mass; FFM, Fat Free Mass

3.4.4.2 WC

In all participants, mean (SEM) WC change was -10.7 (0.4) cm (P<0.001). Mean (SEM) change in males was -12.0 (0.7) cm (P<0.001), which was significantly higher than females -10.3 (0.5) cm (P<0.001). Caucasian having a significantly higher change in mean (SEM) WC of -11.4 (0.5) cm, followed by Other -10.2(1.3)cm and Maori/Pacific -9.6(0.9)cm (P<0.001) (Table 29).

Table 29: Gender and Ethnicity Differences in WC between CID1/Baseline and CID2/Post LED

n=267 (kg)	CID1/Baseline Mean±SEM	CID2/Post LED Mean±SEM	Change Mean±SEM	P value
All	111.8±1.0	101.1±0.9	-10.7±0.4	P<0.001
Male	[1]119.3±2.3	[1]107.3±2.2	-12.0±0.7	[1]P<0.001
Female	109.4±1.0	99.2±0.9	-10.3±0.5	
Caucasian	[2a]109.4±1.1	[2a]98.1±1.0	-11.4±0.5	[2]P<0.001
Maori/Pacific	[b]17.5±2.1	[b]107.9±1.8	-9.6±0.9	
Other	106.1±1.9	95.9±2.0	-10.2±1.3	

Mean±SEM; WC, waist circumference; [1]gender differences using unpaired t-test, P<0.001, [2]ethnicity differences using one way ANOVA, P<0.001; [a]P<0.001 compared to Maori/Pacific, [b]P<0.01 compared to Other

3.4.4.3 Fat mass (FM), Android fat and Fat free mass (FFM)

In all participants at CID2/Post LED, mean (SD) Fat mass (FM) was 41.6 (14.5) kg and 43.7 (7.6) % (P<0.001) (Table 30). All participants significantly lost a mean (SEM) FM of -8.3 (0.2) kg (P<0.001) and -9.1 (0.1) %, (P<0.001). Male lost more absolute FM than female (male -8.9 (0.5) kg vs. female -8.0 (0.2) kg (P<0.05) (Figure 35) but no gender differences in percentage of FM. There is an interaction showing that males lost more FM over the 8-week LED weight loss phase while female had less baseline FM and lose less FM over time. Reflective to the loss in absolute FM, there was also a significantly greater loss in mean (SEM) android fat between male (-1.33 (0.07) kg) and female (-0.95 (0.03) kg), (P<0.001). The LED phase was stronger in improving FM and android fat in male over 8 weeks than in female. The inverse correlation between baseline BW and absolute FM (in Figure 36) was also significant in Caucasian and Maori. The mean (SEM) change in FM for Caucasian was -8.1 (0.2) kg, Maori/Pacific -8.7 (0.3) kg and Other -7.7 (0.6) kg, with all 3 groups decreasing FM during the 8-week LED, however no difference found between the three groups (ns). There were also no differences in FM percentage change between ethnicities (Figure 37). For android fat, all participants lost a mean (SEM) of -1.05 (0.03) kg, P<0.001. Male lost more android fat than female (male -1.33 (0.07) kg vs female -0.95 (0.03) kg. P<0.001), possibly due to higher absolute body weight in males. Percentage android fat was not analysed.

In all participants, mean (SEM) FFM was 54.8(0.7)kg at CID2/Post LED (P<0.001). Mean (SD) FFM significantly decreased over the 8-week LED by -2.9 (0.1) kg, with an increase in percentage FFM (3.5 (0.2) %) (P<0.001). Male had the highest mean (SEM) FFM at CID2/Post LED (68.0 (1.4) kg) when compared to female (50.6 (0.6) kg) (Figure 38). There was also a greater change in absolute FFM in male (-3.6 (0.3) kg) than female (-2.6 (0.1) kg), P<0.001 (Figure 39).

At CID2/Post LED, Maori/Pacific had the highest FFM (61.1 (13.4) kg) than Caucasian (51.4 (0.7) kg, and Other (53.0 (0.4) kg. Maori/Pacific lost more absolute FFM (-3.6 (0.26) kg) when compared to both Caucasian (-2.9 (0.1) kg) and Other (-3.2 (0.4) kg, P<0.05, *post hoc* (Figure 40).

Table 30: FM and FFM between CID1/Baseline and CID2/Post LED: Gender and Ethnic Differences

n = 267	CID1/Baseline	CID2/Post LED	P value	Change in	P value
FM (kg)					
All	49.1±0.9	40.8±0.9	P<0.001	-8.3±0.2	P<0.001
Male	[1ns]47.0±2.3	[1ns(0.0756)]38.1±2.2	P<0.001	-8.9±0.5	[1]P<0.05
Female	49.7±1.0	41.7±0.9	P<0.001	-8.0±0.2	
Caucasian	[2b]47.7±1.1	[2b]39.6±1.0	P<0.001	-8.1±0.2	[2]ns
Maori/Pacific	[d]54.5±1.9	[d]45.7±1.7	P<0.001	-8.7±0.3	
Other	39.5±1.6	31.7±1.7	P<0.001	-7.7±0.6	
FM (%)					
All	46.7±0.4	37.6±0.4	P<0.001	-9.1±0.1	P<0.001
Male	[1***]39.8±0.8	[1***]31.0±0.4	P<0.001	-8.8±0.4	[1]ns
Female	49.0±0.4	39.8±0.4	P<0.001	-9.2±0.1	
Caucasian	[2c]47.3±0.6	[2d]38.0±0.6	P<0.001	-9.3±0.2	[2]ns
Maori/Pacific	[2d]46.7±0.7	[2d]38.0±0.7	P<0.001	-8.7±0.2	
Other	42.5±1.4	33.0±1.6	P<0.001	-9.5±0.5	
Android fat(kg)					
All	4.9±0.1	3.8±0.1	P<0.001	-1.05±0.03	P<0.001
Male	[1***]5.4±0.3	[1ns]4.0±0.3	P<0.001	-1.33±0.07	[1]P<0.001
Female	4.7±0.1	3.8±0.1	P<0.001	-0.95±0.03	
Caucasian	[2b]4.7±0.1	[2e]3.7±0.1	P<0.001	-1.01±0.04	[2]ns
Maori/Pacific	[2d]5.5±0.2	[2e]4.4±0.2	P<0.001	-1.13±0.06	
Other	3.9±0.2	3.0±0.2	P<0.001	-0.96±0.11	
FFM (kg)					
All	57.7±0.7	54.8±0.7	P<0.001	-2.9±0.1	P<0.001
Male	[1***]70.9±1.4	[1***]68.0±1.4	P<0.001	-3.6±0.3	[1]P<0.001
Female	52.9±0.6	50.6±0.6	P<0.001	-2.6±0.1	
Caucasian	[2a]54.2±0.8	[2a]51.4±0.7	P<0.001	-2.9±0.1	[2c]P<0.05
Maori/Pacific	[2d]63.7±1.5	[2e]61.1±1.4	P<0.001	-3.6±0.3	
Other	56.6±2.7	53.0±0.4	P<0.001	-3.2±0.4	
FFM (%)					
All	54.0±0.4	57.5±0.5	P<0.001	3.5±0.2	P<0.001
Male	[1***]60.9±0.9	[1***]64.6±1.1	P<0.001	3.8±0.6	[1]ns
Female	51.8±0.4	55.2±0.4	P<0.001	3.4±0.1	
Caucasian	[2d]53.4±0.6	[2e]57.1±0.6	P<0.001	3.7±0.2	[2]ns
Maori/Pacific	[2e]54.2±0.7	[2e]57.3±0.8	P<0.001	3.1±0.3	
Other	58.3±1.5	61.8±1.9	P<0.01	3.6±1.0	

Mean±SEM; FM, Fat Mass; FFM, Fat Free Mass; [1]gender differences using unpaired t-test, Unpaired t-test ***P<0.001; **P<0.01; *P<0.05; [2]ethnicity differences using one way ANOVA, compared to Maori/Pacific, (P<0.001); [b]ethnic differences using one way ANOVA, Tukeys *post hoc* [a]P<0.001; [b]P<0.01 compared to Maori/Pacific; Tukeys *post hoc* [c]P<0.001; [d]P<0.01; [e]P<0.05, compared to Other, ns, non-significant

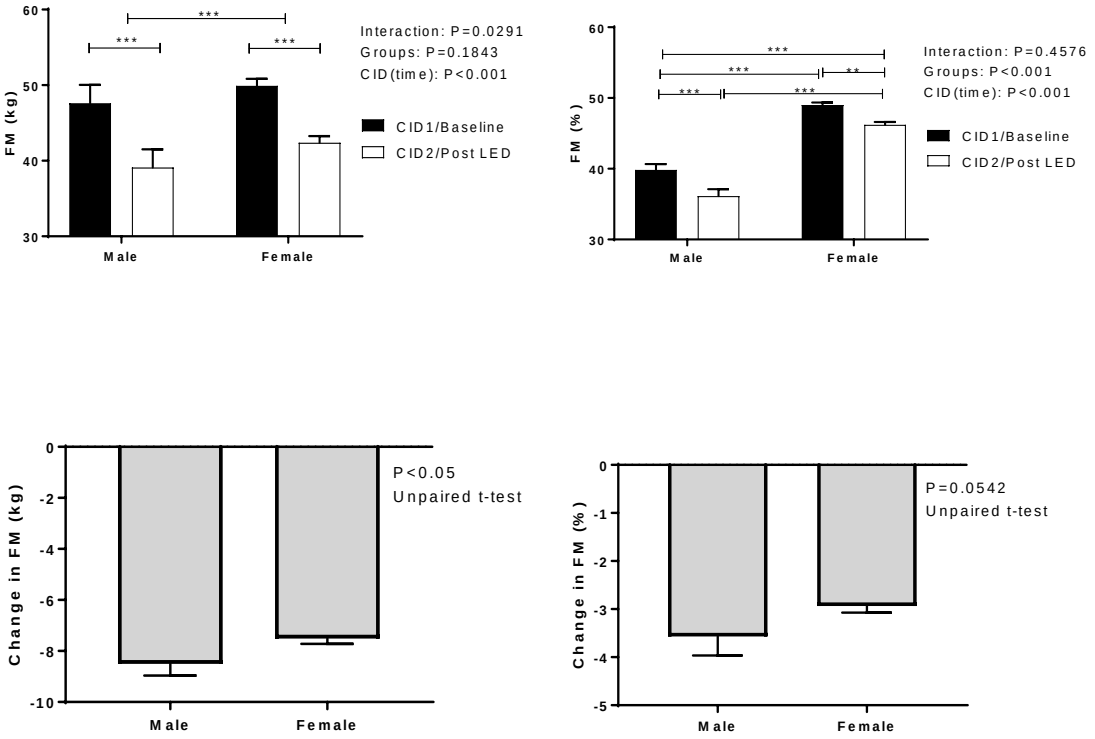


Figure 35: FM and gender differences between CID1/Baseline and CID2/Post LED, Two-way ANOVA (Mean, SEM)

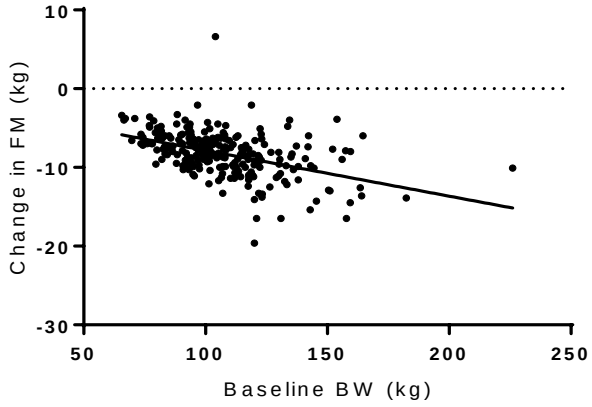


Figure 36: Correlation between change in FM and baseline BW showing gender and ethnicity differences

a) All participants r^2=0.2118, P<0.001; Male, r^2=0.08115, P<0.05; Female, r^2=0.2899, P<0.001; Caucasian, r^2=0.192, P<0.001; Maori/Pacific, r^2=0.2374, P<0.001; Other, r^2=0.1452, P=0.0883

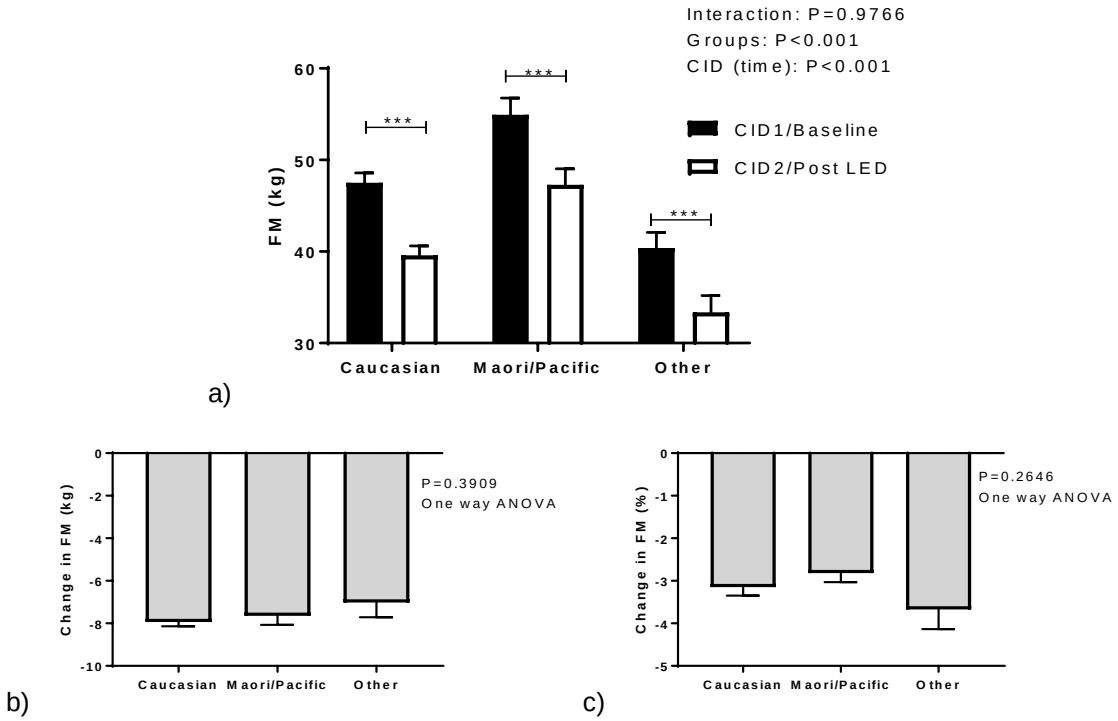


Figure 37: FM and Ethnic differences between CID1/Baseline and CID2/Post LED

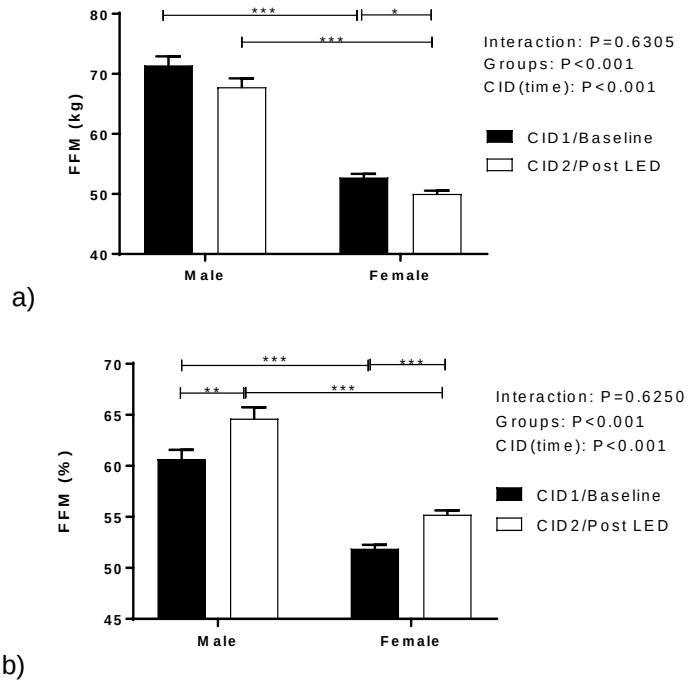


Figure 38: FFM and gender differences between CID1/Baseline and CID2/Post LED, mean (SEM); ***P<0.001; **P<0.01

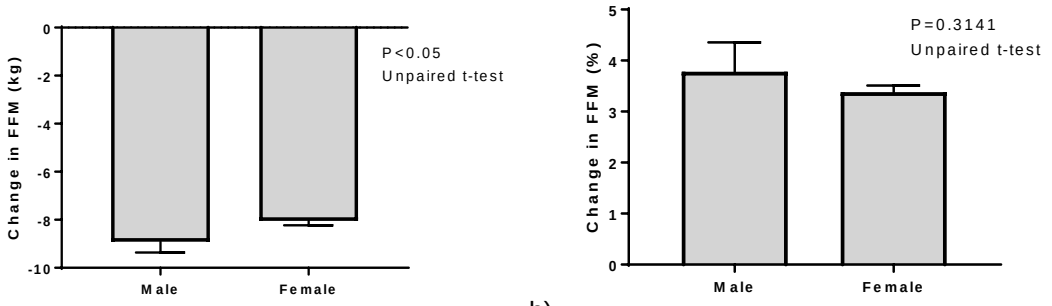


Figure 39: Change in FFM and gender differences between CID1/Baseline and CID2/Post LED, mean (SEM)

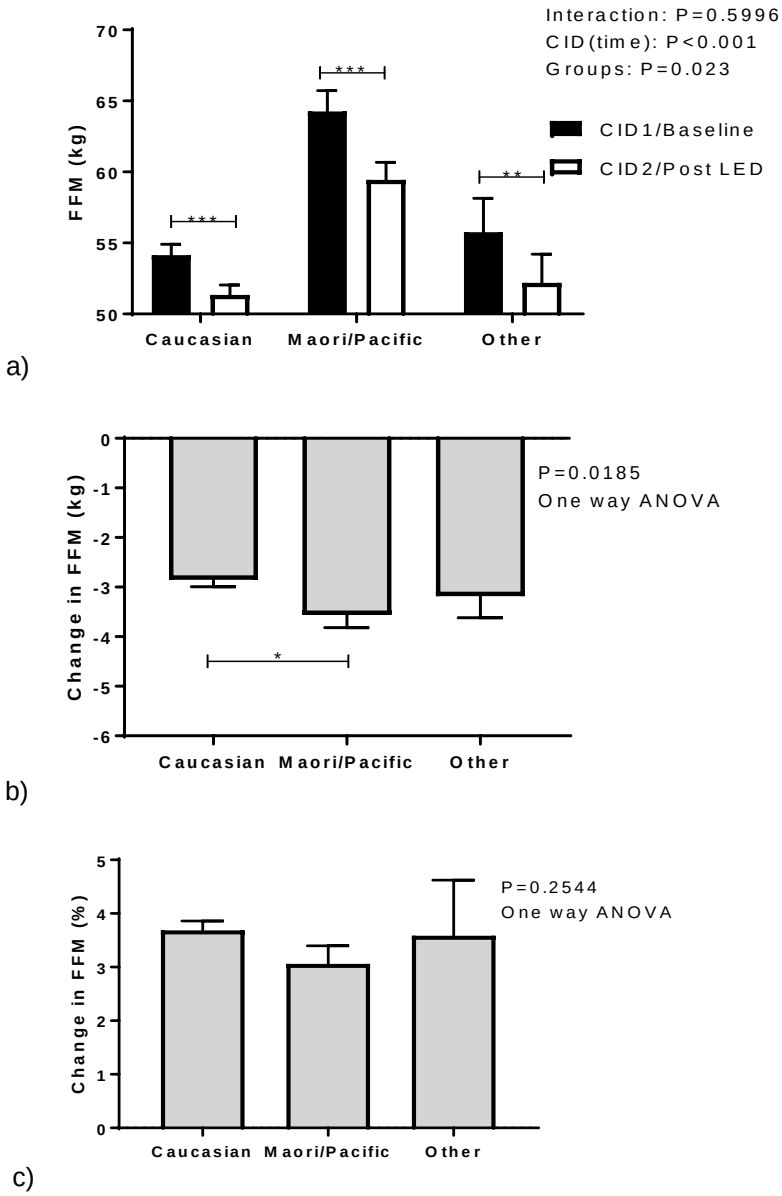


Figure 40: FFM and Ethnic Differences between CID1/Baseline and CID2/Post LED, mean (SEM); ***P<0.001; **P<0.01; a) Interaction, P=0.5996; CID(time), P<0.001; Groups, P=0.0023; b) FFM (kg) P=0.0185; c) FFM (%), P=0.2544

3.4.4.4 Metabolic parameters

All metabolic parameters significantly improved in response to the ≥8% LED-induced weight loss (P<0.05) (Table 31).

Table 31: Changes in metabolic markers of disease risk between CID1/Baseline and CID2/Post LED

n = 267	CID1/Baseline	CID2/Post LED	Change in	P value
FPG(mmol/l)	5.8±0.6	5.5±0.5	-0.3±0.5	P<0.001
HbA_{1C}(mmol/mol)	36.7±3.4	34.5±2.9	-1.9±2.2	P<0.001
Insulin(mU/l)	12.9±7.3	8.3±5.1	-4.7±6.2	P<0.001
HOMA-IR (mU/L)	3.4±2.0	2.1±1.4	-1.3±1.8	P<0.001
C-Peptide(pmol/l)	844.6±311.1	657.1±261.2	-187.5±238.2	P<0.001
hs-CRP (mg/l)	5.5±6.0	4.5±5.4	-1.0±6.2	P<0.05
TC(mmol/l)	5.3±1.0	4.5±0.9	-0.9±0.8	P<0.001
HDL-C(mmol/l)	1.3±0.3	1.2±0.2	-0.2±0.2	P<0.001
LDL-C(mmol/l)	3.4±0.9	2.8±0.8	-0.6±0.6	P<0.001
TG(mmol/l)	1.5±0.8	1.1±0.4	-0.4±0.6	P<0.001
TC:HDL ratio	4.2±1.0	3.9±0.8	-0.3±0.7	P<0.001

Mean±SD; FPG, fasting plasma glucose; HbA_{1c}, Glycated Haemoglobin; Insulin, fasting serum insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; C-Peptide, serum connecting peptide; hs-CRP, high sensitivity C-reactive protein; TC, Total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol, TG, Triglycerides; TC:HDL ratio, Total cholesterol: High density cholesterol ratio; p-values assessed by paired t-test.

3.4.4.5 Glycaemia

FPG, which was within the pre-diabetic range at baseline (5.84(0.60)mmol/l) has considerably improved with the weight loss. With a change of -0.31(0.03)mmol/l (P<0.001), mean FPG dropped to a cut-off of normoglycaemia at CID2/Post LED (Table 32) , with 164 or 61% participants reversing a diagnosis of IFG. No gender-specific or ethnic-specific differences were seen for change in FPG after the weight loss period (Table 32). In line with the results on FPG, HbA_{1C} has also improved significantly at CID2/Post LED, dropping from 36.7 (3.37) mmol/mol to 34.45(2.9)mmol/mol; (-1.92(0.12)mmol/mol, P<0.001). As for FPG, no gender or ethnic differences were found for change in HbA_{1C} (Figure 42).

A number of factors were shown to be associated with the improvements in FPG from CID1/Baseline to CID2/Post LED. A greater change in a BW (kg) (r^2 = 0.1493, P<0.05) and percentage change in BW (%) (r^2 = 0.0691, P<0.001), greater percentage change in FM (r^2 = 0.0515, P<0.001), older age (r^2 = 0.0387, P<0.01) and a higher FDRS score at screen (r^2 = 0.0308, P<0.01) (Figure 39). Other markers of metabolic health, specifically, fasting insulin, IR assessed through HOMA-IR, beta cell function assessed through C-Peptide and inflammation assessed through hs-CRP, significantly improved in all participants following weight loss. Mean (SD) fasting insulin decreased 4.7(0.4) mU/l (P<0.001), accompanied by a decrease in HOMA-IR of 1.3(0.1) units (P<0.001) for all participants (Table 31) and for gender and ethnic subgroups (Table 32). While no gender-specific differences were seen for fasting insulin or HOMA-IR, the latest was clearly different between ethnic subgroups with Maori/Pacific and Other having a

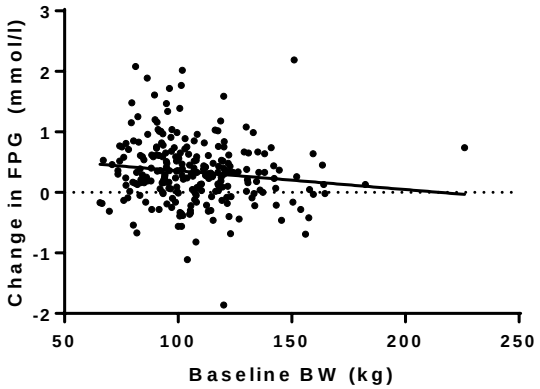
greater mean (SEM)change of -1.6(0.2) units and -1.5(0.3) units, respectively, when compared to -1.1(0.1) units for Caucasians (P<0.001) (Table 32). In all participants, mean (SEM) change in C-Peptide was -187.5(14.2)pmol/l (P<0.001). Male had a significantly greater change in C-Peptide compared to female, -243.9(34.9)pmol/l vs. -169.3(14.9)pmol/l, respectively (P<0.001). In terms of ethnic sub-groups, Maori/Pacific had a significantly greater change in C-Peptide -217.7(25.2)pmol/l, compared to Caucasians (-171.4(18.8)pmol/l) and Other (-178.6(39.3)pmol/l), P<0.001.

3.4.4.6 Blood pressure

SBP was also greatly improved with weight loss, with an improvement of -7.0(0.8)mmHg in all individuals (P<0.001), with greater improvements in male (-9.7(1.6)mmHg) when compared to female (-6.2(0.9)mmHg, P<0.001; and no differences between ethnic sub-groups. DBP also improved -1.1(0.5)mmHg, (P<0.05) in all individuals.

3.4.4.7 Lipid profile

In all participants, mean(SD) TC was 4.5(1.0)mmol/l at CID2/Post LED. Change mean(SEM) in TC was -0.9(0.04)mmol/l (P<0.001). Female had a greater mean (SEM) reduction in HDL-C (-0.16(0.02)mmol/l, P<0.05) than male. However, male had a greater mean (SEM) reduction in TC:HDL ratio (-0.5(0.1), P<0.01) than female. Caucasian had a greater reduction in TC (-1.0(0.06)mmol/l, P<0.01) than Maori/Pacific (Table 33).



a)

Figure 41: Correlation between baseline BW and Change in FPG, gender and ethnic differences

a) All participants r^2=0.01715, P=0.0389; Male, r^2=0.0605, P=0.0560; Female, r^2=0.01183, P=0.0717; Caucasian, r^2=0.01786, P=0.1018; Maori/Pacific, r^2=0.01027, P=0.3805; Other, r^2=0.0715, P=0.2413

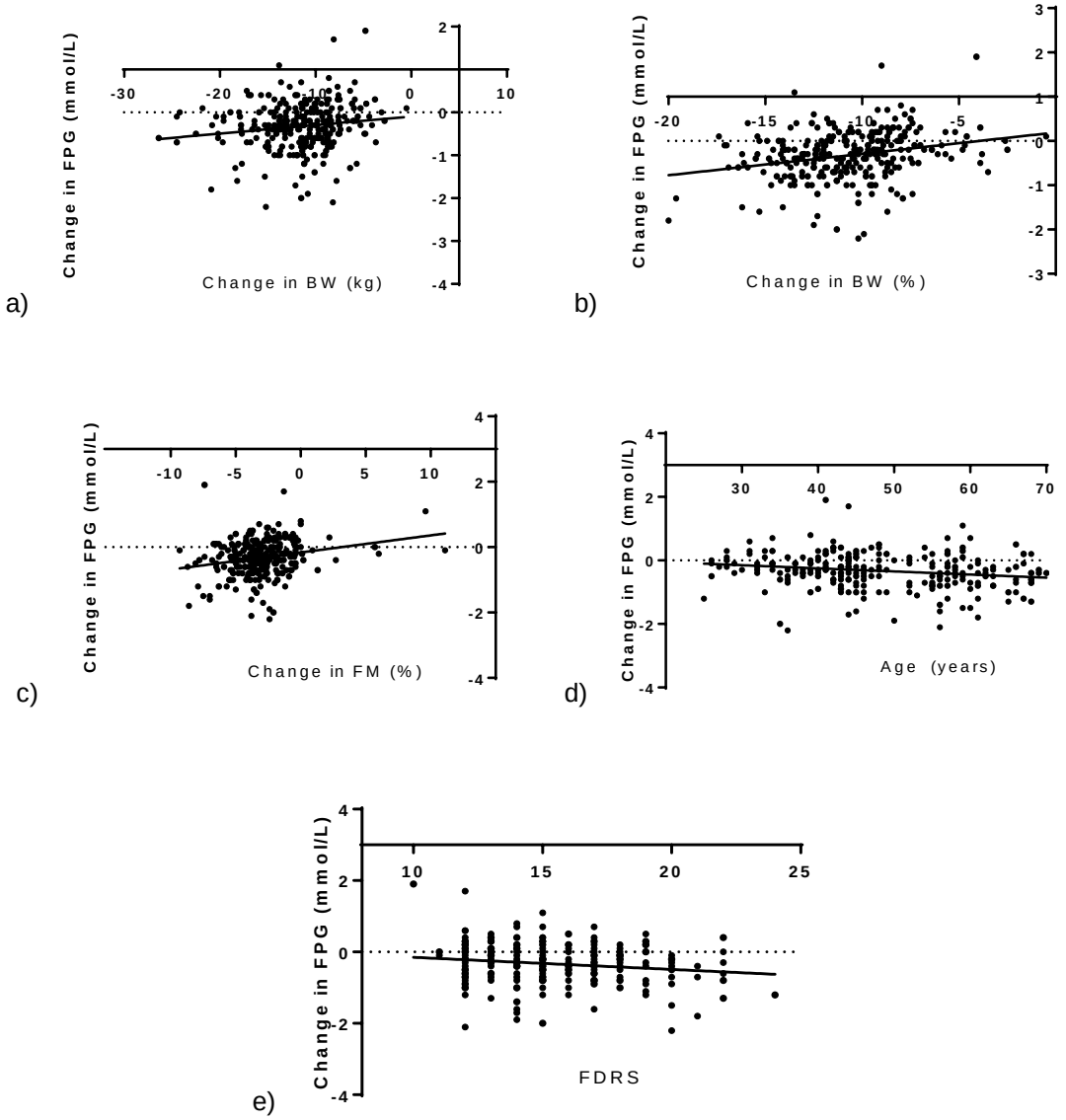


Figure 42: Correlation between change in FPG and a) change in absolute BW; and b) percentage BW and c) percentage FM; d) age and e) FDRS between CID1/Baseline and CID2/Post LED

a) r^2=0.1493, P=0.0146; b) r^2=0.0691, P<0.001; c) r^2=0.05147, P<0.001; d) r^2=0.03868, P=0.0012; e) r^2=0.03075, P=0.0040

Table 32: Glycaemia between CID1/Baseline and CID2/Post LED, Mean (SEM)

n = 267	CID1/Baseline	CID2/Post LED	P value	Change in	P value
FPG - All	5.84±0.03	5.53±0.03	P<0.001	-0.31±0.03	P<0.001
Male	[1ns]5.92±0.07	[1ns]5.57±0.06	P<0.001	-0.34±0.07	[1]ns
Female	5.81±0.04	5.51±0.04	P<0.001	-0.31±0.04	
Caucasian	[2ns]5.86±0.05	[2ns]5.53±0.04	P<0.001	-0.33±0.05	[2]ns
Maori/Pacific	5.77±0.06	5.49±0.04	P<0.001	-0.28±0.05	
Other	5.95±0.16	5.61±0.12	P<0.01	-0.34±0.11	
HbA_{1c} - All	36.4±0.2	34.5±0.2	P<0.001	-1.9±0.1	P<0.001
Male	[1ns]36.6±0.4	[1ns]34.5±0.4	P<0.001	-2.0±0.3	[1]ns
Female	36.3±0.2	34.5±0.2	P<0.001	-1.7±0.1	
Caucasian	[2ns]36.0±0.2	[2ns]34.3±0.2	P<0.001	-1.7±0.2	[2]ns
Maori/Pacific	36.9±0.4	34.9±0.3	P<0.001	-2.0±0.2	
Other	36.5±0.9	34.8±0.8	P<0.001	-1.8±0.4	
Insulin - All	12.9±0.4	8.3±0.3	P<0.001	-4.7±0.4	P<0.001
Male	[1ns]13.7±1.0	[1ns]8.7±0.7	P<0.001	-5.0±1.0	[1]ns
Female	12.7±0.5	8.1±0.3	P<0.001	-4.5±0.4	
Caucasian	[2a]11.0±0.5	[2a]7.0±0.3	P<0.001	-4.0±0.4	[2ac]P<0.001
Maori/Pacific	15.6±0.9	10.0±0.7	P<0.001	-5.7±0.8	
Other	15.2±1.3	10.2±1.2	P<0.001	-5.0±1.2	
HOMA-IR - All	3.4±0.1	2.1±0.1	P<0.001	-1.3±0.1	P<0.001
Male	[1ns]3.2±0.2	[1*]2.2±0.2	P<0.001	-1.5±0.3	[1]P<0.001
Female	3.3±0.1	2.0±0.1	P<0.001	-1.3±0.1	
Caucasian	[2a]2.9±0.1	[2b]1.7±0.1	P<0.001	-1.1±0.1	[2ac]P<0.001
Maori/Pacific	4.1±0.3	2.5±0.2	P<0.001	-1.6±0.2	
Other	4.0±0.4	2.6±0.4	P<0.001	-1.5±0.3	
C-Peptide - All	844.6±19.0	657.1±16.8	P<0.001	-187.5±14.2	P<0.001
Male	[1**]922.1±44.0	[1ns]678.2±37.3	P<0.001	-243.9±34.9	[1]P<0.05
Female	819.7±20.6	650.3±18.8	P<0.001	-169.3±14.9	
Caucasian	[2a]791.0±22.5	[2ns]619.6±20.0	P<0.001	-171.4±18.8	[2b]P<0.01
Maori/Pacific	927.5±35.3	709.8±31.1	P<0.001	-217.7±25.2	
Other	880.9±73.7	702.3±68.9	P<0.001	-178.6±39.3	
hs-CRP - All	5.5±0.4	4.5±0.3	P<0.01	-1.0±0.4	P<0.01
Male	[1ns]6.1±1.0	[1*]5.8±1.0	ns	-0.2±1.1	[1]ns
Female	5.4±0.4	4.1±0.3	P<0.001	-1.2±0.3	
Caucasian	[2ns]5.3±0.5	[2ns]4.3±0.4	ns	-1.0±0.5	[2]ns
Maori/Pacific	6.1±0.7	5.2±0.7	ns	-0.9±0.7	
Other	4.7±0.9	3.4±0.7	P<0.05	-1.3±0.5	

Mean±SEM; FPG, fasting plasma glucose; HbA_{1c}, Glycated Haemoglobin; C-Peptide, serum connecting peptide; HOMA-IR, Homeostasis Model Assessment for insulin resistance; hs-CRP, high sensitivity C-reactive protein; [1]gender differences using unpaired t-test, Unpaired t-test ***P<0.001; **P<0.01; *P<0.05; [2]ethnicity differences using one way ANOVA, compared to Maori/Pacific, (P<0.001); [b]ethnic differences using one way ANOVA, Tukeys *post hoc* [a]P<0.001; [b]P<0.01 compared to Maori/Pacific; Tukeys *post hoc* [c]P<0.001; compared to Other, ns, non-significant

Table 33: Lipid profile between CID1/Baseline and CID2/Post LED, Mean (SEM)

n = 267	CID1/Baseline	CID2/Post LED	P value	Change in	P value
TC - All	5.33±0.06	4.45±0.06	P<0.001	-0.88±0.05	P<0.001
Male	[1***]5.15±0.13	[1*]4.22±0.11	P<0.001	-0.93±0.09	[1]ns
Female	5.39±0.07	4.52±0.07	P<0.001	-0.87±0.05	
Caucasian	[2a]5.57±0.08	[2b]4.58±0.08	P<0.001	-1.0±0.06	[2b]P<0.01
Maori/Pacific	4.98±0.10	4.27±0.10	P<0.001	-0.70±0.08	
Other	5.10±0.20	4.30±0.19	P<0.001	-0.80±0.18	
LDL-C - All	3.38±0.05	2.78±0.05	P<0.001	-0.60±0.04	P<0.001
Male	[1***]3.27±0.12	[1ns]2.63±0.81	P<0.001	-0.64±0.08	[1]ns
Female	3.41±0.06	2.83±0.06	P<0.001	-0.59±0.04	
Caucasian	[2b]b3.54±0.07	[2c]2.86±0.07	P<0.001	-0.67±0.05	[2]ns
Maori/Pacific	3.15±0.09	2.67±0.08	P<0.001	-0.48±0.06	
Other	3.23±0.18	2.64±0.16	P<0.001	-0.59±0.15	
HDL-C - All	1.31±0.02	1.16±0.01	P<0.001	-0.15±0.01	P<0.001
Male	[1**]1.18±0.03	[1**]1.09±0.02	P<0.001	-0.09±0.02	[1]P<0.05
Female	1.35±0.02	1.19±0.02	P<0.001	-0.16±0.02	
Caucasian	[2b]1.36±0.02	[2b]1.20 ±0.02	P<0.001	-0.17±0.02	[2]ns
Maori/Pacific	1.24±0.03	1.11±0.02	P<0.001	-0.13±0.03	
Other	1.24±0.05	1.15±0.04	P<0.05	-0.09±0.04	
TG - All	1.48±0.05	1.13±0.03	P<0.001	-0.35±0.04	P<0.001
Male	[1ns]1.57±0.09	[1ns]1.12±0.05	P<0.001	-0.45±0.08	[1]ns
Female	1.46±0.05	1.14±0.03	P<0.001	-0.32±0.05	
Caucasian	[2ns]1.50±0.05	[2ns]1.15±0.03	P<0.001	-0.34±0.04	[2]ns
Maori/Pacific	1.41±0.09	1.11±0.04	P<0.001	-0.30±0.08	
Other	1.68±0.20	1.10±0.10	P<0.01	-0.58±0.16	
TC:HDL- All	4.22±0.06	3.91±0.05	P<0.001	-0.31±0.04	P<0.001
Male	[1**]4.5±0.1	[1ns]4.0±0.1	P<0.001	-0.5±0.1	[1]P<0.01
Female	4.12±0.06	3.88±0.06	P<0.001	-0.24±0.04	
Caucasian	[2ns]4.23±0.08	[2ns]3.90±0.07	P<0.001	-0.32±0.05	[2]ns
Maori/Pacific	4.17±0.10	3.94±0.09	P<0.01	-0.23±0.07	
Other	4.29±0.24	3.8±0.19	P<0.01	-0.49±0.15	

Mean±SEM; TC; Total cholesterol; LDL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; TG, Triglycerides; TC:HDL, Total Cholesterol: High density lipoprotein ratio; [1]gender differences using unpaired t-test, Unpaired t-test ***P<0.001; **P<0.01; *P<0.05; [2]ethnicity differences using one way ANOVA, compared to Maori/Pacific, (P<0.001); [b]ethnic differences using one way ANOVA, Tukeys *post hoc* [a]P<0.001; [b]P<0.01 and [c]P<0.05 compared to Maori/Pacific; Tukeys *post hoc* [d]P<0.001; [e]P<0.01 and [f]P<0.05 compared to Other, ns, non-significant

3.5 Discussion

In the PREVIEW:NZ study, an 8-week LED aiming for at least, 8% BW loss was highly successful, causing a total weight loss of 11.5kg or 10.7% (completers, n=267) and caused a significant improvement in all anthropometric and metabolic parameters assessed. Men had a higher baseline BW and lost more absolute BW, absolute FM, android fat and absolute FFM. Moreover, male had a greater improvement in HOMA-IR, C-Peptide and TC:HDL ratio. Surprisingly, females lost more HDL-C than male. As per previous literature, this may be due to reduced physical activity during the 8-week LED weight loss phase (Rolland & Broom, 2011). Baseline BW was not a good predictor of weight loss across ethnic groups as Maori/Pacific had the highest baseline BW but lost the least percentage BW (-9.9%) when compared to Caucasian (-11.3%) and Other (-10.8%)

It was hypothesised that an 8-week LED would result in ≥8% BW loss and improvements in glucose metabolism in the PREVIEW:NZ cohort. The results here presented confirmed the hypothesis; 267 participants completed the LED with significant weight loss and a parallel improvement in metabolic markers of T2D risk - FPG, insulin, HbA_{1C}, C-peptide and WC. Metabolic improvements following an LED have been previously described (Leslie et al., 2017; Leslie et al., 2016; Roberts et al., 2017; Sellahewa et al., 2017; Taylor et al., 2017). Metabolic pathways within the metabolic syndrome have shown clear links between IR and hyperinsulinaemia to other risk factors, such as high BP and dyslipidaemia (Grundy et al., 2005). All the cardiovascular factors – BP, TC, LDL-C, TG, TC:HDL ratio - also improved following 8-week LED, with findings comparable to other LED studies (Anderson et al., 2001; Dombrowski. et al., 2014; Foster et al., 1992; Gougeon, 1992; Jackness et al., 2013; Johansson et al, 2013; Lean et al., 2013; Lean et al., 2017; Leslie et al., 2017; Leslie et al., 2016; McCombie et al., 2017; Ohno et al., 1989; Steven et al., 2016; Unick et al., 2015). Jackness et al emphasised that the effects of LED induced weight loss mimics the effects of gastric roux-en-Y bariatric bypass surgery (Hjelmesaeth. et al., 2018; Jackness et al., 2013).

In the PREVIEW:NZ cohort, baseline BW and change in BW predicted the changes in FPG, where the heaviest participant and those who lost the most BW also had the greatest improvements in FPG. Previous studies using similar nutritionally complete meal replacement diets have shown improvement in anthropometric and metabolic parameters, especially linked to IR (Dombrowski. et al., 2014; Gasteyger et al., 2009; Gogebakan et al., 2011; Handjieva-Darlenska et al., 2010; Haywood et al., 2017; Hjelmesaeth. et al., 2018; Jackness et al., 2013; Jebb et al., 2017; Joris et al., 2017; Lean et al., 2017; Leslie et al., 2017; Leslie et al., 2016; McCombie et al., 2017; Rudovich et al., 2016; Taylor et al., 2017; Zhyzhneuskaya et al., 2017). One study confirmed that weight loss improved HOMA-IR, which is calculated using fasting serum insulin and FPG (Geiker. et al., 2018; Hadaegh et al., 2013). New Zealand had the heaviest cohort within the 8 countries undertaking the PREVIEW trial. This is not surprising when considering the worldwide obesity statistics. Among all the OECD countries, New Zealand is the 3rd most obese one, just behind US and Mexico (1st and 2nd, respectively) (OECD, 2017). Indeed, the mean baseline BW of the 267

participants who completed the LED in New Zealand was within the range of obesity class II (obesity class I ≥30kg/m^2, class II ≥35kg/m^2 and class III: ≥40kg/m^2) (Blackstone, 2016; OECD, 2017; World Health Organisation, 2013). Interestingly, this high risk - obese and pre-diabetes - group was younger than expected, suggesting that T2D risk can no longer be attributed to the older.

It was originally hypothesised that baseline BW would predict absolute BW (kg) and FM (kg) loss during LED; and that this may differ between genders (men vs. women) and ethnicity (Caucasian, Maori/Pacific, Other). This was the case between gender differences where male had a higher baseline BW than female and therefore lost more absolute BW. Gasteyger et al confirmed a greater visceral fat loss induced by LED in men is due to the greater adipose stored fat men accumulate when compared to women (Gasteyger et al., 2009). However, this was not observed when comparing ethnicities. Maori/Pacific were significantly heavier than both Caucasian and Other. Interestingly, Maori/Pacific did not lose more absolute BW than Caucasian and Other.

Fat distribution and body composition varies between ethnicities with Maori/Pacific reported to have more muscle and reduced central adiposity when compared to greater central adiposity accumulation in Asian population, classified in this study as Other (Duncan et al., 2004; Liao et al., 2002; Rush et al., 2004; Rush et al., 2009; Swinburne et al., 1999; Wulan et al., 2010). Adipose tissue distributed centrally has been identified as the main cause of IR. Some studies reported that weight loss is more beneficial for men due to men metabolising more intra-abdominal fat than women, whereas women lose more subcutaneous fat (Hadaegh et al., 2013; Williams et al., 2015; Wirth & Steinmetz, 1998). Zhzhneuskaya et al claims that liver fat content is the greatest abnormality in the development of T2D (Zhyzhneuskaya et al., 2017). Due to changes in abdominal visceral fat being linked to intra-abdominal or WC, IDF recommended using WC as a simplified way to monitor and target ectopic fat (centrally distributed fat) with ethnic-specific values for male and female (International Diabetes Federation, 2013).

It was hypothesised that baseline BW would predict change in FM and FFM during LED between gender and ethnicity. Men lost most absolute FM ($P<0.05$) with a trend of a greater reduction in %FM ($P=0.0542$). Men also lost a greater amount of absolute FFM with the weight loss. However, once converted to percentage FFM, both men and women had a positive %FFM gain and there was no difference between gender subgroups. Ethnic differences were not found when comparing FM between ethnic groups. However, when comparing to change in absolute FFM, surprisingly Caucasian lost the least FFM. Other lost the greatest absolute FFM, followed by Maori/Pacific ($P=0.0185$). All ethnic subgroups had a positive %FFM gain and there was no difference between them; significance was also lost when looking at percentage FFM. It was reassuring to see that all participants improved their %FFM profile following LED ensuring maintenance of FFM, while losing a greater proportion of FM. Other interventions using low energy diets have shown that as well as improvements to metabolic parameters, there was also an improvement in overall nutritional status and protein intake, showing an improvement in percentage of FFM with a loss in FM (Geiker. et al., 2018; Hjelmesaeth. et al., 2018). FFM mass

preservation is important for maintaining resting metabolic rate and insulin sensitivity (Stiegler & Cunliffe, 2006).

It was also originally hypothesised that improvements in glucose and other markers of metabolic health during LED may also differ between genders (male vs. female) and ethnicity (Caucasian, Maori/Pacific, Other). However, contrary to what was hypothesised, there were no greater improvements in FPG in men than women, despite the greater weight loss. Similarly, no greater improvements in FPG were seen in Maori/Pacific when compared to Caucasians or Other (ns).

There is a strong positive association between overall obesity, especially centrally distributed adiposity. IR and the risk of T2D (Chan, 2017; Hamman et al., 2006). The findings from this thesis suggest that BW reduction may have led to improvements in FPG through reduction in BW and FM, including central adiposity. HbA_{1c} can also be used a diagnostic tool for T2D and pre-diabetes. According to the WHO, IDF and ADA diagnosis guidelines, the HbA_{1c} cut-off for pre-diabetes is 40mmol/l where 48mmol/l is the cut-off for T2D (American Diabetes Association, 2017; American Diabetes Association, 2018; Whiting et al, 2011; WHO & IDF, 2006; Zimmet. & Alberti, 2016). The New Zealand Study for the Society of Diabetes group has, however, shifted the T2D cut-off to 50mmol/mol (Braatvedt et al., 2012; New Zealand Guidelines Group, 2011). The rationale for this was that an HbA_{1c} of 50mmol/mol would be interpreted as 6.8% in the old metrics (compared to 6.6% if using an HbA_{1c} of 48mmol/mol). Despite not being used for screening during the PREVIEW study, HbA_{1c} was assessed in this study and found to be significantly lower than the expected result in a pre-diabetic population. In fact, only 29% (n=58) would have been classified as diagnosed with pre-diabetes and enrolled in the study if, HbA_{1c} was used as the screening criteria, with a cut-off of ≥40-49mmol/mol.

All the other metabolic markers of T2D improved. These improvements appear to be associated to the large BW loss, overall fat loss and reduced adipose tissue and hence WC. Interestingly, participants were classified as being pre-diabetic at baseline essentially based on IFG, with GT within the cut-off of normoglycaemia. IFG suggests that participants have increased liver IR, potentially due to the notorious excessive central adiposity. At CID1/Baseline, 74% had IFG (62%), IGT (35%) or both (27%). During the 8-week LED phase, 61% reversed the baseline IFG diagnosis. Improvement in glycaemia was predicted as all the metabolic markers of T2D improved following the BW reduction, reduced fat mass and adipose tissue, as assessed by WC. The greater benefits were seen in men, which was consistent with previous data where was shown that men mobilised more intra-abdominal fat than women during weight loss, hence showing more pronounced improvements in the metabolic risk profile (Handjieva-Darlenska et al., 2010; Williams et al., 2015; Wirth & Steinmetz, 1998). At baseline, mean (SD) HOMA-IR was 3.6(2.3) units, confirming IR as defined using the cut-off of 2.5, with moderate IR between 3 to 5 units (Gutch et al., 2015). There were no gender differences. In terms of ethnicity, Maori/Pacific had the highest level of IR, assessed through HOMA-IR, followed by Other and then Caucasian. In parallel with IR, fasting insulin was higher in Maori/Pacific when compared to other ethnic groups. During pre-diabetes, IR causes raised fasting plasma insulin leading to hyperglycaemia

and hyperinsulinemia (Ferrannini, 2014; Garber, 2012; Khavandi et al., 2013). C-Peptide, a marker of insulin secretion was also raised, which is expected in pre-diabetic individuals with hyperinsulinemia and hyperglycaemia. Increased hs-CRP confirmed the presence of inflammation, which is characteristic of obesity and IR (Bullo et al., 2013; Geiker. et al., 2018; Wisse, 2004).

The finding of well-controlled BP was surprising, considering that all the other results were indicative of metabolic syndrome in the study population. It is possible that, by excluding individuals with high BP during screening, the study population would have been biased in terms of the baseline blood pressure. Cholesterol is also a feature of metabolic dysfunction, used as part of the criteria for clinical diagnosis of metabolic syndrome. Raised triglycerides and LDL-C and reduced HDL-C indicate atherogenic dyslipidaemia (Grundy et al., 2005; Lemieux et al., 2001). In the study here reported, at baseline, TG, LDL-C and the TC:HDL ratio was higher than the clinical cut-offs used to define cardiovascular risk (Grundy et al., 2005). As for all the metabolic markers of disease, the lipid parameters improved during the 8-week LED phase. What was surprising was how HDL-C decreased during the LED phase. HDL-C at CID1/Baseline was higher than recommended but had a significant decrease, however still above the preferred cut-off of 1.0mmol/l, post LED (Chapman et al., 2004; Grundy et al., 2005). A meta-analysis of the Framingham Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Coronary Primary Prevention Trial and Multiple Risk Factor Intervention Trial (MRFIT) confirmed these findings and consistently showed that for every 0.06mmol/l decrease in plasma levels of HDL-C there was a 2%-3% increase in the risk of Coronary Heart Disease (Gordon et al., 1989). It is possible that this reduction may have been a result of the advice provided to participants to reduce their physical activity level when on the LED weight loss phase. Rolland et al reported a reduction of HDL-C following VLED in a review article summarising a trend for a decrease in HDL in 4 out of the 5 studies (VLED intervention ranged from 4-14 weeks) (Clement et al., 2004; Haugaard et al, 2007; Hong et al, 2005; Lin et al., 2009; Rolland & Broom, 2011).

One of the strengths of the weight loss phase was the rate of participants completing the 8-week period. In the international PREVIEW study, Huttunen-Lenz et al reported a dropout of 9.2% in 2,224 individuals who attended the baseline visit, with 2,020 participants being analysed at the end of the LED phase. Of these 2,020, 92% or 1,857 achieved ≥8% BW loss target - 'achievers' (Huttunen-Lenz. et al., 2018). The sub-study here reported - the PREVIEW:NZ had 82% success rate, 249 completers achieved the weight loss goal, when compared to 305 who started the study and this was in line with the international attendance rates, showing a high success rate of achieving the ≥8% BW loss goal. Unick et al analysed 2,290 Look AHEAD participants and reported that the more weight loss during the first 8 weeks the higher the success of weight loss maintenance at 8 years (Unick et al., 2015).

Another strength of this thesis is the fact that this study is part of a randomised controlled multi-centred study trial with strict protocols and access to commercial standardised LED weight loss programme for the weight loss phase. An important part of the PREVIEW protocol is the provision

of the 2-weekly group support session led by a Dietitian and an Exercise Physiologist, based on the PREMIT education (Section 2.4.3) (Huttunen-Lenz. et al., 2018; Kahlert et al., 2016) programme (as described in Chapter 2.4). The first group (week 0) session provided information on the LED, instructions on following the LED and supplied the LED for the next 2 weeks. Week 2, 4 and 6 aimed to promote the importance of behavioural change and to motivate self-efficacy through group participation with problem solving techniques discussed. This method of regular support in a group setting have been proven to be successful in many other LED and weight loss studies (Diabetes Prevention Program (DPP) Research Group, 2002; Goyenechea et al., 2011; Handjieva-Darlenska et al., 2010; Jebb et al., 2017; Leslie et al., 2017; Leslie et al., 2016; Lindstrom et al., 2008; McCombie et al., 2017; Sakane et al., 2011).

The limitation of this study chapter was that no postprandial glucose data was collected at CID2/Post LED as this was an international collaboration and a standardised protocol was followed in all countries. As a result, no data on 2h postprandial glucose or the overall glucose tolerance assessed through AUC could be analysed, limiting the amount of data available in terms of glycaemic improvement. Another limitation is the prescriptive counselling sessions given to groups of 8-12 participants with no allowance for the presence or family or whanau again, as this was the international protocol. This may have contributed to the low success rate amongst difference ethnic groups such as Maori/Pacific, which favours the traditional family/whanau based support with the involvement of the family to help promote family based changes and suggestions.

3.6 Conclusions

The use of an 8-week LED is an effective method of weight loss for those overweight and at high risk of developing T2D, achieving significant improvements in anthropometry, blood pressure and metabolic marker profile. Men had an improved glycaemia when compared to women during the 8-week weight loss LED approach due to a greater reduction in change in FM and in particular centrally distributed fat, as assessed by WC. There were no specific ethnic differences in terms of metabolic improvements following LED, but promoting a family based approach, especially to the Maori/Pacific group may improve the success rates and reduce the number of dropouts. These findings are clinically important and support gender-specific changes in men and women after weight loss, whilst no ethnic specific changes between the three ethnic subgroups. Following the LED weight loss phase, more than half of the participants (61%) achieved normoglycaemia.

Chapter 4 PREVIEW:New Zealand – Long term dietary intervention for weight loss maintenance during 2-year follow-up

One of the key issues faced by individuals attempting to lose BW in order to improve metabolic health outcomes is the problem of long-term weight loss maintenance. Whilst there is considerable evidence that short term periods of weight loss can be successfully achieved using strategies such as LED meal replacement (Batsis et al., 2016; de Vos, Runhaar et al., 2016; Geiker. et al., 2018; Haywood et al., 2017; Hjelmesaeth. et al., 2018; Jebb et al., 2017; Joris et al., 2017; Lean et al., 2017; Rudovich et al., 2016; Sellahewa et al., 2017; Taylor et al., 2017; Zhyzhneuskaya et al., 2017) (see review of LED in Chapter 3), maintaining that loss of BW and FM over months and years is a significant challenge. LED meal replacements readily achieve short term weight loss of 10-15% over several months, greater than can be achieved by intensive behavioural lifestyle intervention over a similar duration (American Diabetes Association, 2018; Scottish Intercollegiate Guidelines Network, 2010). Clearly, however, LEDs cannot be the long-term solution even though they are very successful in ameliorating metabolic dysfunction in the short term, including in those with advanced dysglycaemia and T2D. For example, in the recent well known UK DiRECT trial, almost 90% of those who achieved weight loss ≥15kg using an LED rapidly went into T2D remission (Leslie et al., 2017; Lim et al., 2011; Taylor et al., 2017). In this T2D trial Taylor et al postulated that 15% weight loss reduced adipose tissue mass, ectopic infiltration into key organs such as pancreas, and reversed beta cell damage; yet it was also noted that strategies to ensure weight loss maintenance were required to maximise long-term benefits (Taylor et al., 2017).

Lifestyle intervention studies for the prevention of T2D have commonly used lower-fat, higher-CHO, moderate-protein diets (see Chapter 1 for review), which remain the basis of T2D prevention recommendations. These include the large long-term USDPP, the FDPS and China's Da Qing studies (Diabetes Prevention Program (DPP) Research Group, 2002; Gong et al., 2016; Herman et al., 2012; Jaacks et al., 2014; Lehtisalo et al., 2016; Li et al., 2008; Lindstrom et al., 2003; Lindstrom et al., 2008; Lindström et al., 2006; Pan et al., 1997). There is however growing evidence to support the role and use of HP diets for long-term weight loss maintenance. For example, in weight loss maintenance studies comparing higher protein (25en%protein) intake with current recommendations of moderate protein intake (15en%protein) over the long-term, the higher protein groups have shown evidence of improved satiety, greater weight loss, greater FM loss and better preservation of FFM (Astrup, 2004; Astrup et al., 2015; Baum et al., 2006; Cheraghpour et al., 2017; Clifton et al., 2014; Dong et al., 2013; Gogebakan et al., 2011; Larsen et al., 2010; Layman & Baum, 2004; Leidy et al., 2015; Paddon-Jones et al., 2008; Te Morenga et al., 2011; Westerterp-Plantenga et al. , 2012). Reduction in serum triglycerides, BP and WC has also been reported in clinical studies involving participants following HP diets (Gogebakan et al., 2011; Wycherley et al., 2013). The DioGENES weight loss maintenance trial was an early

intervention that was able to demonstrate that low-fat HP diets may be more successful than low-fat high-CHO diets (Larsen et al., 2010; Rudovich et al., 2016).

DioGENES had used a short 2-month period of LED meal replacement to achieve acute weight loss and investigated maintenance of weight loss over 6 months in a trial of ~1000 overweight adults (Larsen et al., 2010). The success of this 6-month weight maintenance trial by a European Union multi-country consortium led to the development of the current International PREVIEW trial, with the aim of extending this HP approach from 6 months to 3 years, and with specific focus on prevention of T2D in overweight, high risk individuals with confirmed pre-diabetes (Fogelholm et al., 2013; Fogelholm et al., 2017; Huttunen-Lenz. et al., 2018; Raben et al., 2013; Raben et al., 2017)

Chapter 3 presents the PREVIEW:NZ study, showing successful LED-driven weight loss which resulted in significant improvements in both anthropometric and metabolic parameters.

4.1 Aim and Hypotheses

The aim of this thesis Chapter was to investigate the effect of a lower-fat higher-protein lower-GI diet on BW and body composition, and also glycaemia and other metabolic outcomes during a 2-year weight maintenance phase.

As mentioned previously, the PREVIEW international RCT with 2 diet intervention groups, to which participants were randomly assigned. At the time of data analysis for this thesis, the randomisation remained “locked” (de-identified) and hence the allocation of participants to LP and HP diet groups and exercise (high and moderate intensity) remained ‘blinded’. Un-blinding of the data will be conducted by the European Union partners in late 2018. Consequently, in this Chapter the participants have been allocated to diet intervention groups based on their reported dietary protein intake (see Methods section 2.5, for details of the diet group allocation).

The primary hypotheses in the PREVIEW:NZ cohort was that:

1). A novel lower fat, higher protein, lower GI diet results in more successful long term BW maintenance over 2-years compared to current recommendations of lower fat, higher CHO, moderate GI diet.

2). Improved weight loss maintenance would in turn this result in better glycaemic control.

The secondary hypotheses are based on the results of the LED weight loss in Chapter 3 and that the secondary hypotheses were that:

1). weight loss maintenance would more successful in individuals with greater BW and FFM (kg): i.e. weight loss maintenance is better in men vs. women and/or in Maori/Pacific vs. Caucasian vs. Other.

2). glycaemic control would be successful in individuals with greater BW and FFM (kg): i.e. greater glycaemic improvement in men vs. women and/or in Maori/Pacific vs. Caucasian vs. Other.

3). Other metabolic measures would be more successful in individuals with greater BW and FFM (kg): i.e. greater metabolic improvement in men vs. women and/or in Maori/Pacific vs. Caucasian vs. Other.

4.2 Methods

There were 267 individuals who were 'completers', defined as those who attended CID2/Post LED (2 months). However, only 249 of these individuals achieved the PREVIEW weight loss goal of ≥8%, as described in Chapter 2.2.

4.2.1 Definition of dietary groups: LP vs. HP

In this thesis the 2 dietary intervention groups were assigned using data from both baseline (CID1/baseline) and 6 months (CID3/6m).

1). Firstly, a dietary protein cut point was determined based on the mean reported en%protein intake for all participants at CID1/Baseline, which was 18.6 en%protein. Hence, LP is defined as <18.6en%protein, HP is defined as ≥18.6en%protein

2). Secondly, reported en%protein was measured at CID3/6m, and participants were in turn allocated to either the LP or HP diet group. CID3/6m was the first diet assessment point during the maintenance phase, by which time participants had been receiving diet counselling for a period of 4 months (as described in Chapter 2.5).

4.2.2 Categorical and Continuous analyses

The data analysis was conducted using both categorical (LP vs HP diet groups) and continuous (en%protein as a continuous variable) methods, as follows:

1) Categorical analysis compared outcomes between LP (<18.6en%protein) and HP (≥18.6 en%protein), n=249; using ITT-LVCF, cut-off defined from the mean en%protein at CID1/Baseline and groups then allocated at CID3/6m using the LP and HP diet group; from 0-24 months

2) Continuous analysis from 2-24 months using:-

a) Observed data as defined by using raw observed data only,

b) ITT-LVCF (see Appendix E),

c) ITT-Multiple imputation (see Appendix F)

4.2.3 Anthropometric outcomes

The anthropometric parameters analysed in this chapter included BW (kg), BMI, FM (kg), FM (%), android fat(kg), FFM (kg), FFM (%), WC, SBP and DBP. The anthropometric measures were collected at CID1/Baseline, CID2/Post LED at 2 months, CID3/6m, CID4/12m, CID5/18m and CID6/24m.

4.2.4 Metabolic outcomes

The metabolic parameters analysed in this chapter included FPG, OGTT, $AUC_{GlucoseT0\text{-}120m}$, HbA_{1C} (mmol/mol), Insulin, HOMA-IR, C-Peptide, hs-CRP, TC, HDL-C, LDL-C, TG and TC:HDL ratio. The metabolic measures were collected at CID1/Baseline, CID2/Post LED at 2 months, CID3/6m, CID4/12m, CID5/18m and CID6/24m. OGTT and $AUC_{GlucoseT0\text{-}120m}$ were only collected at CID1/Baseline, CID3/6m, CID4/12m and CID6/24m.

4.2.5 Food diary record

Diet records were calculated as an average of the 4-day food diary collected at CID1/Baseline, CID3/6m, CID4/12m and CID6/24m. Outcome parameters were: Total energy (TE), percentage energy from protein (en%protein), percentage energy from fat (en%fat), percentage energy from carbohydrate (en%CHO) and GI. The mean (SD) protein intake for all participants at CID1/Baseline (n=267) was 18.6(3.7) en%protein (refer to Table 23, page 75). This mean was used to allocate the 2 diet groups as analysed in this thesis at CID 3/6 months (LP <18.6 en%protein and HP ≥18.6 en%protein).

4.3 Statistical Analyses

The statistical analyses conducted in this Chapter were as follows:-

Mean and SD/SEM were used to describe the baseline characteristics and within group changes in the gender and ethnic subgroups from CID1/Baseline to CID6/24m in all eligible participants who met ≥8% weight loss (n=249). Changes were calculated by subtracting the baseline (CID1/Baseline) from CID2/Post LED, CID3/6m, CID4/12m, CID5/18m and CID6/24m, respectively. Changes between gender and ethnic subgroups from CID1/Baseline to CID6/24m were analysed with independent sample t-test and Two-way ANOVA, respectively. P values for the interaction were shown on the figures. Tukey's *post hoc* analysis was used to compare the different ethnic subgroups. P values for *post hoc* analysis are described in the footnotes of each figure. Analyses were undertaken as ITT, using LVCF (ITT-LVCF) to impute missing data. Data was assumed missing at random. The ITT population was defined as participants who completed and met the ≥8% weight loss goal at CID2/Post LED, n=249. Regression analysis was conducted in two ways:

1. Categorical analysis compared the 2 diet groups, LP vs HP (n=249) between CID2/Post LED to CID6/24m for all participants; using the data imputation method of ITT-LVCF, cut-off defined

as LP<18.6en%protein and HP≥18.6en%protein, using mean en%protein at CID1/Baseline with groups allocated at CID3/6m. Figures present data from all participants, allocated to LP or HP, between CID1/Baseline and CID6/24m, where the assumption was made that participants remained in their allocated diet group throughout the intervention. Multiple missing time points, due to participant drop out or non-attendance at CID as the intervention progressed, prevented a valid 2 diet group categorical analysis of the raw (no imputation) data set between CID2/Post LED to CID6/24m.

2. Continuous multivariant analysis of the observed (raw) data was also conducted, alongside Dr Yannan Jian, Senior Clinical Statistician. Since it was not valid to conduct statistical analyses of the observed data using a categorical model beyond CID3/6m, as diet group allocation may have changed for individuals beyond the 6 month follow up time point, continuous analysis was performed between CID2/Post LED to CID6/24m. Repeated measures mixed models were used to evaluate the linear association between en%protein and clinical outcomes measured at CID3/6m, CID4/12m and CID6/24m. Change outcomes were calculated as change from CID2/Post LED if the parameter was measured at that time point, or from CID1/Baseline if no data collection at CID2/post LED. All regression models controlled for correlation between repeated observations from same participant, using an unstructured correlation structure with a random participant effect. Adjusted regression models also included the CID1/Baseline as a confounding variable, plus gender and ethnicity. With repeated measurements, time was included in all models as a categorical variable with 3 visits at CID3/post LED, CID4/12m and CID6/24m. The interaction effect between en%protein and time was tested, and if statistically significant, the association between en%protein and the outcome was assessed at each CID separately. Model-adjusted coefficient of en%protein was reported, which quantified the mean change in outcome associated with a 1% increase in energy from protein. Missing data at follow up visits were taken into account in the mixed model based on the missing at random assumption using maximum likelihood. Due to the high number of missing follow up data, sensitivity analyses were also conducted to test the robustness of model estimates. This included single imputation method using LVCF from CID1/Baseline, and multiple imputation method under the same assumption of missing data.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided at 5% significance level.

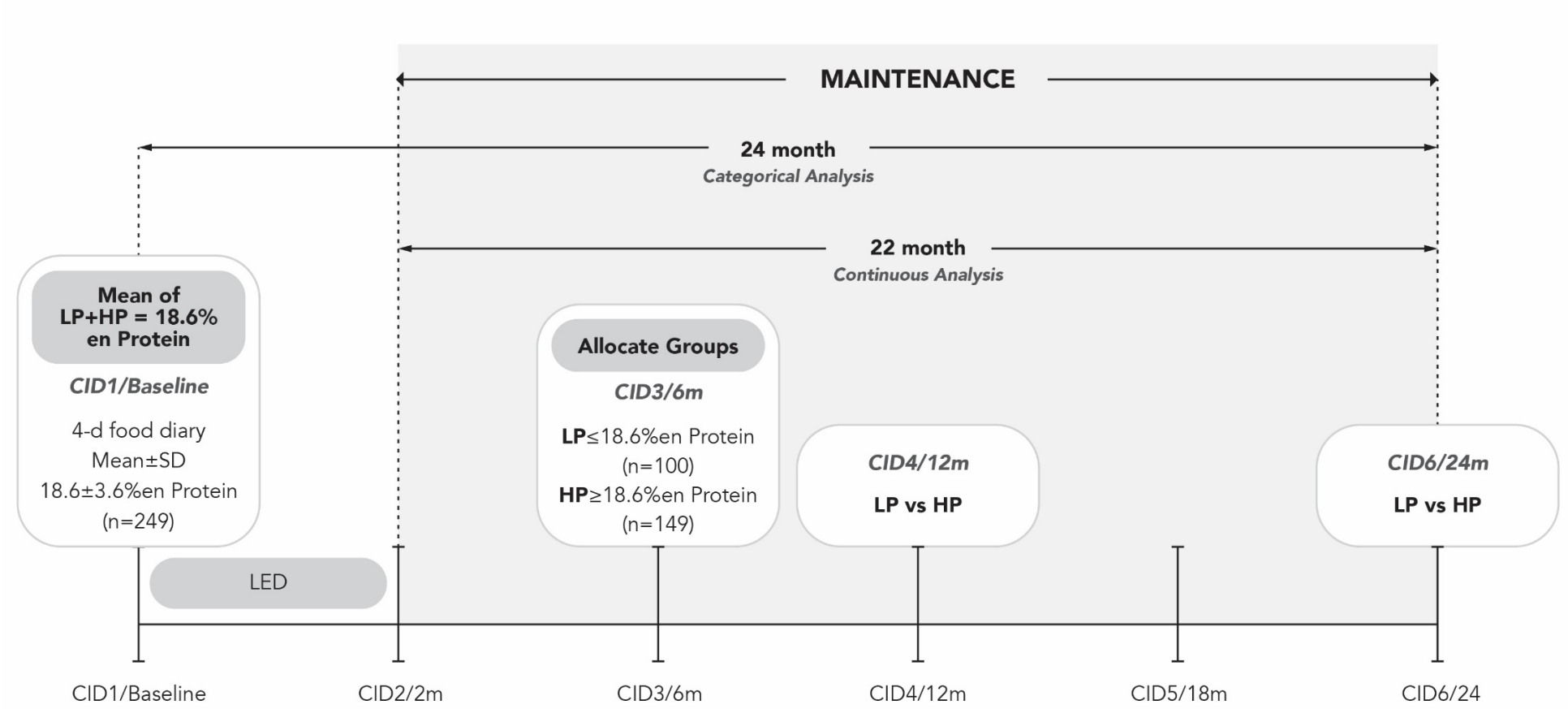


Figure 43: PREVIEW:NZ protocol highlighting the method of diet group allocation for LP and HP categorical analysis using 4-day food diaries over 24 months

4.4 Results

4.4.1 Categorical Analysis

4.4.1.1 LVCF data

(i) Baseline characteristics (n=249)

The baseline characteristics of the study population who completed the 8-week LED, achieved the 8% weight loss goal and then were allocated to LP and HP diet groups are presented in Table 35. LP (<18.6en%protein) comprised 40% of total participants and HP (≥18.6en%protein) comprised 60% of total participants. The mean (SD) age of all participants was 47.2(11.1) years. 76% were females (n=188) and 24% were males. There were 3 ethnic groups, as described in Chapter 3, of which Caucasian comprised the greatest number of individuals (n=151, 61%), followed by Maori/Pacific (n=77, 31%) and then Other (n=21, 8%). The mean (SD) FDRS of all participants was 15.1(2.8), indicating a high risk of developing T2D prior to the start of the 8-week LED. Both groups typically comprised a wide age range, but unexpectedly the LP diet group was a significantly younger group (46.3(10.7) years) compared to HP (49.4(10.9) years, P=0.0289). There were no statistically significant differences between the LP and HP diet groups for any anthropometric characteristics including BW, BMI, FM, FFM, android fat and WC (all, P>0.05); FPG or any glucose measures during the OGTT, or HbA_{1C} or C-Peptide (all, P>0.05). However, there was a significant difference in fasting insulin and HOMA-IR, with lower mean insulin concentration in the HP group. When investigated further, it was clear that these differences were caused by 3 participants in the LP group with extremely high circulating hormone levels, all of which were ≥3SD above the group mean. Removal of these statistical outliers led to a decrease in mean fasting insulin and HOMA-IR in the LP diet group, and no significant difference between LP and HP groups at CID1/Baseline (P>0.05). Cardiovascular parameters full lipid profile and hs-CRP did not differ between LP and HP (all, P>0.05).

Reported food intake data at CID1/Baseline for this cohort of n=249 individuals is shown in Table 23. The assignment of participants to LP or HP groups based on their reported intake at CID3/6m resulted, as expected, in clear separation between the 2 groups at this 6 month time point. Notably the 2 diet groups were already significantly different at CID1/baseline (LP, 16.9en% protein, HP 19.7en% protein; P<0.001). The HP group in turn had a significantly lower TE intake of 9665kJ/d vs. LP (11369kJ/d), P=0.0012, and en% CHO intake compared to the LP diet group. Despite a higher total CHO intake in the LP (42en%CHO vs. HP 40en%CHO, P=0.0364) group, there was no difference in estimated GI of the diet between LP and HP at baseline. Reported en%fat was higher than expected at baseline in both LP (37.8en%fat) and HP (36.9en%fat) groups (ns), with no significant difference between the LP and HP groups.

(ii) 2-year follow-up (n=249)

(a) Dietary Intake

Figure 44 presents the food record data from all participants over the 2-year intervention, for both LP and HP diet groups. There was a significant difference in change from CID1/baseline over time for en%protein between LP and HP (diet*time, interaction P<0.001), as expected based on the pre-determined assignment to the two diet groups based on en%protein at CID3/6m (Figure 44). Reported en%protein was at its highest in the HP group and lowest in the LP group at this 6 month time point, after which the 2 groups began to converge at each subsequent CID up to 24 months. This might be hypothesised to be the result of decreased compliance to diet counselling as the trial progressed. TE intake was also lower in the HP group throughout the 2-year intervention (diet, P<0.001) and decreased in both diet groups from CID1/Baseline onwards (time, P<0.001). There was however no difference in change in TE intake from baseline between the LP and HP groups (diet*time, interaction, P>0.05) up to CID6/24m. There was however a significant difference in change from CID1/baseline over time for en%CHO between LP and HP (diet*time, interaction, P=0.0377), which as expected based on the categorisation at CID3/6m, showed the reverse relationship to en% protein with a higher CHO intake for the LP diet group throughout. However, this increase in en%CHO at CID3/6m was short-lived over time, again possibly reflecting decreased compliance to the dietary counselling, between CID3/6m and CID6/24m. Unexpectedly, GI in both diet groups was similar at CID1/Baseline but with a decrease in the HP group over time, as for en%CHO (diet, P=0.0019). Whilst there was a trend for en%fat to decrease in HP compared to LP over the 2-year intervention, this was not a significant difference between diet groups (diet*time, interaction).

(b) Anthropometric parameters

Changes in BW, BMI and WC over the 2-year intervention are shown in Figure 45, presented as the two LP and HP diet groups. Following the significant decrease in BW during the 8-week LED, there was a gradual regain from CID2 onwards in both diet groups (time, P<0.001). By the end of the 2-year weight maintenance phase at CID6/24m, approximately half of the BW lost during the 2-month LED had been regained. Contrary to the hypothesis of this thesis, there was no significant difference in the rate of BW regain between the LP and HP diet groups by CID6/24m (interaction, P=0.7247). Notably, however, in neither group had BW returned to the pre-weight loss baseline of CID1. Similar findings were observed for % change in BW, BMI and WC, which are also presented in Figure 45.

Figure 46 shows the changes in DXA-assessed body composition up to CID6/24m. Following the significant decrease in FM during the 8-week LED, there was a gradual regain from CID2 onwards for both absolute (kg) and % FM in both diet groups (time, P<0.001). In line with the BW data, there was no difference in FM change over 2 years between the LP and HP diet groups (diet, both, P>0.05). Figure 47 presents the change in android (central) FM, again showing a highly significant decrease during acute LED phase, but then a gradual rebound during the 2-year weight

maintenance phase. Again, there was no difference in rate of rebound between the LP and HP diet groups (interaction, P=0.6715). Figure 48 presents the change in absolute FFM (kg) which again decreased significantly during LED (time, P=0.0188), with rebound following start of the diet intervention at CID2/Post LED. There was no difference in rate of rebound between the LP and HP diet groups (interaction, P=0.9999) during the 2-year intervention.

Following significant loss during the LED-weight loss phase, the anthropometry data shows clear rebound in both FM (adipose) and FFM (lean) from CID2 onwards, as a result of the change to *ad lib* LP and HP diets. Notably, as for the weight loss phase where FM loss was 3x greater than FFM loss, during BW regain after CID2/Post LED FM regain was 2-3x greater than FFM regain (see Figure 46 and Figure 48). As a % of total BW, FFM increased during the 2 month LED and then gradually declined up to CID6/24m as BW and FM were regained (see Figure 48).

(c) Glycaemic parameters

Changes in FPG, 2h-PPG, $AUC_{GlucoseT0\text{-}120m}$ and Hb_{A1c} over the 2-year intervention are shown in Figure 49. Following the significant improvement FPG and Hb_{A1c} during the 8-week LED, there was a gradual worsening from CID2 onwards up to the end of the intervention at CID6/24m. In accordance with the re-gain of BW, FM and FFM there was no difference in rate of worsening in these 2 glycaemia parameters between the LP and HP diet groups (FPG: interaction, P=0.5363; HbA_{1C}: interaction, P=0.8984). Notably, however, neither FPG nor HbA_{1C} had rebounded back to the CID1/baseline levels by the end of the 2-year intervention at CID6/24m.

As the OGTT assessment was not conducted at CID2/post LED, it is not possible to determine whether there was also significant rebound from the end of the LED time point to CID3/6m for either 2h-PPG or $AUC_{GlucoseT0\text{-}120m}$, However, Figure 49 shows that there was very little rebound of 2h-PPG or $AUC_{glucoseT0\text{-}T120m}$ from CID3/6m to CID6/24m, and both were significantly lower than baseline pre-intervention levels at the end of 2-years (both, time, P<0.001). Again, there was no difference in glycaemic response between the LP and HP diet groups (2h-PPG: interaction, P=0.9172; $AUC_{GlucoseT0\text{-}T120m,}$ interaction, P=0.9111) at any time point up to CID6/24m.

Table 34 showed the number of participants who are pre-diabetic based on IFG, IGT and both vs. those with normoglycaemia. The number of those with normoglycaemia improved from 26% to 61%, this improvement was maintained over time and at CID6/24m, there was a lower percentage of 41% which is greater than those at CID1/Baseline.

Table 34: Participants are pre-diabetic based on our IFG, IGT and both criteria vs. normoglycaemia through the intervention

	CID1/Baseline	CID2/Post LED	CID3/6m	CID4/12m	CID6/24m
Total participants (n) Out of 249	IFG n=166 IGT n=88 both n=71	IFG n=103	IFG n=116 IGT n=56 both n=34	IFG n=124 IGT n=50 both n=35	IFG n=130 IGT n=52 both n=35
Pre-diabetic (n)	183	103	138	139	147
Pre-diabetic (% of total)	73%	41%	55%	56%	59%
Normoglycaemia	66 (27%)	164 (61%)	111 (45%)	110 (44%)	102 (41%)

CID, Clinical Investigation Day; LED, Low energy diet; IFG, impaired fasting glucose; IGT, impaired glucose tolerance

Figure 50 shows circulating insulin, HOMA-IR and C-Peptide changes throughout the intervention. Following the significant improvement in all 3 parameters during the 8-week LED, there was a gradual worsening from CID2/post LED to CID6/24m. Whilst a significant effect of LP and HP diet group was observed for all parameters (diet group, P=0.009, P=0.0052, P<0.001) this was due to the significantly higher CID1/baseline values in the LP group for all 3 outcome measures. Most importantly, there was no differential change over time for insulin (interaction, P=0.6327), HOMA-IR (interaction, P=0.5950) or C-Peptide (interaction, P=0.5030), and so, as observed for glucose parameters, no evidence that HP diet group prevented the gradual worsening compared to LP over the 2-year intervention.

(d) Other Metabolic parameters

Figure 51 shows the change in SBP and DBP over the 2-year intervention, with no significant difference in change over time between the LP and HP diet groups (SBP, interaction, P=0.4005; DBP, interaction, P=0.2794). Figure 52 presents other cardiovascular endpoints. There was a trend indicating that the LP diet group had a greater decrease in hs-CRP from CID1/Baseline to CID6/24m (interaction, P=0.0740), but clearly this was driven by the acute decrease during the 8-week LED phase at CID2/Post LED. This has occurred by chance and has little/no clinical relevance to the study. When calculated as change in hs-CRP from CID2/post LED to CID6/24m there was no difference between the diet groups (data not shown). The pattern of improvement during 8-week LED and rebound from CID2/Post LED to CID6/24m is observed in all lipid outcomes. There was no difference between LP and HP diet groups for TC, HDL-C, LDL-C, TG and TC:HDL ratio, as shown on Table 35. In light of the unexpected decrease trend in HDL-C during the acute weight loss LED phase (see Chapter 3), this improvement in HDL-C in the maintenance phase is notable.

Table 35: CID1/Baseline Characteristics (n=249) – Anthropometric and Metabolic outcomes

Weight maintenance ITT population	LP	HP	P value
N (%)	100 (40%)	149 (60%)	
Age (years)	46.4±10.7	49.4±10.9	0.0289
Male (n/%) Female (n/%)	22(36.0%) 78(41.5%)	39(64.0%) 110(58.5%)	
Caucasian (n/%) n=151 M/F (n/%) - out of total gender Out of total (13/61, 38/188, 20/61, 80/188)	51 (34.0%) 13 (25.5%) / 38 (74.5%) 21.3% / 20.2%	100 (66.0%) 20 (20%) / 80 (80%) 32.7% / 42.6%	
Maori/Pacific (n/%) n=77 M/F (n/%)- out of total gender Out of total (6/61, 33/188, 12/61, 26/188)	39 (50.6%) 6 (15.4%) / 33 (84.6%) 9.8% / 17.6%	38 (49.4%) 12 (31.6%) / 26 (68.4%) 19.7% / 13.8%	
Other (n/%) n=21 M/F (n/%) - out of total gender Out of total (3/61, 7/188, 7/61, 4/188)	10 (47.6%) 3 (30%) / 7 (70%) 4.9% / 3.7%	11 (52.4%) 7 (63.6%) / 4 (36.4%) 11.5% / 2.1%	
FDRS	15.1±2.7	15.1±2.8	ns
BW(kg)	106.3±20.8	107.5±23.9	ns
Height(m)	1.68±0.08	1.68±0.09	ns
BMI(kg/m2)	37.8±7.1	38.2±6.7	ns
WC(cm)	110.7±15.0	112.1±16.7	ns
FM (kg)	48.2±14.5	49.7±14.8	ns
FM (%)	46.1±7.1	47.2±6.5	ns
Android fat(kg)	4.8±1.7	4.9±1.8	ns
FFM (kg)	57.7±11.0	57.1±12.2	ns
FFM (%)	54.8±7.2	53.5±6.5	ns
Systolic BP (mmHg)	119.1±16.1	124.0±16.7	ns
Diastolic BP (mmHg)	66.8±8.7	67.6±10.2	ns
FPG(mmol/l)	5.8±0.6	5.8±0.6	ns
30 min glucose (mmol/l)	8.8±1.6	8.9±1.6	ns
60 min glucose (mmol/l)	9.2±2.3	9.4±2.3	ns
90 min glucose (mmol/l)	8.2±2.3	8.5±2.2	ns
2h-PPG(mmol/l)	7.2±1.9	7.4±1.8	ns
$AUC_{GlucoseT0\text{-}120m}$	978.1±201.4	1001.0±192.5	ns
HbA_{1C}(mmol/mol)	36.4±3.5	36.1±3.3	ns
Insulin(mU/l) -3 outliers LP$	14.0±8.2 13.2±6.8	12.0±6.5	0.0346 ns
HOMA-IR -3 outliers LP$	3.7±2.3 3.5±2.0	3.12±1.74	0.0329 ns
C-Peptide(pmol/l)	872.9±327.5	805.5±284.3	ns
hs-CRP (mg/l)	5.7±6.7	5.0±4.8	ns
TC(mmol/l)	5.2±1.0	5.4±1.1	ns
HDL-C(mmol/l)	1.3±0.2	1.3±0.3	ns
LDL-C(mmol/l)	3.4±0.9	3.4±0.8	ns
TG(mmol/l)	1.5±0.6	1.5±0.9	ns
TC:HDL ratio	4.3±1.2	4.3±1.2	ns

Mean±SD. FDRS, Finnish Diabetes Risk Score; BMI, Body Mass Index; WC, waist circumference; FM, Fat Mass; FFM, Fat Free Mass; FPG, Fasting PG; 2h-PPG, Postprandial Plasma Glucose at 2-hour timepoint; $AUC_{GlucoseT0\text{-}120}$, Area under the glucose curve time 0-120 min; HbA_{1c}, Glycated Haemoglobin; Insulin, Fasting serum insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; C-Peptide, serum connecting peptide; hs-CRP, high sensitivity C-reactive protein; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; TC:HDL ratio, Total cholesterol:high density lipoprotein ratio. $Statistical outliers were identified as individuals with circulating levels ≥3xSD of the group mean.

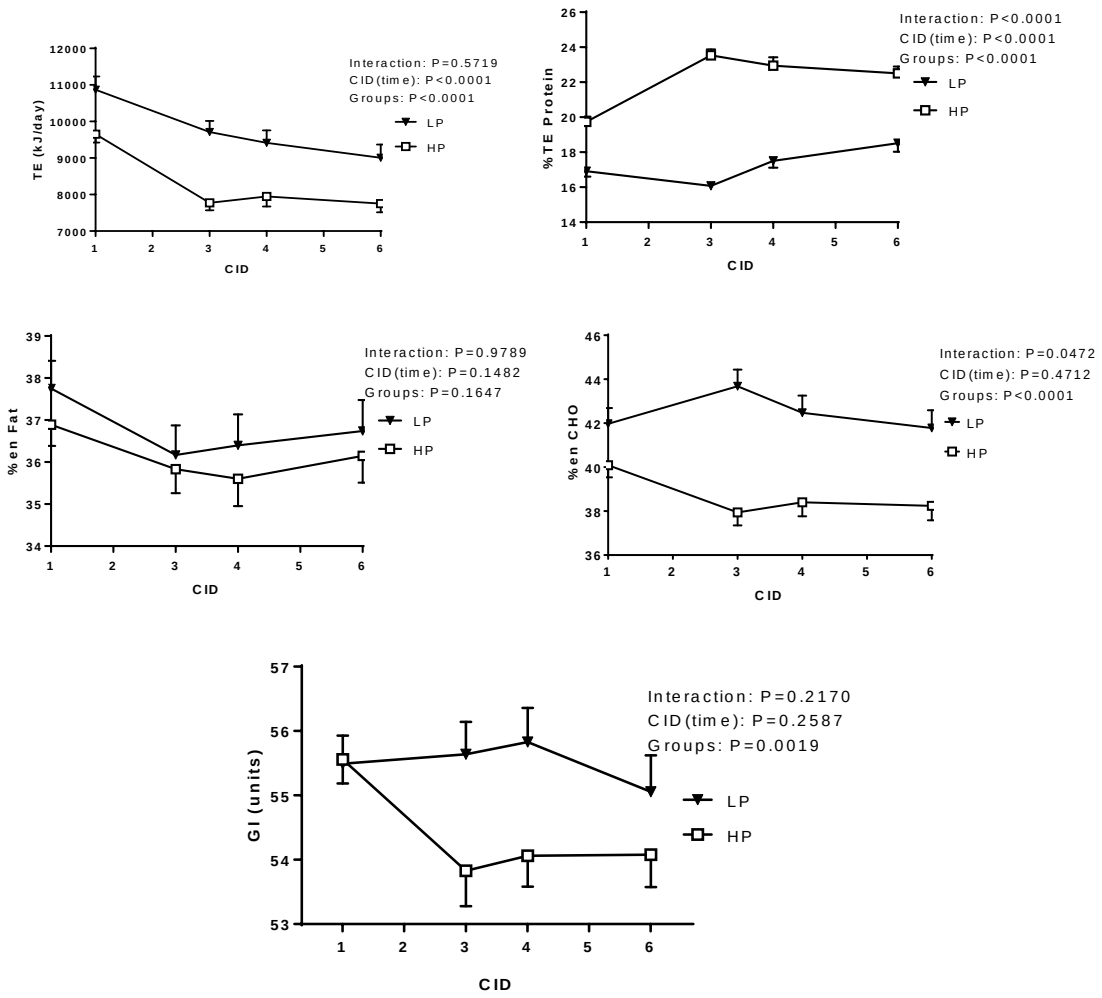


Figure 44: TE, en%protein, en%fat, en%CHO and GI between CID1/Baseline and CID6/24m

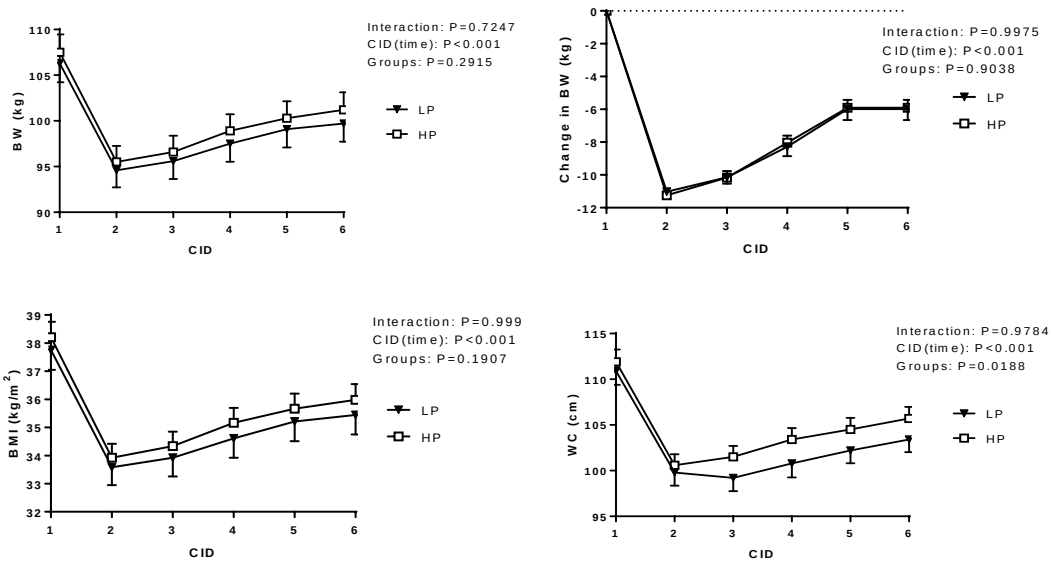


Figure 45: BW, BMI and WC between CID1/Baseline and CID6/24m

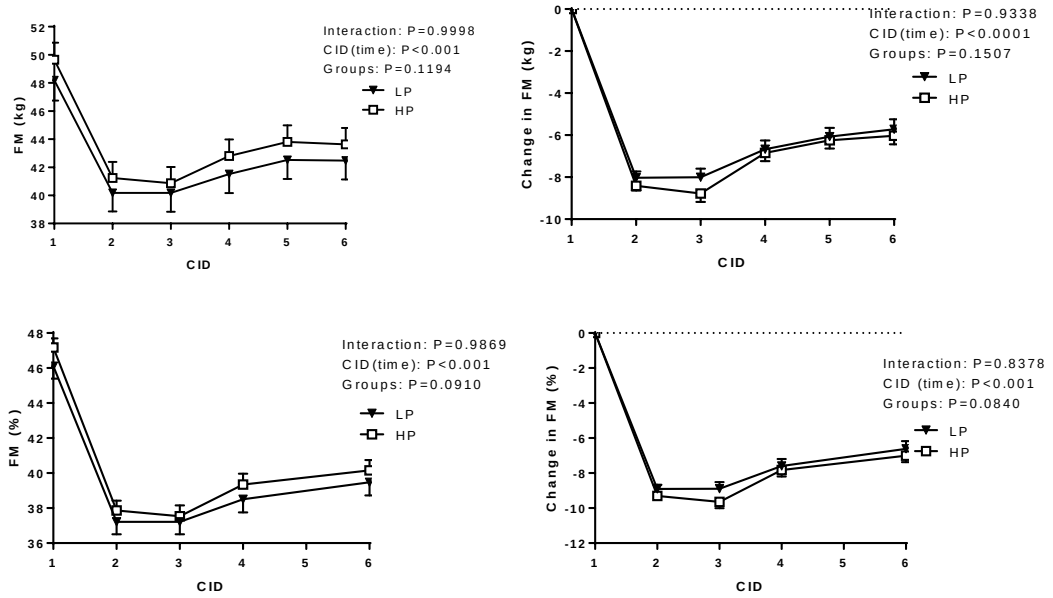


Figure 46: FM between CID1/Baseline and CID6/24m

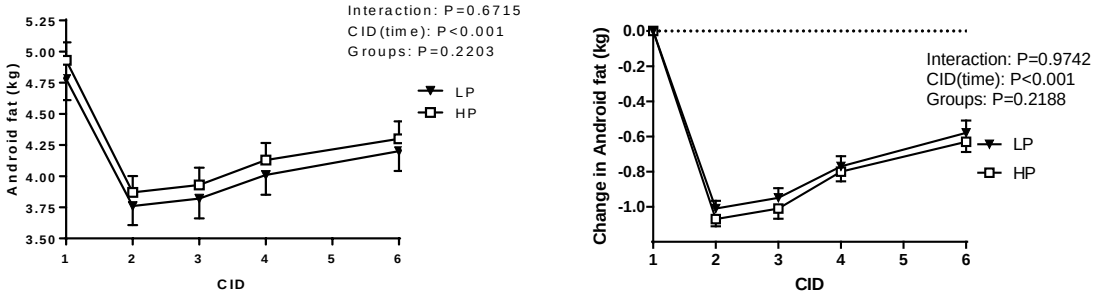


Figure 47: Android fat between CID1/Baseline and CID6/24m

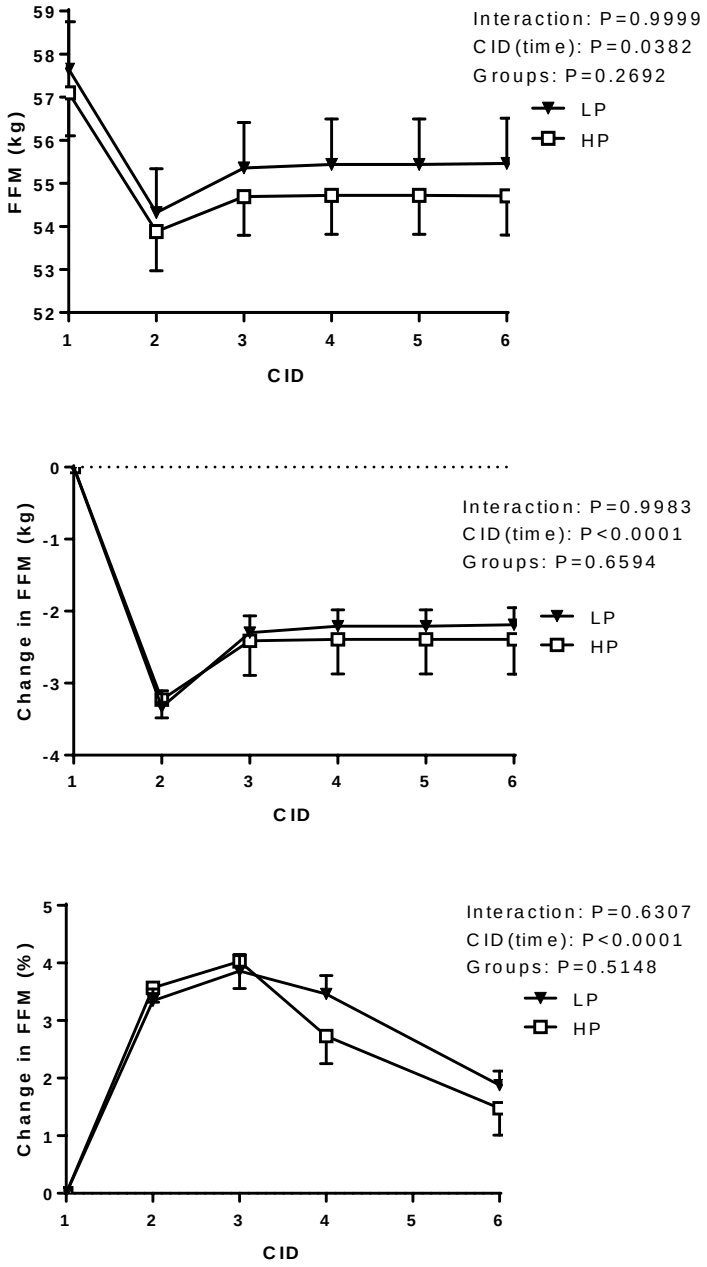


Figure 48: FFM between CID1/Baseline and CID6/24m

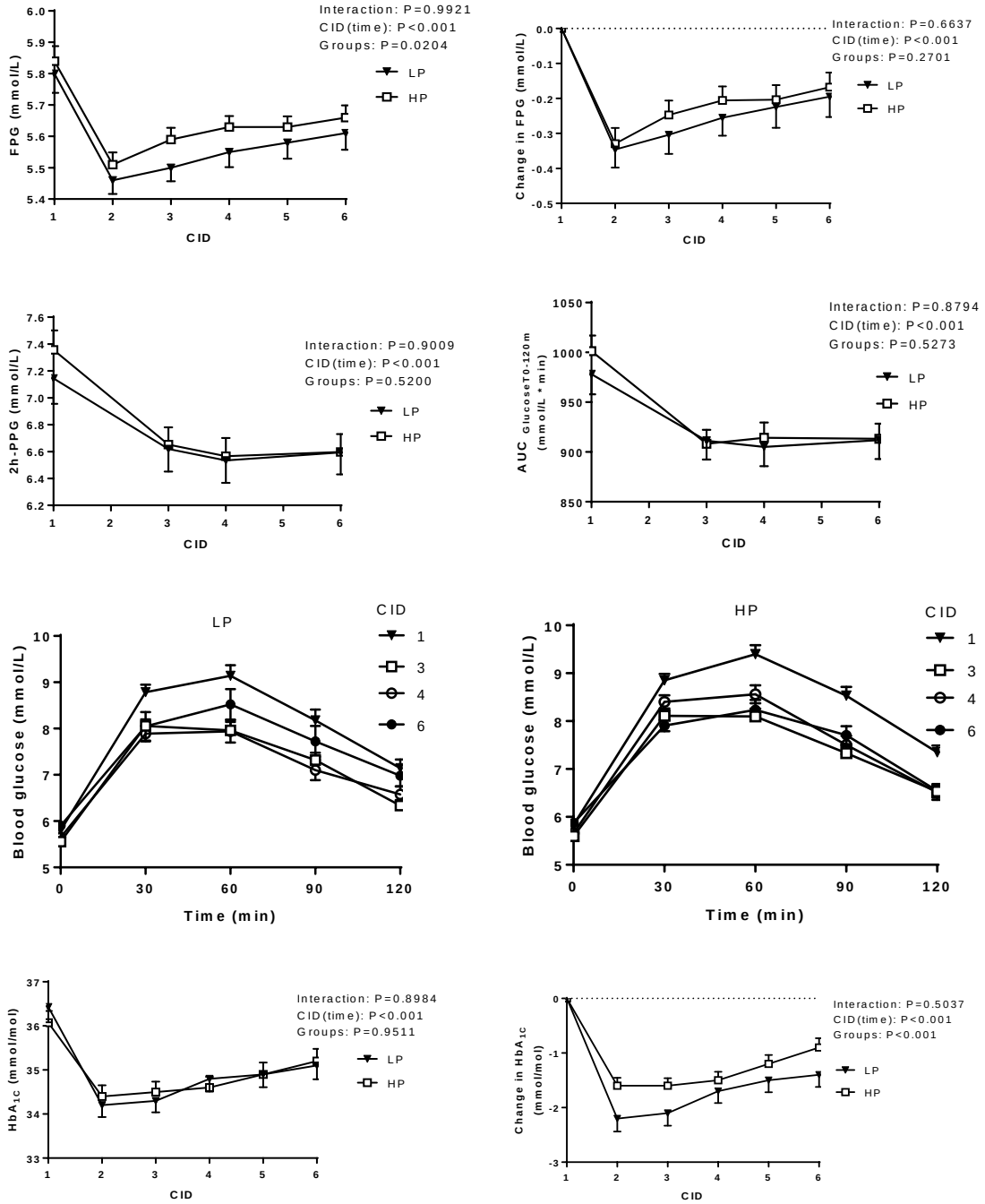


Figure 49: OGTT glucose parameters and HbA_{1C} between CID1/Baseline and CID6/24m

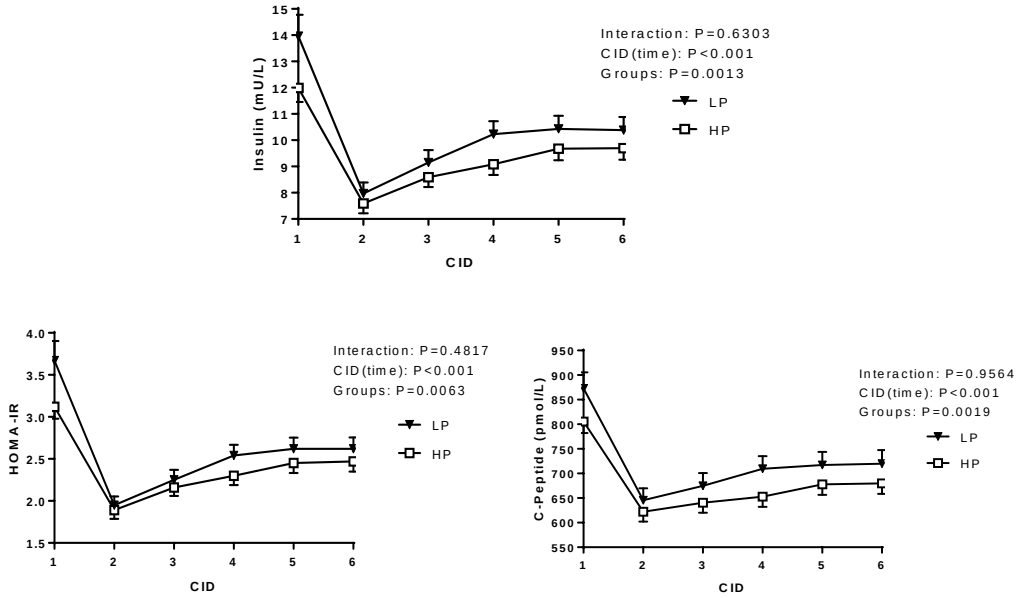


Figure 50: Insulin, HOMA-IR and C-Peptide between CID1/Baseline and CID6/24m (Insulin, HOMA-IR and C-Peptide have been plotted using ALL data)

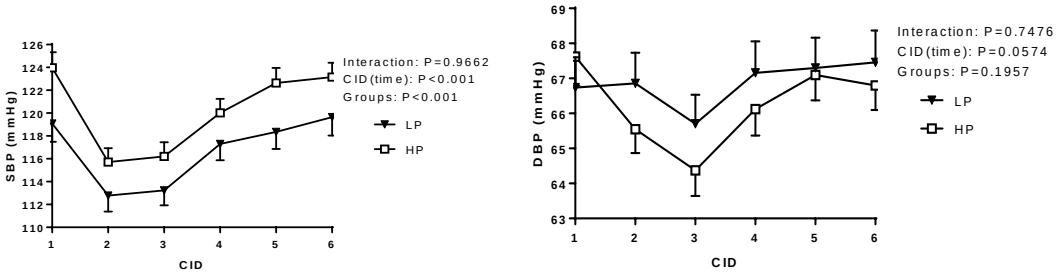


Figure 51: SBP and DBP between CID1/Baseline and CID6/24m

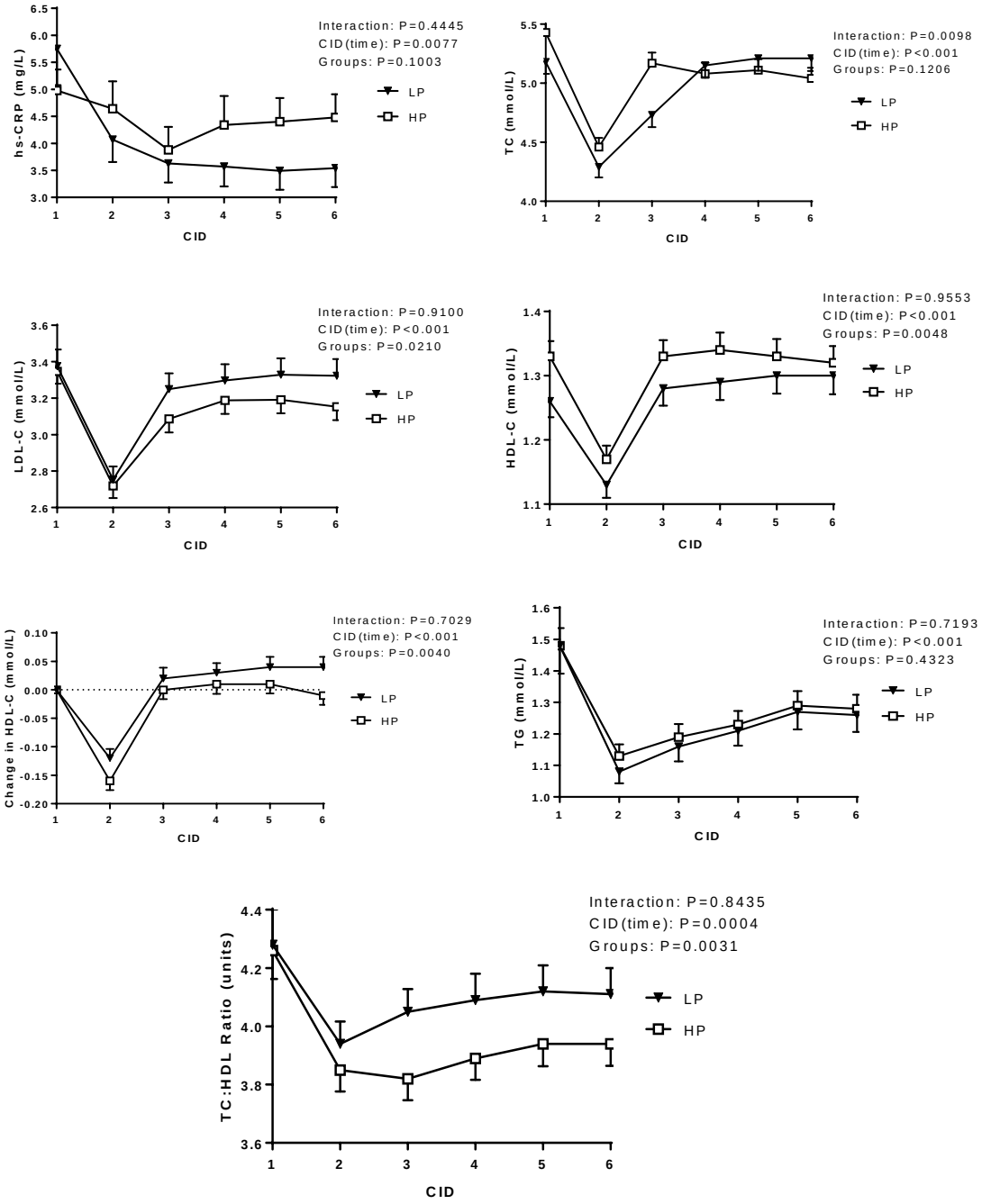


Figure 52: hs-CRP and Lipids between CID1/Baseline and CID6/24m

4.4.2 Continuous Analysis

The continuous regression analysis from 2 – 24 months (CID2/Post LED to CID6/24m) comprised of 3 approaches, which allowed a sensitivity analysis to be conducted to check the robustness of the findings: - (i) observed data with no imputation, (ii) ITT-imputation of missing data using LVCF data and (iii) ITT-multiple imputation of missing data. As noted previously, continuous analysis was performed between CID2/Post LED to CID6/24m since it was not valid to conduct statistical analyses of the observed data using a categorical model beyond CID3/6m, as diet group allocation may have changed for individuals beyond the 6 month follow up time point.

Table 36 shows attendance of all participants at all CID visits. This represents the observed data set. It is notable that attendance declined as the trial progressed.

Table 36: Number of participants for varying variables at each CID visit

Variables	CID1/Baseline	CID2/Post LED	CID3/6m	CID4/12m	CID5/18m	CID6/24m
Food record	249	n/a	169	112	n/a	59
BW (kg)	249	249	187	141	134	107
BMI (kg/m^2)	249	249	187	141	134	107
WC (cm)	249	249	187	141	134	107
FM (kg)	249	249	180	119	n/a	71
FM (%)	249	249	180	119	n/a	71
Android fat (kg)	249	249	180	119	n/a	71
FFM (kg)	249	249	180	119	n/a	71
FFM (%)	249	249	180	119	n/a	71
SBP (mmHg)	249	249	186	119	128	107
DBP (mmHg)	249	249	186	119	128	107
FPG (mmol/l)	249	249	186	119	128	107
2h-PPG (mmol/l)	249	n/a	186	116	n/a	101
$AUC_{GlucoseT0\text{-}120m}$	249	n/a	186	116	n/a	101
HbA_{1C} (mmol/mol)	249	246	177	119	128	107
Insulin (mU/l)	249	246	177	119	128	107
HOMA-IR	249	246	177	119	128	107
C-Peptide (pmol/l)	249	246	177	119	128	107
hs-CRP (mg/l)	249	246	177	119	128	107
TC (mmol/l)	249	246	177	119	128	107
HDL-C (mmol/l)	249	246	177	119	128	107
LDL-C (mmol/l)	249	246	177	119	128	107
TG (mmol/l)	249	246	177	119	128	107
TC:HDL ratio	249	246	177	119	128	107

N; number of participants. n/a, no assigned clinic visit; BW, Body weight; BMI, Body Mass Index; WC, waist circumference; FM, Fat Mass; FFM, Fat Free Mass; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting Plasma Glucose; 2h-PPG, Postprandial Plasma Glucose at 2-hour timepoint; $AUC_{GlucoseT0\text{-}120m}$, Area under the glucose curve time 0-120 min; HbA_{1c}, Glycated Haemoglobin; Insulin, Fasting serum insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; C-Peptide, serum connecting peptide; hs-CRP, high sensitivity C-reactive protein; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; TC:HDL ratio, Total cholesterol:high density lipoprotein ratio

4.4.2.1 Observed data

Table 37 presents the continuous regression analysis of the observed data set, showing the association between change in estimated en%protein intake (predictor variable), from CID2/Post LED to CID6/24m, and change in diet, anthropometric and metabolic outcome variables. Data were analysed both (i) unadjusted and (ii) adjusted for 3 potential confounders CID1/Baseline value, gender and ethnicity since these were factors of interest in this thesis. The beta coefficient is presented as the degree of changes in the outcome variable (e.g. BW) for every 1 unit of change in the continuous predictor variable (e.g. en%protein) or category change for the categorical variables (e.g. gender – Male or Female; ethnicity – Caucasian, Maori/Pacific or Other).

i. Unadjusted model

Table 37 presents dietary treatment as 'en%protein', and change over time from CID2/Post LED, measured repeatedly at 6, 12 and 24 months as 'visit 12m vs. 6m' and 'visit 24m vs 6m', respectively. Hence change in outcome variable from CID2/Post LED to CID3/6m was compared with change from CID2/Post LED to CID4/12m and change from CID2/Post LED to CID6/24m.

Simple linear regression equation

Y	=	b_0 (e.g. BW)	+	b_1X_1 (e.g. en%protein)
Outcome/dependent variable Coefficient, SE (P value)	=	(exposure variable)	+	(risk factor/ independent variable)

The regression analysis for the unadjusted dataset (coefficient, SE) showed that, as expected based on the diet counselling advice, an increase in 1en%protein was significantly associated with a lower dietary GI of -0.333 (0.059) units (P<0.001). Unexpectedly, it was not significantly associated with a lower reported TE (24.88, 33.396kJ/d; P=0.4572). However, an increase in 1en%protein was significantly associated with a reduction in BW of -0.098 (0.031) kg, (P=0.0020) and BMI of -0.029 (0.011) kg/m^2, (P=0.0096). An increase, for example, from 15en% to 25en% dietary protein as per the PREVIEW diet counselling advice (equivalent to +10en%protein) was associated with ~1kg lower BW and ~0.3kg/m^2 lower BMI. There was however no significant association between en%protein and change in any of WC, absolute FM, android fat, absolute FFM and %FFM, but a significant association with change in %FM, where an increase in 1en%protein was associated with -0.062 (0.027) % decrease in FM (P=0.0223). There was also no significant association with change in SBP, DBP, or any other the glycaemic endpoints including FPG, 2h-PPG, $AUC_{GlucoseT0\text{-}120m}$, HbA_{1C}, Insulin and HOMA-IR; other than a trend for decreased C-Peptide of -2.854 (1.497) pmol/l, (P=0.0582). There was also no significant relationship between en%protein and change in CVD related endpoints, including hs-CRP, TC, LDL-C, TG, other than HDL-C where an increase in 1en%protein was positively correlated with an increase of 0.004 (0.002) mmol/l, (P=0.0178), and decrease in TC:HDL ratio of -0.015 (0.004) units (P=0.0007). Here a 10en% increase in dietary protein intake as per diet counselling was association with improved HDL-C of 0.04mmol/l and TC:HDL ratio of -0.15 units.

Change in the outcome variable over time from CID2/Post LED measured repeatedly at 6(CID3/6m), 12(CID4/12m) and 24(CID6/24m) months, is also presented in Table 37. Some data were not collected at CID2/Post LED (diet records, OGTT) and so the regression analysis was conducted as change from CID1/Baseline. In this unadjusted model, there was no significant effect of time on TE, i.e. after the initial decrease in TE during the first 6 months of the intervention between CID1/Baseline and CID3/6m (shown clearly in the categorical analysis), there was no further decrease or rebound in energy intake at CID4/12m (134, 362kJ/day; P=0.7103) or CID6/24m (-432, 625kJ/day; P=0.4914). This was also observed for reported GI. There was no significant change in GI over time, hence no difference between change from CID1/Baseline to CID4/12m (P=0.1872) and CID6/24m (P=0.7306) compared to CID3/6m. However, BW, BMI and all body composition parameters other than FFM did increase over time due to rebound during the maintenance phase; commonly with a greater worsening by CID4/12m and CID6/24m compared to the change from CID2/Post LED to CID3/6m (all, P<0.01). This resulted in turn in significant worsening in many of the glycaemic-related parameters, e.g. insulin, HOMA-IR and C-Peptide at both CID4/12m and CID6/24m compared with change from CID2/Post LED to CID3/6m (all, P<0.01). FPG also increased over time from the low values observed at CID2/Post LED, with higher circulating glucose at CID4/12m compared to CID3/6m (0.105, 0.041mmol/l, P=0.0121), and a trend for continued worsening up to CID6/24m (0.139, 0.083mmol/l, P=0.0965). Since the OGTT was not conducted at CID2/Post LED, the regression analysis was conducted as change from CID1/Baseline.

The unadjusted model showed no significant change in 2h-PPG over time, hence no worsening at CID4/12m (P=0.6234) or CID6/24m (0.2285) when compared to the initial decrease from CID1/Baseline at CID3/6m. Change in AUC was also not significantly different between CID4/12m (P=0.8041) and CID6/24m (0.1165) when compared to the initial decrease from baseline at CID3/6m. All of the various CVD parameters showed some worsening over time beyond CID3/6m, with significant changes at either CID4/12m or CID6/24m when compared with change from CID2/Post LED to CID3/6m (all, P<0.01).

ii. Adjusted model

Table 37 presents dietary treatment as ‘en%protein’, and change over time to year-1 (CID4/12m) and year-2 (CID6/24m) as ‘visit 12m vs. 6m’ and ‘visit 24m vs. 6m’, respectively. In addition, 3 potential confounding variables were investigated, including baseline value shown as ‘Baseline’, gender shown as ‘Male vs. Female’, and ethnicity shown as ‘Maori/Pacific vs. Caucasians’ and ‘Other vs. Caucasian’. In each case, the multiple regression model produced an estimate of the association between the outcome variable (e.g. BW) and predictor en%protein intake that accounted for the differences due to baseline values, gender and ethnicity.

Multiple linear regression equation

Y	=	b_0 (e.g. BW)	+	b_1X_1 (e.g. en%protein)
Outcome/dependent variable Coefficient, SE (P value)	=	(exposure variable)	+	(risk factor/ independent variable)

+ b_2X_2 (e.g. baseline BW) + b_3X_3 (e.g. gender) b_4X_4 (e.g. ethnicity)

+ (continuous variable) + potential confounders (yes/no)

After the dataset was adjusted for CID1/Baseline value, gender and ethnicity, there were clear relationships between en%protein and both dietary parameters TE and GI, when analysed for all data across all time points. For each 1en%protein increase GI decreased by -0.37(0.053) units (P<0.001) and TE also decreased by -120 (30.73) kJ/day (P=0.001). Notably, there was a significant interaction between en%protein and duration of the intervention for TE (diet*time, interaction, P<0.001), but not for GI. The adjusted (interaction) regression for TE identified baseline TE and ethnicity as significant confounders. There was a significantly higher TE intake in Maori/Pacific than Caucasian (971, 359 kJ/day; P=0.0075), and there was a similar non-significant trend for male vs. female (591, 347 kJ/day; 0=0.090).

In turn, there was a consistent association showing an increase in 1en%protein was significantly associated with a reduction in BW of -0.091(0.031)kg, (P=0.0042) and BMI of -0.028(0.011)kg/m2, (P=0.0136); again confirming the primary hypothesis of this thesis. BW loss is likely to be due to the lower TE intake of the HP diet, as presented above. Notably, both coefficients for BW and BMI were lower after adjustment for baseline, gender and ethnicity compared with the unadjusted model, hence part of the association between these BW, BMI and en% protein was explained by the confounders. The adjusted analysis also presents data for change over time, where there was an overall increase in BW over 2 years from CID2/Post LED onwards (P<0.001). The protective effect of dietary protein for BW maintenance in this adjusted model was small (again, +10en%protein was associated with ~1kg lower BW), and overall there was an increase in change in BW from CID3/6m to CID4/12m, of 3.526(0.399) kg, (P<0.001) and from CID3/6m to CID6/24m of 8.102(0.726) kg, (P<0.001). Also, a gain in BMI of 1.272(0.141) kg/m^2, (P<0.001); and 2.854(0.244) kg/m^2, (P<0.001), respectively. Adjusting for baseline BW and BMI did not significantly alter the model, i.e. did not show confounding effects. Gender also did not show significant confounding effects for BW (P=0.1544) or BMI (P=0.2314), with no difference between men and women in relationship between en%protein and BW or BMI. Ethnicity however did influence the model with significantly greater BW gain of 3.064(0.86) kg (P<0.001) in Maori/Pacific than Caucasian, and hence also a greater increase in BMI of 1.003(0.311) kg/m^2, (P=0.0015).

Again, in the adjusted model as for unadjusted, there was no significant association between change in en%protein and any anthropometric outcomes of WC, absolute FM, android fat, absolute FFM and %FFM, but a trend towards a significant association with %FM where an increase in 1en%protein was associated with -0.05(0.027)% decrease in FM (P=0.0724). Based on the PREVIEW recommendations of 10en% increase in protein intake, this was equivalent

to -0.5%FM loss. Again, ethnicity contributed as a confounder in this model, such that Maori/Pacific had higher %FM gain of 2.152(0.703)% (P=0.0026) than Caucasian. Baseline %FM and gender did not show significant confounding effects.

There was also no significant association of en% protein intake with SBP, DBP, or any of the glycaemic endpoints including FPG (P=0.7872), 2h-PPG (P=0.3007), $AUC_{GlucoseT0\text{-}120m}$ (P=0.3580), HbA_{1C} (P=0.7525), Insulin (P=0.2373), and HOMA-IR (P=0.2412) in the adjusted model. The trend for a negative association between en%protein and C-Peptide in the unadjusted model was lost when the model was adjusted for baseline value, gender and ethnicity.

There was also no significant association between en%protein and many of the CVD related endpoints, including hs-CRP, TC, LDL-C and TG. However, in the adjusted as for the unadjusted model, an increase in 1en%protein was positively correlated with an increase in the CVD-protective cholesterol fraction HDL-C of 0.0004(0.002)mmol/l, (P=0.0228). Baseline values, gender and ethnicity were all significant confounders in the model with baseline contributing -0.139 (0.061)mmol/l (P=0.0232), male contributing -0.077 (0.033)mmol/l (P=0.0214) relative to female, and Maori/Pacific contributing -0.079 (0.034)mmol/l (P=0.0199) relative to Caucasian. All of these confounders resulted in an adverse decrease in HDL-C. Also in the adjusted model, an increase of 1en%protein was associated with -0.015(0.004)mmol/l decrease in TC:HDL ratio, again a protective effect for CVD. There was a strong effect of time in the adjusted model however, with the change from CID2/Post LED to CID4/12m (0.186, 0.059 units; P=0.002) and CID6/24, (0.315, 0.091 units; P=0.001) significantly worsening the ratio vs. change to CID3/6m. Confounders in the adjusted model acting in opposite directions were baseline TC:HDL ratio (-0.174, 0.047 units; P<0.001) and male gender (0.210, 0.088 units; P=0.0176).

Interaction

In the multivariate regression analysis, only 2 outcome variables showed a significant interaction between en%protein and duration of the intervention (diet*time, interaction).

Table 37: Multiple regression analysis of dietary, anthropometric and metabolic outcome variables presented as change from 2 month CID2/Post LED over the 24-month weight maintenance phase: unadjusted and adjusted (baseline, gender, ethnicity) model – observed data

Variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value	Adjusted model (interaction) (SE)	P value
Δ$GI (units)						
-en%protein	-0.333(0.059)	<0.001	-0.37(0.053)	<0.001		
-visit 12m vs. 6m	0.778(0.587)	0.1872	0.815(0.578)	0.1603		
-visit 24m vs. 6m	-0.401(1.164)	0.7306	-0.854(0.989)	0.3888		
-Baseline GI			-0.851(0.078)	<0.001		
-Male vs. Female			0.397(0.795)	0.6183		
-Maori/Pacific vs. Caucasian			1.881(0.873)	0.0325		
-Other vs. Caucasian			2.619(1.311)	0.0472		
Δ$TE (kJ/d)						
-en%protein	24.88(33.396)	0.4572	-10.416(25.666)	0.6853	-120.353(30.731)	<0.001
-12m vs. 6m	134.8(362)	0.7103			-6685.36(1144.43)	<0.001
-24m vs. 6m	-431(625)	0.4914			-5414.53(1904.3)	<0.001
-Baseline TE					-0.795(0.047)	<0.001
- Male vs. Female					591.816(347.237)	0.090
-Maori/Pacific vs. Caucasian					971.883(359.769)	0.0075
-Other vs. Caucasian					248.419(545.326)	0.6493
ΔBW (kg)						
-en%protein	-0.098(0.031)	0.0020	-0.091(0.031)	0.0042		
-visit 12m vs. 6m	3.557(0.4)	<0.001	3.526(0.399)	<0.001		
-visit 24m vs. 6m	8.131(0.719)	<0.001	8.102(0.726)	<0.001		
-Baseline BW			0.007(0.019)	0.6980		
-Male vs. Female			1.215(0.849)	0.1544		
-Maori/Pacific vs. Caucasian			3.064(0.86)	<0.001		
-Other vs. Caucasian			0.527(1.28)	0.6809		
ΔBMI (kg/m^2)						
-en%protein	-0.029(0.011)	0.0096	-0.028(0.011)	0.0136		
-visit 12m vs. 6m	1.284(9.141)	<0.001	1.272(0.141)	<0.001		
-visit 24m vs. 6m	2.868(0.242)	<0.001	2.854(0.244)	<0.001		
-Baseline BMI			0.022(0.022)	0.3275		
-Male vs. Female			0.358(0.298)	0.2314		
-Maori/Pacific vs. Caucasian			1.003(0.311)	0.0015		
-Other vs. Caucasian			0.197(0.463)	0.6704		

Variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value	Adjusted model (interaction) (SE)	P value
ΔWC (cm)						
-en%protein	-0.042(0.06)	0.4866	-0.032(0.061)	0.5992		
-visit 12m vs. 6m	2.81(0.767)	0.0003	2.72(0,772)	<0.001		
-visit 24m vs. 6m	8.044(1.039)	<0.0001	7.891(1.031)	<0.001		
-Baseline WC			-0.087(0.033)	0.0099		
-Male vs. Female			1.31(1.103)	0.2366		
-Maori/Pacific vs. Caucasian			0.552(1.12)	0.6230		
-Other vs. Caucasian			-2.514(1.676)	0.1356		
ΔFM (kg)						
-en%protein	-0.033(0.031)	0.2977	-0.013(0.032)	0.6946		
-visit 12m vs. 6m	3.749(0.379)	<0.0001	3.737 (0.372)	<0.001		
-visit 24m vs. 6m	8.031(1.151)	<0.0001	8.267(1.213)	<0.001		
-Baseline FM kg			-0.035(0.024)	0.1485		
-Male vs. Female			-0.151(0.738)	0.8380		
-Maori/Pacific vs. Caucasian			2.681(0.744)	<0.001		
-Other vs. Caucasian			1.268(1.125)	0.2613		
ΔFM (%)						
-en%protein	-0.062(0.027)	0.0223	-0.05(0.027)	0.0724		
-visit 12m vs. 6m	3.742(0.341)	<0.0001	3.73(0.338)	<0.001		
-visit 24m vs. 6m	6.962(0.601)	<0.0001	7.043(0.619)	<0.001		
-Baseline FM %			-0.036(0.051)	0.4889		
-Male vs. Female			-0.163(0.852)	0.8486		
-Maori/Pacific vs. Caucasian			2.152(0.703)	0.0026		
-Other vs. Caucasian			1.101(1.077)	0.3080		
ΔAndroid fat (kg)						
-en%protein	-0.005(0.003)	0.1183	-0.003(0.003)	0.2817		
-visit 12m vs. 6m	0.427(0.043)	<0.0001	0.422(0.043)	<0.001		
-visit 24m vs. 6m	0.893(0.088)	<0.0001	0.919(0.09)	<0.001		
-Baseline Android fat			0.008(0.025)	0.7334		
-Male vs. Female			0.072(0.086)	0.4025		
-Maori/Pacific vs. Caucasian			0.387(0.088)	<0.001		
-Other vs. Caucasian			0.112(0.135)	0.4078		

Variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value	Adjusted modelP value (interaction) (SE)
ΔFFM (kg)					
-en%protein	-0.016(0.016)	0.3371	-0.017(0.016)	0.3025	
-visit 12m vs. 6m	-0.154(0.186)	0.4087	-0.151(0.186)	0.4176	
-visit 24m vs. 6m	0.286(0.282)	0.3114	0.283(0.283)	0.3196	
-Baseline FFM kg			0.019(0.021)	0.3637	
-Male vs. Female			0.829(0.471)	0.0802	
-Maori/Pacific vs. Caucasian			0.324(0.372)	0.3840	
-Other vs. Caucasian			0.051(0.521)	0.9219	
ΔFFM (%)					
-en%protein	-0.01(0.015)	0.4830	-0.013(0.015)	0.3898	
-visit 12m vs. 6m	0.110(0.131)	0.4024	0.111(0.131)	0.4003	
-visit 24m vs. 6m	0.623(0.365)	0.0900	0.645(0.375)	0.0874	
-Baseline FFM (%)			-0.026(0.024)	0.2848	
-Male vs. Female			1.223(0.391)	0.1544	
-Maori/Pacific vs. Caucasian			3.064(0.86)	0.0021	
-Other vs. Caucasian			0.138(0.508)	0.7865	
ΔSBP (mmHg)					
-en%protein	-0.098(0.132)	0.456	-0.056(0.121)	0.6433	
-visit 12m vs. 6m	6.482(1.491)	<0.0001	5.649(1.437)	<0.001	
-visit 24m vs. 6m	12.002(2.53)	<0.0001	12.059(2.533)	<0.001	
-Baseline SBP			-0.479(0.054)	<0.001	
-Male vs. Female			2.077(1.951)	0.2886	
-Maori/Pacific vs. Caucasian			-1.185(2.015)	0.5573	
-Other vs. Caucasian			2.404(2.992)	0.4228	
ΔDBP (mmHg)					
-en%protein	-0.042(0.072)	0.5625	-0.081(0.068)	0.2347	
-visit 12m vs. 6m	2.937(0.802)	0.0003	2.62(0.786)	0.0010	
-visit 24m vs. 6m	3.508(1.416)	0.0141	2.99(1.299)	0.0225	
-Baseline DBP			-0.427(0.056)	<0.001	
-Male vs. Female			2.287(1.138)	0.0461	
-Maori/Pacific vs. Caucasian			-1.365(1.167)	0.2438	
-Other vs. Caucasian			5.11(1.748)	0.0039	

Variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value	Adjusted modelP value (interaction) (SE)
ΔFPG (mmol/l)					
-en%protein	0.001(0.004)	0.7726	0.001(0.004)	0.7827	
-visit 12m vs. 6m	0.105(0.041)	0.0121	0.088(0.04)	0.0308	
-visit 24m vs. 6m	0.139(0.083)	0.0965	0.121(0.083)	0.1459	
-Baseline FPG			-0.517(0.043)	<0.001	
-Male vs. Female			0.086(0.06)	0.1543	
-Maori/Pacific vs. Caucasian			0.005(0.061)	0.9288	
-Other vs. Caucasian			0.047(0.093)	0.6130	
Δ2h-PPG (mmol/l)					
-en%protein	0.009(0.013)	0.4863	0.011(0.01)	0.3007	
-visit 12m vs. 6m	-0.092(0.187)	0.6234	-0.036(0.172)	0.8336	
-visit 24m vs. 6m	0.302(0.25)	0.2285	0.286(0.243)	0.2400	
-Baseline 2h-PPG			-0.538(0.041)	<0.001	
-Male vs. Female			-0.149(0.182)	0.4130	
-Maori/Pacific vs. Caucasian			-0.001(0.194)	0.9965	
-Other vs. Caucasian			0.042(0.277)	0.8810	
$\Delta AUC_{GlucoseT0\text{-}120m}$					
-en%protein	0.446(1.337)	0.7393	1.118(1.213)	0.3580	
-visit 12m vs. 6m	4.242(17.08)	0.8041	9.206(16.81)	0.5847	
-visit 24m vs. 6m	41.867(26.54)	0.1165	48.952(26.783)	0.0694	
-Baseline $AUC_{GlucoseT0\text{-}120m}$			-0.428(0.046)	<0.001	
-Male vs. Female			12.18(21.33)	0.5688	
-Maori/Pacific vs. Caucasian			20.62(22.28)	0.3559	
-Other vs. Caucasian			42.48(32.38)	0.1914	
ΔHbA_{1c} (mmol/mol)					
-en%protein	-0.004(0.016)	0.7802	-0.005(0.015)	0.7525	
-visit 12m vs. 6m	0.254(0.178)	0.1545	0.283(0.178)	0.1140	
-visit 24m vs. 6m	1.306(0.392)	0.0011	1.348(0.393)	0.0008	
-Baseline HbA_{1c}			-0.183(0.036)	<0.001	
-Male vs. Female			0.237(0.261)	0.3647	
-Maori/Pacific vs. Caucasian			0.626(0.264)	0.0189	
-Other vs. Caucasian			0.028(0.404)	0.9447	

Variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value	Adjusted model (interaction) (SE)	P value
ΔInsulin (mIU/L)						
-en%protein	-0.04(0.028)	0.1538	-0.032(0.027)	0.2373		
-visit 12m vs. 6m	1.247(0.312)	<0.001	1.245(0.309)	<0.001		
-visit 24m vs. 6m	2.107(0.606)	0.0006	2.143(0.613)	0.0006		
-Baseline Insulin			-0.303(0.069)	<0.001		
-Male vs. Female			-0.231(0.615)	0.7080		
-Maori/Pacific vs. Caucasian			1.054(0.621)	0.0915		
-Other vs. Caucasian			1.024(0.968)	0.2917		
ΔHOMA-IR						
-en%protein	-0.011(0.007)	0.1499	-0.008(0.007)	0.2412		
-visit 12m vs. 6m	0.354(0.087)	<0.0001	0.354(0.087)	<0.001		
-visit 24m vs. 6m	0.579(0.169)	0.0007	0.579(0.169)	0.0005		
-Baseline HOMA-IR			-0.008(0.007)	0.2412		
-Male vs. Female			-0.032(0.168)	0.8468		
-Maori/Pacific vs. Caucasian			0.246(0.169)	0.1474		
-Other vs. Caucasian			0.365(0.264)	0.1688		
ΔC-Peptide (pmol/l)						
-en%protein	-2.854(1.497)	0.0582	-2.078(1.445)	0.1521		
-visit 12m vs. 6m	46.289(16.936)	0.0069	44.878(16.524)	0.0073		
-visit 24m vs. 6m	111.923(30.853)	0.0004	111.481(31.731)	0.0006		
-Baseline C-Peptide			-0.209(0.054)	0.0002		
-Male vs. Female			-7.305(27.681)	0.7922		
-Maori/Pacific vs. Caucasian			84.313(28.094)	0.0031		
-Other vs. Caucasian			24.344(42.978)	0.5718		
Δhs-CRP (mg/l)						
-en%protein	0.011(0.045)	0.8055	0.045(0.037)	0.2224		
-visit 12m vs. 6m	0.407(0.653)	0.5341	0.253(0.632)	0.6901		
-visit 24m vs. 6m	1.256(0.677)	0.0651	1.352(0.661)	0.0425		
-Baseline hs-CRP			-0.667(0.046)	<0.001		
-Male vs. Female			-0.896(0.57)	0.1179		
-Maori/Pacific vs. Caucasian			0.075(0.577)	0.8965		
-Other vs. Caucasian			-0.67(0.882)	0.4483		

Variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value	Adjusted model (interaction) (SE)	P value
ΔTC (mmol/l)						
-en%protein	-0.001(0.007)	0.8772	-0.003(0.006)	0.6509		
-visit 12m vs. 6m	0.229(0.083)	0.0064	0.211(0.083)	0.0119		
-visit 24m vs. 6m	0.137(0.116)	0.2380	0.059(0.661)	0.6020		
-Baseline TC			-0.219(0.054)	<0.001		
-Male vs. Female			0.003(0.105)	0.9786		
-Maori/Pacific vs. Caucasian			-0.265(0.111)	0.0181		
-Other vs. Caucasian			-0.315(0.171)	0.0669		
ΔHDL-C (mmol/l)						
-en%protein	0.004(0.002)	0.0178	0.004(0.002)	0.0228	0.004(0.002)	0.1359
-visit 12m vs. 6m	0.001(0.022)	0.9619			0.165(0.063)	0.3436
-visit 24m vs. 6m	-0.069(0.029)	0.0199			0.059(0.095)	0.1934
-Baseline HDL-C					-0.132(0.061)	0.0317
-Male vs. Female					-0.079(0.033)	0.0192
-Maori/Pacific vs. Caucasian					-0.078(0.034)	0.0226
-Other vs. Caucasian					-0.031(0.051)	0.5396
ΔLDL-C (mmol/l)						
-en%protein	-0.001(0.005)	0.8755	-0.002(0.005)	0.7542		
-visit 12m vs. 6m	0.180(0.068)	0.0089	0.165(0.063)	0.0158		
-visit 24m vs. 6m	0.128(0.095)	0.1811	0.059(0.095)	0.5351		
-Baseline LDL-C			-0.197(0.052)	<0.001		
-Male vs. Female			0.0056(0.085)	0.5100		
-Maori/Pacific vs. Caucasian			-0.175(0.09)	0.0539		
-Other vs. Caucasian			-0.276(0.14)	0.0506		
ΔTG (mmol/l)						
-en%protein	-0.004(0.003)	0.2868	-0.004(0.003)	0.3061		
-visit 12m vs. 6m	0.079(0.037)	0.0326	0.076(0.036)	0.0379		
-visit 24m vs. 6m	0.195(0.076)	0.0107	0.193(0.075)	0.0114		
-Baseline TG			-0.175(0.07)	0.0127		
-Male vs. Female			0.025(0.066)	0.7113		
-Maori/Pacific vs. Caucasian			0.006(0.067)	0.9272		
-Other vs. Caucasian			0.022(0.102)	0.8265		

Variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value	Adjusted modelP value (interaction) (SE)
ΔTC:HDL ratio					
-en%protein	-0.015(0.004)	0.0007	-0.015(0.004)	0.0007	
-visit 12m vs. 6m	0.201(0.059)	0.0009	0.186(0.059)	0.0020	
-visit 24m vs. 6m	0.361(0.089)	<0.0001	0.315(0.091)	0.0007	
-Baseline TC:HDL			-0.174(0.047)	<0.001	
-Male vs. Female			0.21(0.088)	0.0176	
-Maori/Pacific vs. Caucasian			-0.038(0.09)	0.6737	
-Other vs. Caucasian			-0.054(0.139)	0.6737	

Δ, Change in outcome variable from CID2/Post LED. [$]Where variables were not measured at CID2/Post LED (e.g. diet records, OGTT glucose), change was calculated from CID1/Baseline. BW, body weight; BMI, Body Mass Index; WC, waist circumference; FM, Fat Mass; FFM, Fat Free Mass; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting Plasma Glucose; 2h-PPG, Postprandial Plasma Glucose at 2-hour timepoint; $AUC_{GlucoseT0\text{-}120m}$, Area under the glucose curve time 0-120 min; HbA_{1c}, Glycated Haemoglobin; Insulin, Fasting serum insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; C-Peptide, serum connecting peptide; hs-CRP, high sensitivity C-reactive protein; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; TC:HDL ratio, Total cholesterol:high density lipoprotein ratio; TE, Total Energy 4 day diet record; GI, Glycaemic Index

Using continuous analysis of the observed data, the interaction between en%protein calculated from the 4-day food record and CID visits from CID1/Baseline to CID6/24m visit is summarised on Table 38. The summary table showed a significant interaction (diet*time) for change in HDL-C (P=0.0248) and TE (P<0.001).

Table 38: Interaction between en%protein and CID visit

Outcome Variables – Change	P value
ΔBW (kg)	0.8227
ΔBMI (kg/m^2)	0.8230
ΔWC (cm)	0.5283
ΔFM (kg)	0.2471
ΔFM (%)	0.9741
ΔAndroid fat (kg)	0.1890
ΔFFM (kg)	0.1744
ΔFFM (%)	0.1952
ΔSBP (mmHg)	0.7708
ΔDBP (mmHg)	0.1991
ΔFPG (mmol/l)	0.9754
Δ2h-PPG (mmol/l)	0.5497
$\Delta AUC_{GlucoseT0\text{-}120m}$	0.2082
ΔHbA_{1C} (mmol/mol)	0.3702
ΔInsulin (mU/l)	0.4764
ΔHOMA-IR	0.5898
ΔC-Peptide (pmol/l)	0.6340
Δhs-CRP (mg/l)	0.8915
ΔTC (mmol/l)	0.3383
ΔHDL-C (mmol/l)	0.1359
ΔLDL-C (mmol/l)	0.2977
ΔTG (mmol/l)	0.0709
ΔTC:HDL ratio	0.6640
ΔGI (units/d)	0.2995
ΔTE (kJ/d)	**<0.001**

BW, body weight; BMI, Body Mass Index; WC, waist circumference; FM, Fat Mass; FFM, Fat Free Mass; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting Plasma Glucose; 2h-PPG, Postprandial Plasma Glucose at 2-hour timepoint; $AUC_{GlucoseT0\text{-}120m}$, Area under the glucose curve time 0-120 min; HbA_{1c}, Glycated Haemoglobin; Insulin, Fasting serum insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; C-Peptide, serum connecting peptide; hs-CRP, high sensitivity C-reactive protein; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; TC:HDL ratio, Total cholesterol:high density lipoprotein ratio; GI, Glycaemic Index; TE, Total Energy

Due to critique around observed data only, further statistical analysis was conducted as ITT with imputation (LVCF and multiple imputation).

4.4.2.2 ITT-LVCF data

Conducting a continuous analysis using LVCF data, the association between changes in estimated en%protein calculated from the 4-day food record and anthropometric and metabolic outcomes from CID2/Post LED to CID6/24m were also calculated (as shown in Appendix E). Notably this data set which used imputed data based on the LVCF principle showed very similar findings to the observed (no imputation) data described in detail above. To highlight some key points:

i. Unadjusted

As reported for the observed (no imputation) dataset above, the unadjusted regression analysis showed that an increase in 1en%protein was significantly associated with a reduction in BW of -0.007(0.033)kg, (P=0.8235) and a trend for reduction in BMI (-0.002(0.012)kg/m^2, (P=0.8882)). Again, in line with the observed dataset, there was no significant association between change in en%protein and WC, absolute FM, %FM, android fat, absolute FFM and %FFM. Also no association with change in SBP, DBP, or glycaemic parameters FPG, 2h-PPG, $AUC_{GlucoseT0\text{-}120m}$, HbA_{1C}, Insulin, HOMA-IR. Also, as previously change in C-Peptide was close to a significant association with en%protein (-2.854(1.497)pmol/l, P=0.0582). Change in CVD parameters again were non-significant for hs-CRP, LDL-C and TG, but conversely 1en%protein increase in turn significantly increased TC by 0.01(0.005)mmol/l, P=0.0487; and decreased TC:HDL ratio by -0.007(0.003)mmol/l, (P=0.0396). In line with the observed data, there was also a significant association with HDL-C showing an increase in 1en%protein correlated with an increase in 0.007(0.003)mmol/l, (P=0.0396) and decreased TC:HDL ratio by -0.007(0.003)mmol/l, (P=0.0396). Using the food diary analysis, as for the observed data there was a significant association with change in GI, an increase of 1en%protein reduced GI by -0.282(0.038)units, (P<0.001). Similar to the observed analysis for TE intake, there was no significant association in either unadjusted or adjusted models but a significant interaction (en%protein*time) was observed such that an increase in 1en%protein decreased TE by -126, 24.7kJ/day (P<0.001).

ii. Adjusted

After the model was adjusted for potential confounders, baseline value, gender and ethnicity, BW lost significance. No association was seen for BW, BMI, WC, absolute FM, %FM, android fat, absolute FFM, %FFM, SBP, DBP, FPG, 2h-PPG, Insulin, HOMA-IR, C-Peptide, hs-CRP, TC, LDL-C and TG. An unexpected observation was the lack of significant association between change in en% protein and change in BW and BMI in this adjusted model (both, P>0.95). A significance was seen in HDL-C, similar to the observed data analysis where an increase in 1en%protein results in an increase of 0.005(0.001)mmol/l, P<0.001. There was also a significance found in TC:HDL ratio showing that an increase in 1en%protein reduced TC:HDL ratio by -0.008(0.003), P=0.0223. Using the food diary analysis, there was significance found in GI. An increase of 1en%protein reduced GI by -0.284(0.036)units in this adjusted analysis, P<0.001.

Interaction

Similar to the observed analysis, there was no significant association between en% protein and change in TE in the unadjusted model but in the adjusted model, a significant interaction (en%protein*time) was observed. Baseline values and ethnicity were significant confounders contributing to the model, whilst gender was not a significant contributor.

4.4.2.3 ITT-Multiple imputation data

Conducting a continuous analysis using multiple imputation data, the association between changes in estimated en%protein calculated from the 4-day food record and anthropometric and metabolic outcomes from CID2/Post LED to CID6/24m were also calculated (as shown in Appendix F). Multiple imputation modelled without repeated measures, adjusted and unadjusted for potential confounders, but without interaction analysis was conducted. Notably this data set which used imputed data based on the multiple imputation principle showed very similar findings to the observed (no imputation) data described in detail above. To highlight some key points:

i. Unadjusted

As reported for the observed (no imputation) dataset above, the unadjusted regression analysis showed that an increase in 1en%protein was significantly associated with a reduction in BW of -0.104 (0.052)kg, P=0.0706 and a trend in BMI of -0.035(0.018)kg/m^2, P=0.081. Again, in line with the observed dataset there was no significant association between en%protein and WC, absolute FM, %FM, android fat, absolute FFM and %FFM. Also no association with change in SBP, DBP, or glycaemic parameters FPG, 2h-PPG, $AUC_{GlucoseT0\text{-}120m}$, HbA_{1C}, Insulin, HOMA-IR, C-Peptide. Change in CVD parameters again were non-significant for hs-CRP, TC, LDL-C and TG, but also for HDL-C an increase in which was significantly associated with en%protein in the observed data set. There was however still a significant association with change in TC:HDL ratio where a 1en%protein decrease was associated with decrease of -0.015(0.006), (P=0.0432). Using the food diary analysis again in agreement with the observed data analysis, an increase of 1en%protein reduced GI by -0.377(0.055)units, P<0.001, as expected based on the dietary advice for PREVIEW. There was however no significant relationship between en% protein and change in TE in this multiple imputation unadjusted model

ii. Adjusted

After the model was adjusted for potential confounders baseline value, gender and ethnicity, the results were similar to the unadjusted analysis. An increase in 1en%protein was significantly associated with a reduction in BW of -0.101 (0.051) kg, P=0.0749 and a trend in BMI of -0.034(0.018)kg/m^2, P=0.0876. Again, in line with the observed dataset there was no association between en%protein and WC, absolute FM, %FM, android fat, absolute FFM and %FFM. Also no association with change in SBP, DBP or glycaemic parameters FPG, 2h-PPG, $AUC_{GlucoseT0\text{-}120m}$, HbA_{1C}, Insulin, HOMA-IR, C-Peptide. Change in CVD parameters again were non-significant for hs-CRP, TC, HDL-C, LDL-C and TG. Change in HDL-C has been observed as significantly associated with change in en%protein in the observed dataset. There was however still a significant association with change in TC:HDL ratio where a 1en%protein decrease was associated with decrease of -0.015(0.006) P=0.0375. Using the food diary analysis, again

in agreement with the observed data analysis, an increase of 1en%protein reduced GI by -0.39(0.05)units, (P<0.001), as expected based on the dietary advice for PREVIEW. There was however no significant relationship between en% protein and change in TE in this adjusted model.

4.5 Discussion

This Chapter presented the results of the weight loss maintenance phase of PREVIEW:NZ, analysed in 2 main ways. Firstly as a categorical analysis during the initial 6 months of the intervention, where LP (<18.6en% protein) vs HP (≥18.6en% protein) cut-offs were defined at CID1/Baseline and then diet groups allocated based on the CID3/6m diet records, using an imputed data set. Secondly as a continuous regression analysis of factors that correlate with change in dietary en%protein throughout the full 2 years of intervention, using both observed and imputed data sets. The various methods were used as a form of sensitivity analysis, to consider the robustness of the findings. Also, it was not statistically valid to extend the categorical LP vs HP analysis beyond the 6-month timepoint. The overall findings from these various modelling approaches confirmed that continuous analysis of the imputed datasets, using both ITT-LVCF and ITT-Multiple Imputation for missing values, generated similar results to that of the observed data.

The two imputation models were consistent, although the standard errors using the multiple imputation approach were slightly larger (possibly due to imputation uncertainty). Both used a random effects mixed modelling approach where missing data from participants was incorporated using maximum likelihood modelling. These findings confirmed that it is not always necessary to impute missing values within a dataset, even with a high percentage of missing values such as the current PREVIEW:NZ study where participants dropped out at various stages of the intervention for a wide variety of reasons, before running such models (see Appendix D). Imputation of missing values is commonly used to prevent bias in the interpretation of the data, e.g. participants who are not doing well in the intervention dropping out early, but conversely not all statisticians agree with this imputation approach. Following this sensitivity analysis it was concluded that the preliminary findings from categorical LP vs HP analysis could be compared with the findings obtained from continuous analysis using the observed data set without imputed values.

Notably, this supported the primary hypothesis of this thesis that a higher protein, lower GI diet would result in better BW maintenance over 2 years. In previous studies, weight loss of at least 5% BW has been shown to result in approximately 40-70% reduction in risk of developing T2D for those with pre-diabetes (Alibasic et al., 2013; Ferrannini, 2014; Khavandi et al., 2013; Leslie et al., 2017). Based on this, it was a sensible target for PREVIEW:NZ to aim to maintain much of the weight lost in the acute LED, which was at least 8% for every participant, over the following 2 years. That was likely to have a positive effect for T2D prevention. In this thesis T2D cases was

not used as an endpoint, as it requires a very large sample size to have disease as an endpoint, but instead in this study, PREVIEW:NZ followed some of the markers of T2D and also CVD. Chapter 3 showed the results of acute weight loss of ≥8% over the 8-week LED phase of the study. It was very successful for improvement of circulating plasma glucose and the associated endpoints measured in PREVIEW:NZ. FPG, 2h-PPG and $AUC_{GlucoseT0\text{-}120m}$ for OGTT glucose measures all decreased significantly. However, it was clear that in the 2-year *ad lib* diet follow-up, this weight loss was not maintained by either HP or LP diets. There was rapid rebound from 2-months onwards in both diet groups. It was very interesting though to consider whether the weight loss and the improvement in glucose parameters caused by the LED was completely reversed by the end of the 2-year follow up. Despite rapid weight regain, improvement in glucose parameters remained below the pre-trial baseline level in both diet groups. That is expected to be an advantage to the participants, both in terms of their personal desire for weight loss and also in terms of metabolic health. PREVIEW:NZ showed that mean FPG, 2h-PPG and AUC of the OGTT curve glucose were all still below pre-intervention levels at 2-year follow up. Whilst BW regain over the months may have led to disappointment and discouragement to the participants, and very likely to be a big contributor to the high level of drop out in the study, it did not result in return of T2D related parameters to baseline pre-diabetic levels. This may represent a big health improvement for these men and women. By 2 years only approximately half of the participants were still classified as pre-diabetic using the ADA criteria (American Diabetes Association, 2017), with about 40% still normoglycaemic.

The primary objective of PREVIEW:NZ was to determine whether the higher protein, lower-GI diet helped to prevent weight regain versus a lower protein, higher–CHO, moderate GI diet. Perhaps surprisingly, and contrary to the primary hypothesis, categorical analysis of the first 6 months of the intervention found, no significant difference between LP and HP diet groups. Both groups lost significant amounts of BW during the LED phase as expected, and both had significant weight regain over the 22-month maintenance phase between CID2/Post LED to CID6/24m; but with no difference in BW between the LP and HP diet groups over the 2 years of PREVIEW:NZ. As expected, the HP group reported a lower en% CHO and GI diet. Also as hypothesised, the HP group reported a lower total energy intake than the LP group. This aligns with the possibility that HP diet may result in negative energy balance and so be better for prevention of BW regain, but as noted above, there was not significantly greater weight loss maintenance in the HP group. One reason might be that there was also a decrease in physical activity and therefore energy expenditure in the HP group, but that could not be tested in this thesis.

Clearly the lack of effect of diet group does not agree with the findings of the DioGENES trial (Larsen et al., 2010), which was both one of the early successful higher protein for weight loss maintenance studies and also may be considered a forerunner to the international PREVIEW trial with many of the same investigators involved with both studies. DioGENES was only a 6-month study in total, whereas international PREVIEW study will continue for a much longer 3-year follow-up, but the 6-month analysis of the PREVIEW:NZ data in this thesis allows a

comparison between the 2 studies. Noting though that PREVIEW:NZ diet groups were not randomised at baseline as for DioGENES (Larsen et al., 2010), but still a comparison is useful. DioGENES had clear evidence of better post-LED weight loss maintenance at 6 months with higher protein, lower CHO, lower GI than any of the other diet groups tested in this intervention.

Conversely, in agreement with the hypothesis of this thesis and the PREVIEW:NZ study, when dietary protein intake was analysed as a continuous variable over the full 2 years of the intervention, there was a significant relationship between en% protein in the diet and BW. Higher protein intake was significantly correlated with lower BW between CID2/post-LED and CID6/24m, i.e. better maintenance of weight loss. For every 1en% increase in protein intake across the whole cohort, there was a suppression of BW regain of -0.098kg. This was not a large effect on BW, and may well not be clinically significant. A very large change in protein intake of 10en%, i.e. from 15en% to 25en%, was associated with approximately 1kg better BW maintenance. This was a consistent finding in both the unadjusted and adjusted models. So higher protein does result in better post-LED weight loss maintenance in the 2 years following acute weight loss, but in PREVIEW:NZ cohort the effect is very small.

Comparison of the analyses can also be made for the glucose outcomes. Firstly in the 6-month categorical analysis, not surprisingly, since there was no difference in weight regain between the diet groups, there was also no difference in any of the glucose parameters in the higher protein diet group. There was no opportunity to test the hypothesis that better weight maintenance would lead to better glucose control, although that hypothesis does still seem reasonable. Also in the continuous analysis, with no prior allocation of participants to LP or HP diet groups, there was also no evidence that 1en% protein was associated with improved FPG, or any other glycaemic endpoint. Perhaps this was a little surprising as the continuous analysis had shown an effect of higher protein, lower CHO on BW, but this was not carried across to the glucose endpoints. As noted earlier though, by the end of the 2-year follow up glucose and other metabolic endpoints had not returned to the baseline pre-intervention levels. Although the lifestyle intervention did not show evidence of better response to dietary protein, the acute weight loss from the LED resulted in a big improvement in metabolic outcomes, including glucose. For example, >70% of participants were classified as pre-diabetic at CID1/Baseline whilst 2 years later at CID6/24m only ~50% (=half) were now pre-diabetic. The LED was the main reason for this improvement, but the lifestyle program may have helped to maintain better glucose in both low-fat intervention arms – but with no difference between the 2 diets. Possibly both were contributing to prevention of glucose rebound up to pre-trial rates. The design of the international PREVIEW trial, and so PREVIEW:NZ, does not allow that to be tested as this was a lower fat-higher protein comparison with current standard practice of lower fat-higher CHO, and there was no control arm without low-fat intervention. Although this was not an endpoint for PREVIEW:NZ that only 12 cases of T2D were diagnosed up to CID6/24 months, which equates to 4% after 2-years. This is much lower percentage than would be expected based on a study such as FDPS, where T2D incidence was 23% in the control arm when compared to 10% in the intervention arm of the 3-year study (Lindstrom et al., 2003). In the International PREVIEW trial, it was estimated that the HP group

would decrease T2D incidence by approximately half, from a pre-trial baseline risk of ~21% to ~10% over the full 3-year intervention (Fogelholm et al., 2017). Using the figures above, after 3 years, we should be expecting n=31 (10%) to be diagnosed with T2D, however as PREVIEW:NZ commenced their 3-year intervention in May 2018, total T2D diagnosed was only n=17 (6%). This further improvement could be due to several reasons, including the greater weight loss goal of ≥8% in PREVIEW:NZ when compared to only ≥5% in the FDPS (Fogelholm et al., 2017; Lindstrom et al., 2008).

Gender

There was a majority of female (76%) in the PREVIEW-NZ study. There was a higher number of male in the HP group (n=39/64%) when compared to female (n=110/58.5%). Using the multiple linear regression model where en%protein was a continuous variable, gender differences were investigated as potential confounders. As previously described, there was an inverse relationship in both the adjusted and unadjusted model between BW and change in en%protein. In this Chapter, we hypothesised that men would have maintained a greater body weight when compared to women due a higher baseline BW and more FFM in men (Liang et al., 2018; Meisinger et al., 2006); also since a higher FFM or lean muscle mass is a predictor for IR it was also hypothesed that men would have better glycaemia than women. The results from the FDPS supported this, with an overall 58% reduction in T2D risk for all participants, with an improved reduction of 63% in men when compared to only 54% improved risk reduction in women (Lindstrom et al., 2008). There was no evidence of gender effects for BW or glucose endpoints. In this thesis however, using the continuous analysis when adjusted for gender as a potential confounder. There were also no differences found in diet (GI and TE) or any of the anthropometric body composition parameters (i.e. BW, BMI, WC, FM, android fat and FFM). Both genders regained weight over the 2-year maintenance phase. Men had a higher DBP than women, and a lower HDL-C and higher TC:HDL ratio when holding baseline parameters and ethnicity constant. From the Framingham study, HDL-C is protective factor against coronary heart disease and well established to be lower, and hence less protective in women (Chapman et al., 2004; Lemieux et al., 2001; Rolland & Broom, 2011; Rye et al., 2009). Body fat distribution, particularly central fat distribution in men increases visceral fat and therefore IR increasing risk of T2D and chronic conditions (Liang. et al., 2018; Meisinger et al., 2006). But there was no evidence in this thesis. No difference was found when adjusted for other CVD parameters (i.e. hs-CRP, TC, LDL and TG).

Ethnicity

The majority of ethnicity in this PREVIEW:NZ study was made up of Caucasian (61%) followed by Maori/Pacific (31%) and only 8% for Other. All the participants lost BW during the LED phase and regained weight over the 2-year maintenance phase. When using continuous multivariant analysis, the unadjusted model found an inverse relationship between en%protein using the diet records and change in BW. When BW was adjusted for baseline as continuous variable, and

gender and ethnicity as potential confounders, this inverse relationship remained. When adjusted for the difference in ethnicities as potential confounders, there was a significant difference between the 3 ethnic subgroups, predominately between Maori/Pacific and Caucasian. In this chapter thesis, it was correctly hypothesised that Maori/Pacific would have the highest baseline BW. Body composition studies also showed that Maori/Pacific had more FFM with less visceral fat than Caucasian at baseline, which has been shown to increase metabolism, improve insulin sensitivity and glucose control (Duncan et al., 2004; Rush et al., 2007; Rush et al., 2004; Rush et al., 2009). Also, as Asians (or Other) have been shown to have a higher percentage of FM (Chandalia et al., 2007; Lin et al., 2009; Schutz et al., 2002; Wang et al., 1994) and therefore increased IR, despite a lower BMI, it was hypothesised that Other group would perform worse metabolically when compared to the other two groups. However not in agreement with the hypothesis, the results of this thesis showed that Maori/Pacific had less success than Caucasians and re-gained more BW. This was surprising, Maori/Pacific also did not lose more BW over the LED phase, despite being the heaviest cohort. Possible reasons may be related to body composition as described above, with greater FFM in Maori/Pacific which is denser and 3 times heavier than FM (Duncan et al., 2004; Rush et al., 2007; Rush et al., 2004; Rush et al., 2009). Another more likely reason could be the lack of compliance. As previously pointed out during the LED phase, the standardised international PREVIEW protocol lacked a family/whanau based education interaction. When assessing the diet records, the increase in BW re-gain is reflective of the trend with an increase in TE in Maori/Pacific when compared to Caucasian.

In the regression model in line with high BW re-gain, Maori/Pacific re-gained more FM than Caucasian but not FFM. Reflective of the increase in FM, Maori/Pacific also gained more android fat when compared to the Caucasian group. The increase in FM and visceral fat increases IR, but an increase in FFM would be expected to increase insulin sensitivity. As per previous body composition studies, Maori/Pacific have an increased FFM when compared to Caucasian which is more protective to IR (Rush et al., 2007; Rush et al., 2004; Rush et al., 2009). Despite this however, Maori/Pacific have >2 times risk of developing T2D when compared to Caucasians (Ministry of Health, New Zealand Health Strategy, 2016; Coppell et al., 2013; Krebs et al., 2013; Tipene-Leach et al., 2013); likely due to a higher absolute BW. In New Zealand, 1 in 3 adults were overweight, from which 32% were obese. Over half (50.2%) of Maori adults were obese and 68.7% of Pacific adults were obese, compared to 30.5% in Caucasian and 14.8% in Asian (Ministry of Health, 2017).

In the regression model, no ethnicity differences were found in most glycaemia endpoints (i.e. FPG, 2h-PPG, $AUC_{GlucoseT0\text{-}120m}$, Insulin and HOMA-IR). However, Maori/Pacific had a higher HbA_{1C} by 0.626mmol/mol, while holding baseline BW and gender constant. Maori/Pacific also had a higher increase in C-Peptide, which is reflective of IR and risk of developing T2D (Jung et al., 2018). Other metabolic parameters showed no difference in LDL-C, TG and TC:HDL ratio when adjusted for ethnicity in the continuous analysis. Surprisingly, Maori/Pacific had a lower TC, a trend for lower LDL-C plus as expected a lower HDL-C when compared to Caucasians.

Strengths and Limitations

There were a number of strengths and limitations of the PREVIEW:NZ study and so the findings of this thesis. One strength of this thesis is that the Auckland intervention was part of a randomised controlled multi-centre intervention with a carefully designed protocol to follow for both inclusion of participants, diet recommendations and also the day to day running of the intervention. Standardised SOPs were used to try to ensure that all 8 study sites followed the same procedures throughout the trial. However due to the 'locked' data set and inability to identify randomised diet groups until after the 'unlock' date in October 2018, it was not possible to analyse the participants in their randomised diet groups. Instead, the PREVIEW:NZ cohort were divided into the two protein diet groups, LP vs HP, based on their reported 4-day food diary data at the 6-month CID (CID3/6m). This was the first assessment of diet made during the weight maintenance phase, and so was thought to be a reasonable way to allocate diet group, making the assumption that those who had higher protein intake at 6 months were likely to be receiving advice from the PREVIEW:NZ dietetics team on increasing protein intake (limit red meat and processed meat). Conversely those who reported a lower protein intake at 6 months were likely to be receiving advice from the PREVIEW:NZ dietetics team on decreasing protein intake. It was not possible however to verify this whilst research was ongoing for this thesis. The cut-off for LP and HP was determined by calculating the mean intake at baseline, i.e. the reported habitual diet of the participants before they started the diet intervention or received any advice from PREVIEW:NZ dietetics team. Other publications have used a range of values for LP and HP (Keller, 2011; Pesta & Samuel, 2014), with recommendations that 1.2g/kg BW may be an appropriate level for HP (Westerterp-Plantenga et al., 2012), and there were a number of different ways that this could have been allocated in PREVIEW:NZ. For example, it an alternate approach could have been using the New Zealand average protein intake based on the most recent adult diet survey data (Parnell et al., 2011), where mean energy from protein was 16.5 en% for both male and female with little variation across age groups (Parnell et al., 2011).

Although physical activity was also a factorial within the international PREVIEW trial, this was not included in the current analysis of PREVIEW:NZ and again the data remains locked until end of 2018. No proxy measures of exercise were available to estimate actual activity, as was done for the categorical diet data. Notably, both exercise groups had the same energy expenditure level as the target but different ways of achieving this expenditure, i.e. either low level activity for a long time period each week, or high level activity for a short period each week. Hence the data presented in the thesis is for diet only.

As noted above, PREVIEW:NZ compared 2 active diet arms with each other, i.e. standard/current best practice with novel higher protein approach. There was no control arm, without diet intervention. This limits some of the interpretations that can be made. It might be hypothesised that both resulted in better glucose control at 2 years than would have occurred without dietary advice and counselling sessions with the PREVIEW:NZ dietetics research team. Another limitation of this thesis Chapter was that no OGTT data was collected at CID2/Post LED. This

was a decision made by the international PREVIEW consortium. It was in order to not further increase the burden on participants who already had a complicated study protocol to follow, with long CID visits and 'homework' to complete before each clinic visit. Hence PREVIEW:NZ also followed this protocol with OGTT only at CID1/Baseline and CID3/6m. It seems very likely that the post-LED 2h-PPG glucose response would have improved along with the 8% BW loss at the end of the 8-week LED, based on other published studies (Jackness et al., 2013; Leslie et al., 2017; Taylor et al., 2017).

There were also practical aspects of the Protocol that might have improved outcomes for PREVIEW:NZ. For example, steps that might have been put in place to prevent weight regain. There was no 'rescue plan' or titration from the LED over a set time, unlike for example the recent DiRECT study in T2D patients; where there was an option to access follow-up support as well as return to the LED meal replacement plan or even weight loss drugs such as Orlistat to try to improve the weight maintenance (Lim et al., 2011; McCombie et al., 2017; Taylor et al., 2017; Zhyzhneuskaya et al., 2017). Another limitation was the prescriptive clinical based support which was very much ocused on the individual participant. Unlike the New Zealand traditional family/whanau based support that is used in healthcare and also some public health lifestyle interventions (Henwood, 2007; Krebs et al., 2013; Tipene-Leach et al., 2013); with the involvement of the family to promote family based changes, support and suggestions. Finally, PREVIEW:NZ followed a fading visit design, where the time period between diet counselling sessions expanded as the study went on. At the beginning of the LED, participants came for counselling and support every 2 weeks. At the end of the study they came only every 6 months, That did not help to prevent drop-outs, and maybe another reason why many PREVIEW:NZ participants dropped out of the study before the end of 2 years. There are several studies which have shown that regular attendance and support with any type of diet intervention recommendation may result in success. Where attendance or any other factors that can push up adherence is more important rather than the composition of the diet advice itself (Tobias et al., 2015). This has sometimes been termed 'The best weight loss diet is the one that you can stick to'. This is being investigated further in early clinical studies where the intervention is based on 'Patient Preference', where the alternative design is to optimise motivation by ascertaining patients' preferences, e.g. higher protein when assigned to lower protein or intermittent fasting (Brewin & Bradley, 1989; McCaffrey et al., 2007; Wing et al., 2001). The high drop-out rate in PREVIEW:NZ was worst in Maori/Pacific cohort (Appendix D: Dropout rates). Perhaps that lack of family based structure made staying in the trial more difficult for these individuals than other ethnicities such as European Caucasians or Asian New Zealanders. Notably New Zealand was the only study centre in the international PREVIEW study that had varied ethnicities. All of the European sites and even Australia have reported interim results based largely on European Caucasian ethnicity (Raben et al., 2017).

Diet records are known to be unreliable, particularly in O/W and obese population. Ideally urine nitrogen losses should be used to calculate dietary N intake, as an estimate for reporting

accuracy. Urine samples were analysed at central PREVIEW lab. However, the data was not available as the trial is still ongoing.

4.6 Conclusions

Following the 8-week LED weight loss phase, this Chapter showed that weight was regained over the 2 years of weight maintenance phase, using categorical and continuous multivariant analysis. The categorical analysis showed that weight regain, improvements to anthropometric (BW, BMI, WC, FM, android fat, FFM, BP) and glucose parameters (FPG, 2h-PPG, $AUC_{GlucoseT0\text{-}120m}$ of the OGTT glucose curve, HbA_{1C}) remained below the pre-trial baseline level in both LP and HP groups with no differences the two diet groups.

Using the continuous analysis, a higher protein, lower GI and low fat intake was beneficial to BW and FM maintenance in the unadjusted model (increase of 10en%protein results in BW loss of ~1kg). When adjusted for gender and ethnicity, there was no differences between gender for diet, anthropometric and metabolic parameters, except that men had a slightly higher DBP, HDL-C and TC:HDL ratio than women. During the weight maintenance phase, Maori/Pacific gained more BW, FM and android fat than Caucasians. No difference was found in glycaemia (FPG, 2h-PPG, AUC, Insulin, and HOMA-IR), however, Maori/Pacific had a worse HbA_{1C} and C-Peptide when compared to Caucasians. Overall, Maori/Pacific did not do as well as Caucasians, contrary to the thesis hypothesis for both BW re-gain and glycaemia.

In summary, the clinical significance of the weight loss was clear in terms of health benefits following the LED weight loss phase. However, there was no clinical significance between protein groups in the weight loss maintenance phase. The anthropometric and metabolic benefits remained at 2 years despite weight re-gain when compared to pre-trial baseline levels, as shown in other weight management studies (Dale et al., 2009a; Lean. & Hankey., 2018; Leslie et al., 2017). The effects of weight loss were important, and along with the support around weight loss maintenance (i.e. group visits, CID, phone call follow-up, social media support) greatly contributed to prevent the anthropometric and metabolic parameters from returning to pre-trial baseline. The practical significance of the increase in 10en%protein leading to ~1kg BW loss is low. Dietary protein messaging can be confusing for the general public. Promoting increase in protein usually also equates to an increase in total fat intake e.g. eggs, salmon, chicken. Practically, it is difficult to modify a single macronutrient component without affecting other macronutrients. When educating patients or the general public, it is important to keep the advice simple and easy-to-follow. Confusion around making changes based on en%protein and other macronutrients is a difficult public health approach and not recommended. Instead, advice around adjustments to the diet, including consideration of individual patient preference, but taking into consideration the evidence around increased satiety effects of protein maybe a better practical approach.

Chapter 5 Determining Glycaemic Index (GI) of New Zealand Kumara – a PREVIEW substudy

Sweet Potato or 'kumara' (*Ipomoea batatas*) is a popular dietary item; ranked seventh among all food crops worldwide with an annual production of 115 million metric tons. Kumara are a rich source of energy (377kJ/100g), carbohydrates, dietary fibre, anti-oxidants, vitamins (meet 100% recommended daily allowance for Vitamin A, 49% RDA for Vitamin C) and minerals (provides 10% RDA for iron and 15% RDA for potassium) (Bovell-Benjamin, 2007; Fernandes et al., 2005; Lebot, 2010; Mohanraj & Sivasankar, 2014; Teow et al., 2007; vegetables co nz, 2018). They are commonly consumed within the New Zealand diet, and were an important food item for participants in PREVIEW:NZ.

GI is a physiological response of BG to a food, and is defined as the area under the curve (AUC) of circulating BG after the test food is eaten. A L-GI is defined as a rating of 55 units or below; a H-GI is defined as above 70 units. Inclusion criteria were participants who are lean (BMI 18.5-29.9kg/m^2), healthy (no diagnosed chronic conditions), men or women, aged 18-65 years, and healthy by self-report (Wolever et al., 2003; Wolever. et al., 1991). Those with impaired glucose tolerance/T2D were excluded from the study. Study participants were recruited from the Auckland region by advertising on University campus. This was a 6-arm randomized, crossover, dietary intervention study conducted in 10 individuals, using a Latin-square randomisation. Twelve participants were recruited, in order to ensure 10 participants completed the full study. Each participant was tested in random order on separate days. Each study day was separated by a minimum of 3 days washout. Due to intra- and inter-individual variation, outliers are defined as three or more standard deviations above the mean (Knox & Ng, 1998; Leys et al., 2013).

Physiological testing is required to assign a GI value to each individual food item. Of note is the contradictory published data for kumara. In the 1995 International Table of GI, kumara was assigned a L-GI of 44 units (Foster-Power & Miller., 1995); whereas in 2002, it was assigned a GI of 77 (high GI) (Foster-Power et al., 2002); both using a reference standard of 50g glucose. An International resource 'www.glycaemicindex.com,' which is widely used in dietary trials and clinical practice, now assigns kumara a L-GI of 50 units (University of Sydney, 2017). In New Zealand, kumara is grown in abundance and is used as a staple CHO source (vegetables co nz, 2018). Yen published a paper on the adoption of kumara by the New Zealand Maori in 1961, showing that kumara was the major cultivated crop plant of the New Zealand Maori at the time of the early European contacts (Yen, 1961). The kumara tradition was introduced to New Zealand from tropical Polynesia in the 14th Century A.D, making kumara a wide tradition for the Pacific and the Maori population and culture (Cambie & Ferguson, 2003; Rossel et al., 1999; Yen, 1961). Traditionally, Maori people use kumara in a hangi (traditional feast steam cooked under the ground) or boiled in casseroles or 'boilups' (Bovell‐Benjamin, 2007; Cambie & Ferguson, 2003; Lebot, 2010). New Zealanders still boil or roast kumara, as a primary source of CHO intake,

especially in the Maori and Pacific population (Cambie & Ferguson, 2003; Rossel et al., 1999; vegetables co nz, 2018; Yen, 1961).

Due to the availability and use of kumara in New Zealand, there was a need to conduct this substudy in order to determine the GI value of this high CHO source. Advice to participants in the LP group was M-GI, whilst in the HP group it was L-GI (Fogelholm et al., 2013; Fogelholm et al., 2017). In New Zealand, there are different varieties of kumara commercially available (vegetables co nz, 2018). The most common is 'Red' the red-skinned, 'Owairaka Red', which has a creamy white flesh; the 'Gold' golden kumara, 'Toka Gold' has a golden skin and golden flesh with a sweeter taste; lastly the least common is the orange kumara, 'Beauregard', which has a rich orange flesh and sweeter than both 'Red' and 'Gold'. The nutritional content of kumara is only available for one variety 'red' with 17.5g carbohydrates per 100g (Plant and Food Research & Ministry of Health, 2016). There is no consistent GI data available for kumara varying from L-GI (GI 44) in 1995 to H-GI (GI 77) in 2002 with no variability with different varieties (Foster-Powell & Miller, 1995; Foster-Powell et al., 2002). In this chapter, two kumara and GI sub-studies were conducted to investigate the GI of kumara and compare this to standard potato (peeled). In the PREVIEW study, we investigate whether a HP (HP), and L-GI diet is efficacious for weight loss maintenance.

The first study used available CHO content calculated 'KumaraGI$_{calculated}$'. Available CHO content was calculated from The Concise New Zealand Food Composition Tables 2016 (Plant and Food Research Limited & Ministry of Health, 2016). GI testing was conducted using the International GI methodology where a standardised (50g) content of available CHO of a food is compared with 50g monosaccharide glucose; and BG changes measured over 2 hours (Atkinson et al., 2008; Brand-Miller et al., 2008; Brouns et al., 2005). The second study used available CHO content analysed 'KumaraGI$_{analysed}$' using an International Standards Organisation accredited (ISO/IEC 17025) food analysis company, AsureQuality Ltd.

5.1 Aim and Hypotheses

The aim of this thesis chapter was to conduct two substudies to investigate the GI of different varieties of kumara, prepared and consumed under different conditions including cold vs. hot and skin vs. no skin, compared with a standard potato (peeled).

The primary hypothesis was that kumara has a lower GI than standard potato (peeled) and hence appropriate to be recommended as a L-GI food option for the PREVIEW-NZ study participants.

The secondary hypotheses were that:

- cooked and cooled kumara was lower in GI than hot kumara; due to the change in resistant starch
- kumara with intact skin was lower in GI than peeled kumara; due to the additional dietary fibre content

To test these hypotheses 2 kumara and GI substudies were conducted in healthy individuals. Firstly available CHO content of kumara and standard potato were calculated; secondly available CHO content were measured by an accredited local food analysis company.

5.2 Methods

Human ethical approval for the PREVIEW substudy, Kumara and GI study was obtained from University of Auckland Human Participants Ethics Committee (UAHPEC) reference number: 015119.

5.2.1 Participants

Participants were lean healthy adults, with inclusion criteria described in Chapter 2.14.

5.2.2 Study Protocol

This was a 6 arm randomized, crossover, dietary intervention study to be conducted in 10 individuals.

The 6 arms of the study were:
i. sweet potato/kumara variety #1, served hot – red hot (rk/h)
ii. sweet potato/kumara variety #2, served hot – golden hot (gk/h)
iii. sweet potato/kumara variety #3, served hot – red with skin hot (rk/hs)
iv. sweet potato/kumara variety #1, served cold – red cooled (rk/c)
v. standard potato, served hot – (p/h)
vi. 50g glucose, control – glucose control (c)
Participants completed a 2-hour GI test on 6 occasions, comprising 5 test foods and a glucose control. There was a minimum of 3 days washout between each test day. Participants arrived fasted at the HNU at 0830h. They were seated in individual testing booths and fasting blood glucose (0 mins) assessed using a capillary fingerprick monitor. At 0900h the test food or glucose control was consumed. Follow up FP samples were measured on 6 occasions over the next 2 hours at 15, 30, 54, 60, 90 and 120 mins. Participants were allowed no other foods or water during the test, and were required to remain seated through the 2 hour testing period. They were not allowed to sleep.

5.2.3 Study 1: GI and Kumara, $KumaraGI_{calculated}$

In study 1, the available CHO content of kumara and standard potato were calculated using data provided by the NZ Institute for Plant and Food Research Ltd (Plant and Food Research, 2009;

Plant and Food Research Limited & Ministry of Health, 2016). The weight of food calculated to provide 50g of available CHO is shown in Table 39.

Test Protocol A: Hot - following calculation, 50g available CHO equated to 250g weight of raw kumara and 285g weight of raw standard potato, cut into 2cm cubes, placed in a plastic container, 1 teaspoon of water added and a plastic lid placed lightly on top, and cooked in a 1000 watt microwave for 3 min 30 seconds on high (100%). The food was then removed from the microwave and placed on the benchtop for 8 minutes, and then served to the participant. Test Protocol B: Cooled – As for Protocol A, the food was then removed from the microwave and placed on the benchtop for 45 minutes until cooled, and then served to the participant. Test Protocol C - Peeled: The test food was peeled to remove the skin. The peeled test food was then cut and cooked as per Protocol A and B. Test Protocol D (control): 50ml of monosaccharide glucose syrup was given as the reference control food.

Participants were given instruction for the day prior and the day of the test to avoid smoking, no abnormal or excessive exercise, no excessive alcohol consumption and no excessive nutrient intake e.g. CHO and fat (Brouns et al., 2005; Wolever. et al., 1991). Capillary fingerprick BG was measured using the Caresens N (CareSens, Pharmaco, Korea) BG device. All devices were tested using the three CareSens N calibration control solutions covering high (13-20mmol/l), moderate (7-12mmol/l) and low BG (2.5-4.5mmol/l).

Table 39: Weight of food required to provide 50g available CHO: calculated values

Test Food	Abbreviation	Weight (g)	Available CHO (g)	Test Protocol
Red Kumara, Hot	rk/h	250	50	A, C
Gold Kumara, Hot	gk/h	250	50	A, C
Red Kumara, Hot Skin	rk/hs	250	50	A
Red Kumara, Cool	rk/c	250	50	B, C
Standard Potato, Hot	p/h	285	50	A, C
Glucose control (ml)	c	50	50	D

rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cool; p/h, standard potato hot; c, glucose control

5.2.4 Study 2: GI and Kumara, $KumaraGI_{analysed}$

In study 2, analysis of the available CHO content of the test food was conducted for red kumara (rk), golden kumara (gk) and standard potato (p) at an accredited (ISO/IEC 17025) food analysis company, AsureQuality Ltd (131 Boundary Road, Blockhouse Bay, Auckland, New Zealand). The weight of food required to provide 50g available CHO is shown in Table 40. The results from the analysis is summarized in Table 41.

Table 40: Weight of food required to provide 50g available CHO: measured values

Test Food	Abbreviation	Weight (g)	Available CHO (g)	Test Protocol
Red Kumara, Hot	rk/h	183	50	A, C
Gold Kumara, Hot	gk/h	185	50	A, C
Red Kumara, Hot Skin	rk/hs	170	50	A
Red Kumara, Cool	rk/c	183	50	B, C
Standard Potato, Hot	p/h	352	50	A, C
Glucose control (ml)	c	50	50	D

rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cool; p/h, standard potato hot; c, glucose control

Table 41: Analysis of Test Food

AsureQuality reference: 16-51301
CHO by difference – Calculated via IANZ
Energy – 1.2.8 FSANZ Food Standard Code IANZ
Protein, via Kjeldahl
Fat (SBR), 07-IN-HOUSE_Method
(rk) 1. Red Kumara without skin - CHO by difference 27.3%, Energy 491 kJ/100 g, Protein 0.9%, Fat 0.3%
(gk) 2. Gold Kumara without skin - CHO by difference 27.1%, Energy 482 kJ/100 g, Protein 0.8%, Fat 0.2%
(rk/s) 3. Red Kumara with skin - CHO by difference 29.4%, Energy 523 kJ/100 g, Protein 0.9%, Fat 0.2%
(p) 4. Potato without skin - CHO by difference 14.2%, Energy 286 kJ/100 g, Protein 2.4%, Fat 0.1%

CHO; carbohydrates, measured as percentage; IANZ, International Accredited New Zealand; FSANZ, Food Standards Australia and New Zealand; Energy kJ/100g, Protein, measured as percentage; Fat, measured as percentage

Test Protocol A: Hot - following calculation, 50g available CHO equated to 183g weight of raw red kumara with no skin (rk/h), 185g weight of golden kumara with no skin (gk/hs), 170g weight of red kumara with skin left on (rk/s) and 352g weight of raw standard potato (p/h), cut into 2cm cubes, placed in a plastic container, 1 teaspoon of water added and a plastic lid placed lightly on top, and cooked in a 1000 watt microwave for 3 min 30 seconds on high (100%). The food was then removed from the microwave and placed on the benchtop for 8 minutes, and then served to the participant. Test Protocol B: Cooled – As for Protocol A, the food was then removed from the microwave and placed on the benchtop for 45 minutes until cooled, and then served to the participant. Test Protocol C - Peeled: The test food was peeled to remove the skin. The peeled test food was then cut and cooked as per Protocol A and B. Test Protocol D (control): 50ml of monosaccharide glucose syrup was given as the reference control food.

As for study 1, prior to the test, participants were given instruction for the day prior and the day of the testing to avoid smoking, no abnormal or excessive exercise, no excessive alcohol consumption and no excessive nutrient intake e.g. CHO and fat (Brouns et al., 2005; Wolever. et al., 1991). Capillary fingerprick BG was measured using the Caresens N (CareSens, Pharmaco, Korea) BG device. All devices were tested using the 3 CareSens N calibration control solutions covering high (13-20mmol/l), moderate (7-12mmol/l) and low BG (2.5-4.5mmol/l).

5.3 Statistical Analysis

The AUC for glucose T0-120mins, delta change glucose, and iAUC was calculated using GraphPad PRISM (GraphPad PRISM 7.0) statistical software. The statistical significance between the 6 treatments was assessed using ANOVA for study 1 and study 2, and *post hoc* testing was performed using Tukey's pair-wise comparisons, at baseline and 15, 30, 45, 60, 90 and 120 min. Comparison of the glucose control between Study 1 and Study 2 was conducted using one-way ANOVA and *post hoc* testing was performed using Sidak multiple comparisons (to compare the set of means from both studies), at baseline and 15, 30, 45, 60, 90 and 120 min. Statistical significance was allocated as $P<0.05$.

5.4 Results

5.4.1 Results from Study 1 $KumaraGI_{calculated}$

The baseline characteristics of the 10 participants who completed Study 1 are presented in Table 42, and included 8 women and 2 men. All participants completed all 6 arms of the study, and there were no dropouts. Participants were young, lean and healthy. Ethnicity was 60% Caucasian, 20% Chinese and 20% Indian. Mean (SD) age was 26.9(6.3) years. Mean (SD) BW was 64.6(8.7)kg with a mean (SD) BMI of 22.9(2.1)kg/m^2. All participants had normoglycaemia with a mean (SD) FBG of 4.7(0.4)mmol/l (Table 42).

Table 42: Baseline Characteristics (n=10)

$KumaraGI_{calculated}$	Mean±SD	(range)
Age (years)	26.9±6.3	(21-35)
Gender	80% women,	20% men
Ethnicity	60% Caucasian,	40% Asian
BW(kg)	64.6±8.7	(52.0-82.0)
Height (m)	1.70±0.05	(1.6-1.78)
BMI(kg/m^2)	22.9±2.1	(20.2-27.4)
FBG (mmol/l)	4.7±0.4	(4.0-5.3)

Mean±SD, BW, body weight; BMI, body mass index; FBG, fasting blood glucose

Figure 53 shows individual capillary BG (mmol/l) data for the 10 participants who consumed all 5 test foods and the reference glucose control. All participants were confirmed to be normoglycaemic at the start of each study day, and all demonstrated an increase in BG in response to consumption of each test food and the glucose reference. The peak in BG in response to the 5 test foods occurred at between 15 to 60 minutes with an increase up to 12mmol/l, compared to the baseline FBP of ≤6mmol/l. At the end of the GI test, most participants had returned to close to fasting levels, which was expected in normoglycaemic participants. There was no evidence of any outlier(s), with results greater than 3 standard deviations from the mean; therefore all participants were included in the iAUC analyses. The dotted line represents the glucose control curve for each individual, again highly variable between individuals, with a peak in BG curve of between 7-11mmol/l. Some individuals (e.g. KS4104, SC4108) had very little

increase in BG in response to the glucose challenge, likely a result of good insulin sensitivity. Most participants (e.g. JS4107, RC4110) showed a greater increase in BG following the glucose control when compared to individual test foods, however in many individuals (e.g. JG4101, LS4102, AL4103, KS4104) JB4105, JS4106, SC4108 and AT4109) where the BG peak following the test foods was higher than the glucose control, which was unexpected. This may have been due to incorrect food composition data (available CHO) and hence weight of test food presented to the participants. Notably this was not observed in all individuals.

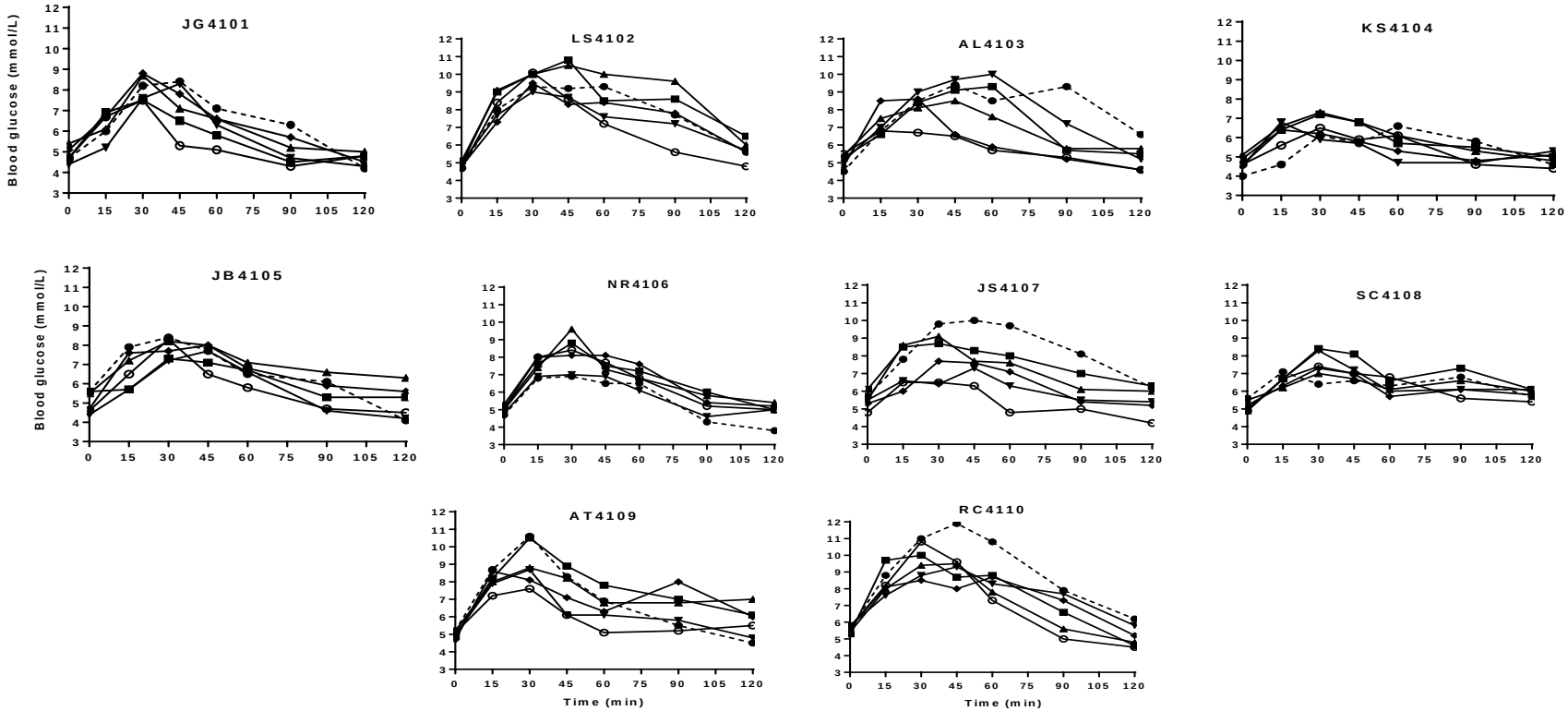


Figure 53: Capillary BG changes in response to 5 test foods plus glucose control (shown as dotted lines) n=10 individual participants

rk/h, red kumara hot (shown with closed square ■); gk/h, gold kumara hot (shown with closed inverted triangle▼); rk/hs, red kumara hot with skin (shown with closed triangle▲); rk/c, red kumara cool (shown with closed diamond ❁); p/h, standard potato hot (shown with open circle ○); c, glucose control (shown with closed circle and dotted line)

Table 43 shows the mean (SEM) capillary BG for each of the test foods at baseline, after 15, 30, 45, 60, 90 and 120 minutes. The mean (SEM) FBG ranged from 5.0(0.1) -5.3(0.1)mmol/l, and was within the healthy fasting BG range.

Table 43: Mean (SEM) capillary BG for the 5 test foods and glucose control at 0, 15, 30, 45, 60, 90 and 120 minutes

	c	rk/h	gk/h	rk/hs	rk/c	p/h
T0	5.0(0.2)	5.2(0.1)	5.0(0.1)	5.3(0.1)	5.0(0.1)	5.0(0.1)
T15	7.3(0.4)	7.5(0.4)	6.8(0.3)	7.5(0.3)	7.4(0.3)	7.1(0.3)
T30	8.5(0.5)	8.7(0.4)	7.8(0.4)	8.6(0.3)	8.1(0.3)	8.0(0.5)
T45	8.4(0.6)	8.2(0.4)	7.7(0.4)	8.0(0.4)	7.4(0.3)	7.0(0.4)
T60	7.8(0.5)	7.4(0.4)	6.8(0.5)	7.3(0.4)	6.8(0.4)	6.1(0.3)
T90	6.8(0.5)	6.4(0.4)	5.8(0.4)	6.3(0.4)	6.2(0.4)	5.1(0.1)
T120	5.2(0.3)	5.5(0.2)	5.2(0.2)	5.7(0.2)	5.3(0.2)	4.8(0.1)

Mean (SEM); c, glucose control; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cool; p/h, standard potato hot;

Figure 54 shows individual capillary BG delta change from baseline, where the range between individuals was from -1.5 to 6.3mmol/l, for the different test foods. The two participants (e.g. KS4104, SC4108) with little increase in BG, possible due to good insulin sensitivity, is more prominently seen in this figure, where neither participants exceeded 4mmol/l above the FBG, and returned to FBG level at 120 min. Figure 54 also shows that 17/50 or 34% of the calculated glucose AUC for the test food was greater than the glucose control, as displayed by the dotted lines. This indicates that the calculated amounts of available CHO may have been inaccurate, which in turn may have led to >50g being presented within the test foods to the participants. Figure 54 showed individual capillary BG, delta change from baseline for the 5 different test foods plus glucose control, n=10. Figure 55 shows calculated glucose iAUC for the each of the 6 test food.

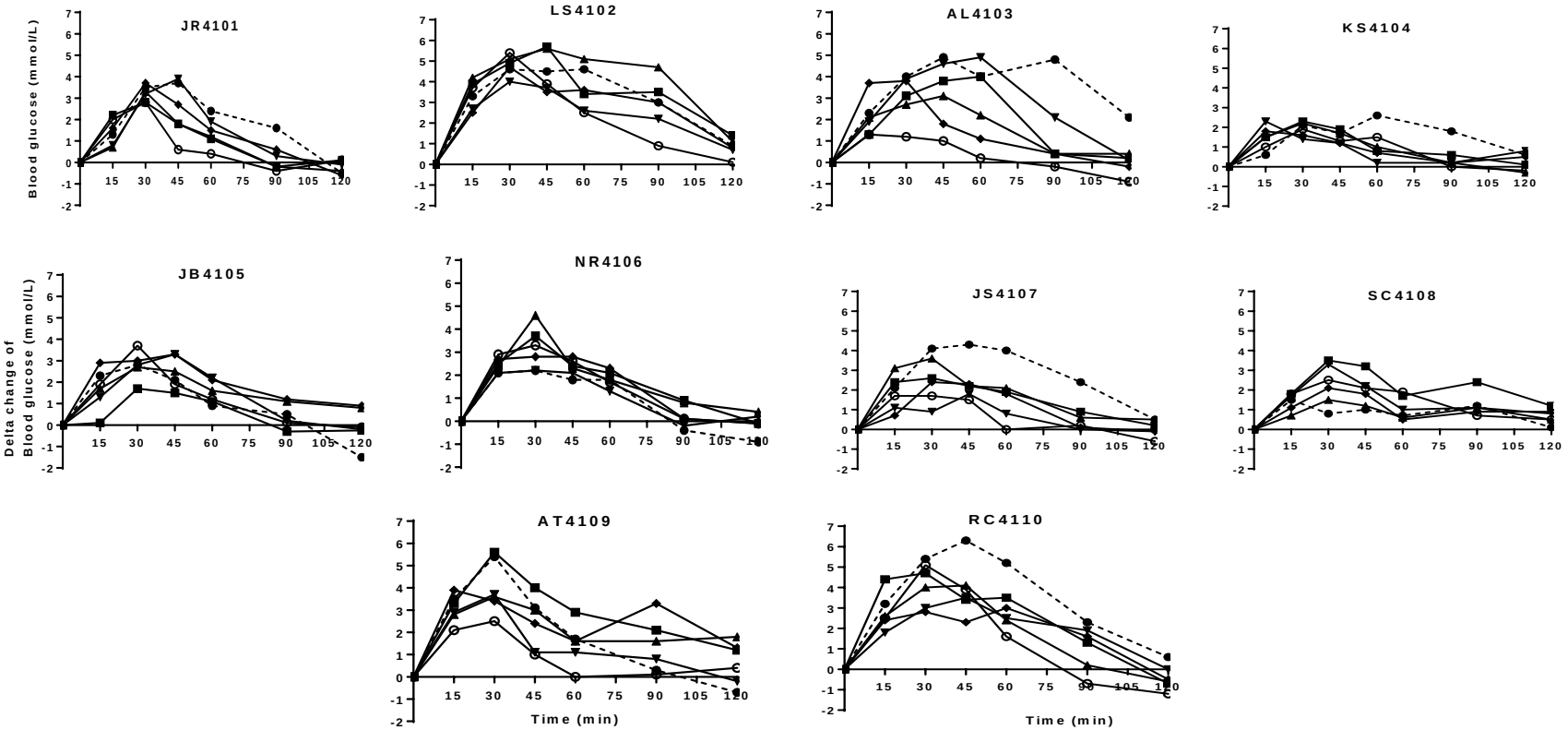


Figure 54: Capillary BG, delta change from baseline for the 5 different test foods plus glucose control, n=10 individuals

rk/h, red kumara hot (shown with closed square ■); gk/h, gold kumara hot (shown with closed inverted triangle▼); rk/hs, red kumara hot with skin (shown with closed triangle▲); rk/c, red kumara cool (shown with closed diamond ◆); p/h, standard potato hot (shown with open circle ○); c, glucose control (shown with closed circle and dotted line)

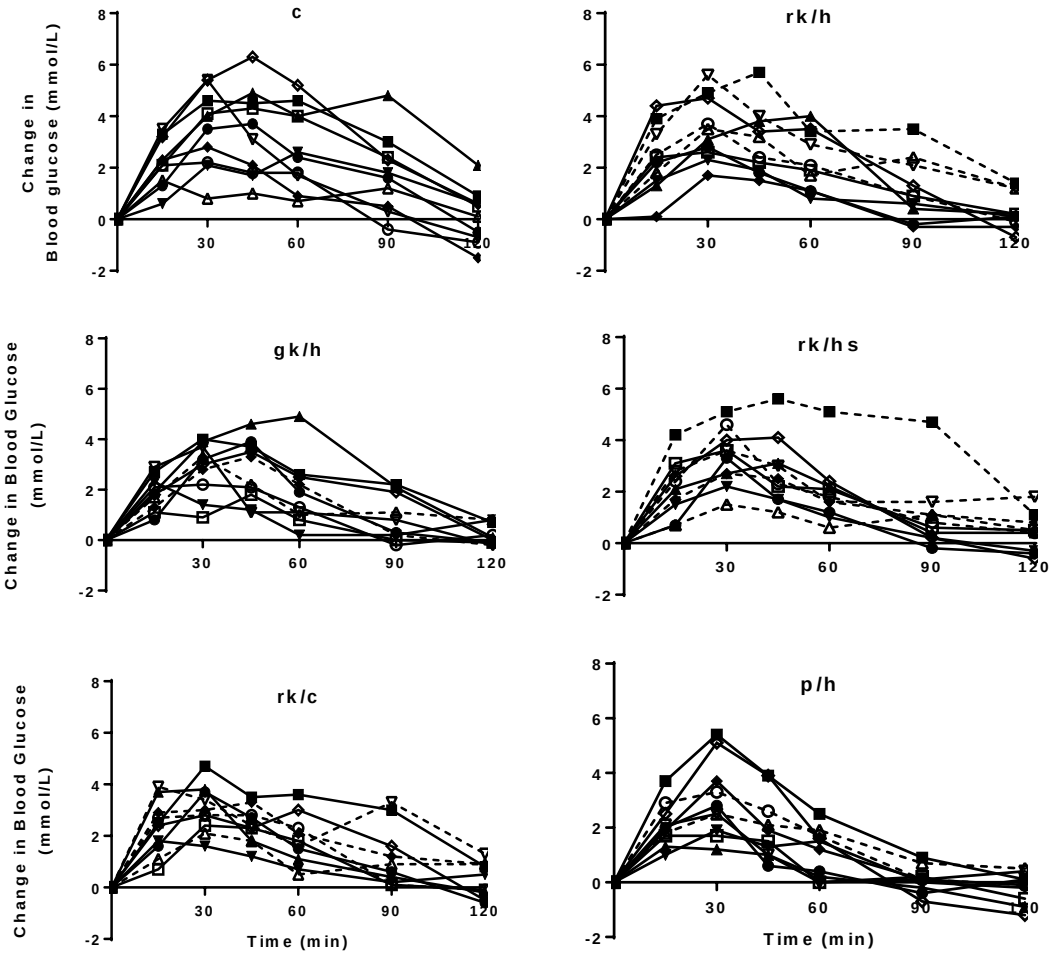


Figure 55: Change in BG for each of 6 test foods, n=9 (minus outlier) individuals, test food greater than glucose curve shown as per dotted line)

RW4111 (closed circle); AL4113 (closed triangle); KS4114 (closed inverted triangle); AW4115 (closed diamond); AZ4116 (open circle); NR4117 (open square); AT4118 (open triangle); FR4119 (open inverted triangle); SC4120 (open diamond)

The iAUC for BG in the 10 participants is shown in Table 44. The mean iAUC shows inter-individual variation, with 50% of the participants (5/10) with unexpected iAUC test food results greater than their respective glucose control (LS4102, JB4105, NR4106, SC4108, AT4109). There was no pattern or consistency to these results. The incremental area under the glucose curve at time 0-120min using one way ANOVA showed significance between glucose control and test food, as shown in Figure 56 (P=0.0230) with no statistical differences shown in *post hoc* analysis. However, there may still be differences

Table 44: Incremental Area Under the Curve (iAUC) (mmol/l * min) for the 10 participants at time 0-120 min

Participant no.	c	rk/h	gk/h	rk/hs	rk/c	p/h
1 (JR4101)	225.6	127.2	169.5	120.9	171.8	95.1
2 (LS4102)	393.0	420.0	291.0	495.8	343.5	279.8
3 (AL4103)	433.5	228.0	330.8	186.0	175.3	73.5
4 (KS4104)	187.5	123.0	96.0	110.4	98.25	99.8
5 (JB4105)	154.5	79.9	166.5	184.5	234.8	142.5
6 (NR4106)	147.7	202.1	126.1	210.0	179.3	173.3
7 (JS4107)	327.0	180.8	76.5	206.3	124.5	84.0
8 (SC4108)	102.8	255.8	175.5	105.0	126.8	167.3
9 (AT4109)	231.5	339.8	162.5	252.0	300.0	93.0
10 (RC4110)	418.5	302.1	237.8	225.0	224.1	232.9

c, glucose control; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot

Table 45 shows the GI units calculated using iAUC for the individual participants as per International GI methodology (Chapter 1.5.8). 50% of the 10 participants had at least one GI value greater than 100, when compared to the glucose control. The GI for rk/h ranged from 52 to 249 units, gk/h ranged from 51 to 171 units, rk/hs ranged from 43 to 142 units, rk/c ranged from 38 to 152 units and p/h ranged from 17 to 163 units. This wide variation resulted in a standard deviation (SD) of between 36 to 63 units and the SEM between 11.4 to 20.1 units (Figure 56). The highest mean (SD) GI food was rk/h being 99.4(63.5) units. Literature shows that changes to cooking process, increasing dietary fibre and change in resistance starch decreases overall GI. To ensure consistency, the cooking process was standardised, however, increasing dietary fibre by keeping the kumara skin on (rk/hs) when compared to rk/h tended to reduce the GI to 87.1(36.1) units (ns). Consumption of the cooked red kumara cold (rk/c) by delaying holding time, expected to change the resistance starch composition and reduced the GI to 87.3(41.6)units. Different varieties of kumara also had a different GI. The gk/h had a lower mean (SD) GI of 79.0(39.3) units when compared to the rk/h. Overall, p/h had the lowest GI of 67.7(45.0)units, classified as M-GI and lower GI than all of the kumara varieties.

Table 45: GI (units) calculated using the iAUC BG in 10 participants

Participant no.	rk/h	gk/h	rk/hs	rk/c	p/h	P value
1 (JR4101)	56	75	54	76	42	
2 (LS4102)	107	74	126	87	71	
3 (AL4103)	53	76	43	40	17	
4 (KS4104)	66	51	59	52	53	
5 (JB4105)	52	108	119	152	92	
6 (NR4106)	137	85	142	121	117	
7 (JS4107)	55	23	63	38	26	
8 (SC4108)	249	171	102	123	163	
9 (AT4109)	147	70	109	130	40	
10 (RC4110)	72	57	54	54	56	
Mean	99.4	79.0	87.1	87.3	67.7	0.6333
SD	63.5	39.3	36.1	41.6	45.0	
SEM	20.1	12.4	11.4	13.2	14.2	

rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot,

Figure 56 showed a significance when comparing $iAUC_{GlucoseT0\text{-}120m}$ on different test food but *post hoc* analysis found no significance. Figure 57 showed the GI for each of the test food when compared to the glucose standard as control. The highest GI was the rk/h and the lowest GI was p/h. Data from study 1 showed that 34% (17/50) of test foods unexpectedly generated an iAUC greater than the glucose control reference (see Figure 54). If this data was valid, it would indicate the 50g available CHO from the kumara/potato test food resulted in a higher BG response than 50g glucose control solution. A number of possible reasons may explain this discrepancy, including (i) unexpected high intra-individual variation, or (ii) inaccurate data for available CHO content of kumara published within the New Zealand Concise Composition Table. In order to test the second hypothesis, a second study was then conducted using the identical International protocol. For this study, there was a need to analyse the test food using an accredited company to determine the measured CHO content of the test food. Results are presented in $KumaraGI_{analysed}$ (Chapter 5.4.2).

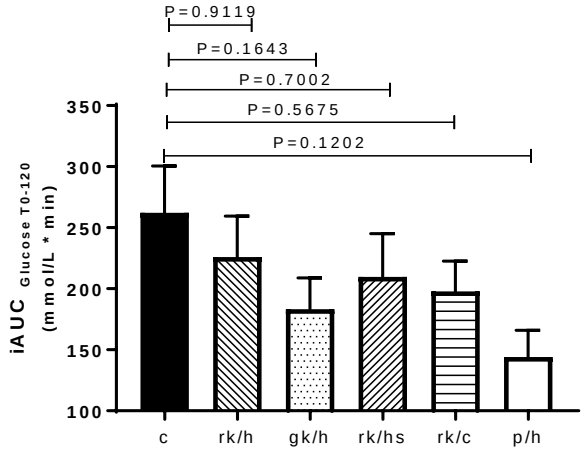


Figure 56: Incremental area under the glucose curve at time 0-120 repeated measures using one way ANOVA (P<0.05) and Tukey's test (ns), n=10 individuals, (Mean±SEM). c, glucose control; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot, One way ANOVA, P=0.0230, Tukey's test, ns

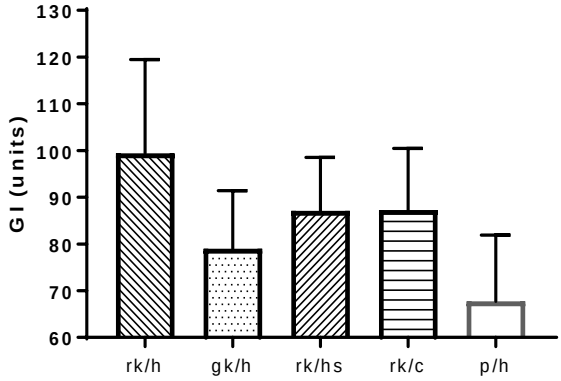


Figure 57: GI using one way ANOVA (ns) and Tukey's test (ns); n=10 individuals, (Mean±SEM); GI, Glycaemic Index; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot, One way ANOVA, P=0.6333, Tukey's test, ns

5.4.2 Results from Study 2, KumaraGI$_{analysed}$

The baseline characteristics of the ten participants who completed Study 2 are presented in Table 46 and included 8 females and 2 males (Table 46). All participants completed all 6-arms of the study, and there were no dropouts. Participants were young, lean and healthy. Ethnicity was 60% Caucasian, 30% Chinese and 10% Indian. Mean (SD) age was 25.1(6.5) years. Mean (SD) weight was 62.3(7.6) kg with a mean (SD) BMI of 22.1(1.7) kg/m^2. All participants had normoglycaemia with a mean (SD) FBG of 5.3(0.2) mmol/l (Table 46). The individual capillary BG (mmol/l) for the 10 participants for KumaraGI$_{analysed}$, is shown in Figure 58. The dotted lines represent the glucose control for comparison with the test food. Participant AD4112 had an unusually low BG response to the control arm when compared to the other test foods with no clear glucose peak. There was a need to determine this as an outlier where iAUC was ≥3 SD of the mean (Figure 59). This individual was excluded from the group analysis, hence all data presented in this section is for n=9 participants.

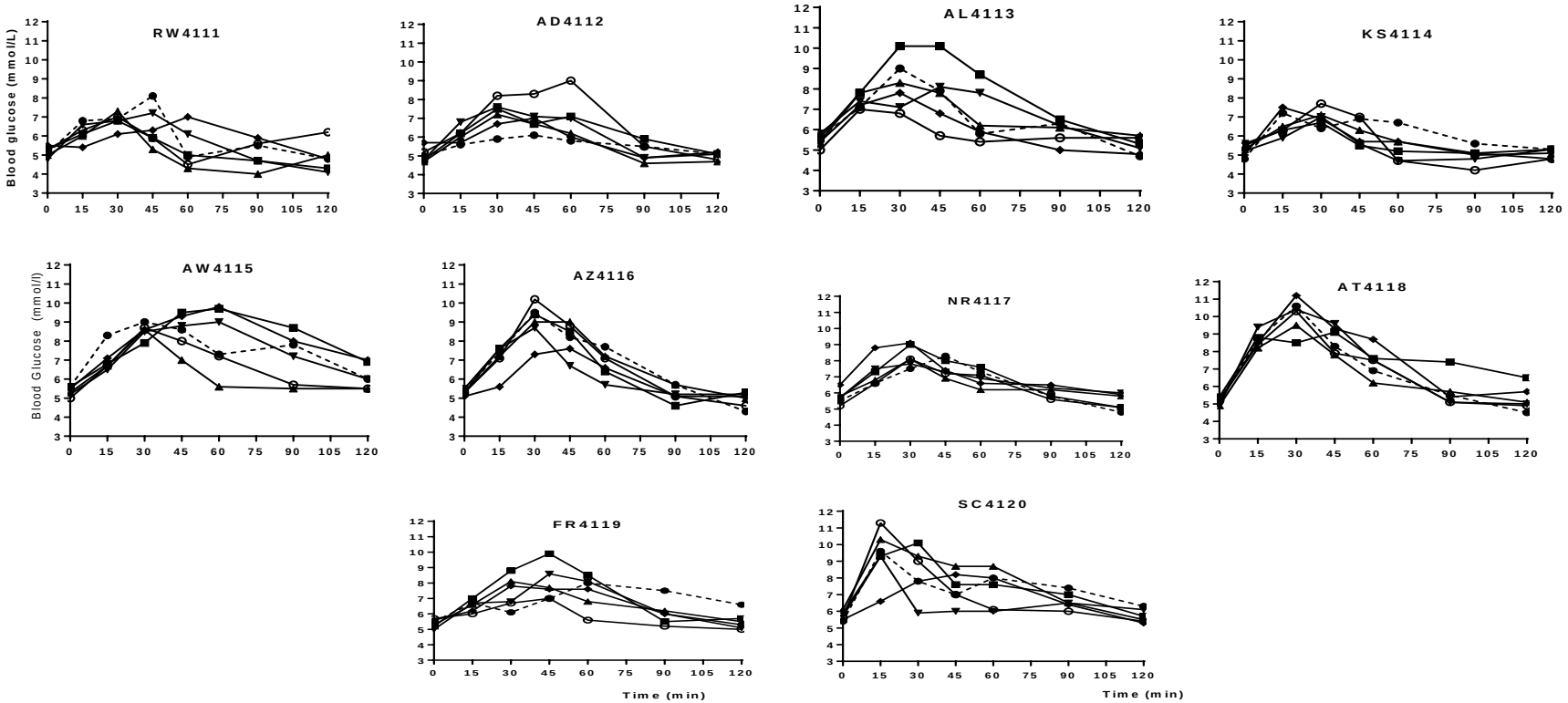


Figure 58: Capillary blood glucose changes in response to 5 test foods plus glucose control (shown as dotted lines) n=10 individuals.

rk/h, red kumara hot (shown with closed square ■); gk/h, gold kumara hot (shown with closed inverted triangle▼); rk/hs, red kumara hot with skin (shown with closed triangle▲); rk/c, red kumara cool (shown with closed diamond ❁); p/h, standard potato hot (shown with open circle ○); c, glucose control (shown with closed circle and dotted line

Table 47 shows the mean capillary BG for the test foods at baseline (Time 0), after 15, 30, 45, 60, 90 and 120 minutes. The mean FBG ranged from 5.3-5.5mmol/l, and was within the healthy fasting BG range. The mean BG at 120 minutes returned within 0.2mmol/l of the FBG for the 9 participants (excluded outlier). The mean FBG ranged from 5.3-5.5mmol/l, and was within the healthy fasting BG range. The mean BG at 120 minutes returned within 0.2mmol/l of the FBG for the 9 participants (excluded outlier).

Table 46: Baseline Characteristics (n=10)

n=10	Mean±SD (range)
Age (years)	25.1±6.5 (19-36)
Gender	80% female
Ethnicity	60% Caucasian, 40% Asian
BW(kg)	62.3±7.6 (47-76)
Height (m)	1.68±0.08 (1.55-1.78)
BMI(kg/m^2)	22.1±1.7 (20.2-27.4)
FPG(mmol/l)	5.3±0.2 (5.0-5.5)

Mean±SD (range), BW, body weight; BMI, Body Mass Index; FPG, Fasting plasma glucose

Table 47: Mean (SEM) capillary BG for the 5 test foods and glucose control at 0, 15, 30, 45, 60, 90 and 120 minutes, n=9 individuals

	c	rk/h	gk/h	rk/hs	rk/c	p/h
T0	5.3 (0.1)	5.4 (0.1)	5.3 (0.1)	5.3 (0.1)	5.5 (0.1)	5.3 (0.1)
T15	7.4 (0.4)	7.3 (0.3)	7.4 (0.4)	7.2 (0.4)	6.9 (0.4)	7.2 (0.5)
T30	7.9 (0.5)	8.5 (0.4)	7.7 (0.4)	8.3 (0.3)	7.9 (0.5)	8.2 (0.4)
T45	7.6 (0.3)	8.1 (0.5)	7.5 (0.4)	7.3 (0.4)	7.5 (0.4)	7.3 (0.3)
T60	6.8 (0.3)	7.3 (0.5)	6.9 (0.4)	6.3 (0.4)	7.2 (0.4)	6.5 (0.4)
T90	6.4 (0.3)	6.1 (0.4)	5.9 (0.3)	5.6 (0.3)	6.2 (0.4)	5.6 (0.3)
T120	5.2 (0.3)	5.2 (0.2)	5.3 (0.2)	5.3 (0.1)	5.4 (0.2)	5.2 (0.2)

c, glucose control; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot

Notably, as for study 1, 3 participants (e.g. RW4111, KS4114, NR4117) had little increase in BG, again possibly due to good insulin sensitivity, for all test foods. In general, the glucose curves were much lower than in KumaraGI$_{calculated}$ (Study 1). The increase in BG occurred in all 9 participants, where their highest BG reading ranged from 15-60 minutes post ingestion of the test food. This BG peak usually dropped back to FBG levels by 120 minutes. In these 9 participants, 33% (15/45) of the test foods exceeded the glucose control. Figure 60 shows individual delta change in capillary BG, from baseline for the 5 test foods plus glucose control for 9 participants, where the change ranged between -1.1 to 5.7mmol/l.

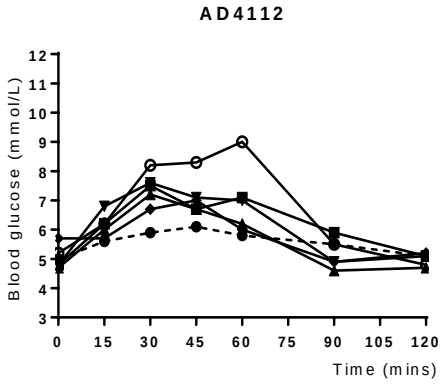


Figure 59: Outlier participant excluded from Study 2; absence of plasma glucose peak following consumption of the 50g glucose control treatment

rk/h, red kumara hot (shown with closed square ■); gk/h, gold kumara hot (shown with closed inverted triangle▼); rk/hs, red kumara hot with skin (shown with closed triangle▲); rk/c, red kumara cool (shown with closed diamond ❁); p/h, standard potato hot (shown with open circle ○); c, glucose control (shown with closed circle and dotted line

Figure 61 shows the delta change in BG for 9 participants for each of the test foods plus glucose control. The unexpectedly high glucose peaks where test food is greater than control are highlighted as dotted lines. These plots were then used to calculate iAUC glucose and also GI values.

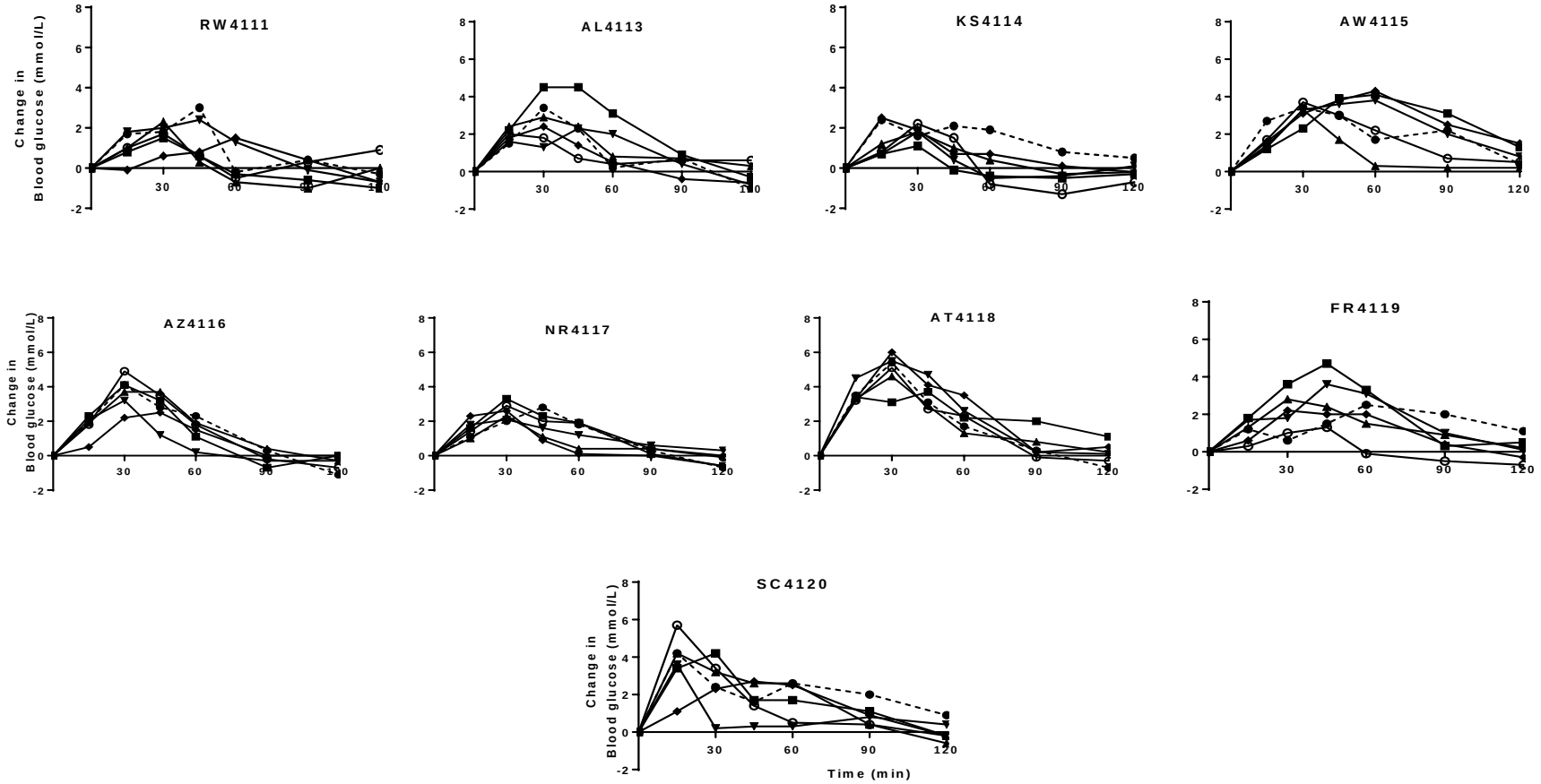


Figure 60: Individual capillary BG, delta change from baseline for the 5 different test food plus glucose control, n=9 individuals

rk/h, red kumara hot (shown with closed square ■); gk/h, gold kumara hot (shown with closed inverted triangle▼); rk/hs, red kumara hot with skin (shown with closed triangle▲); rk/c, red kumara cool (shown with closed diamond ❁); p/h, standard potato hot (shown with open circle ○); c, glucose control (shown with closed circle and dotted line

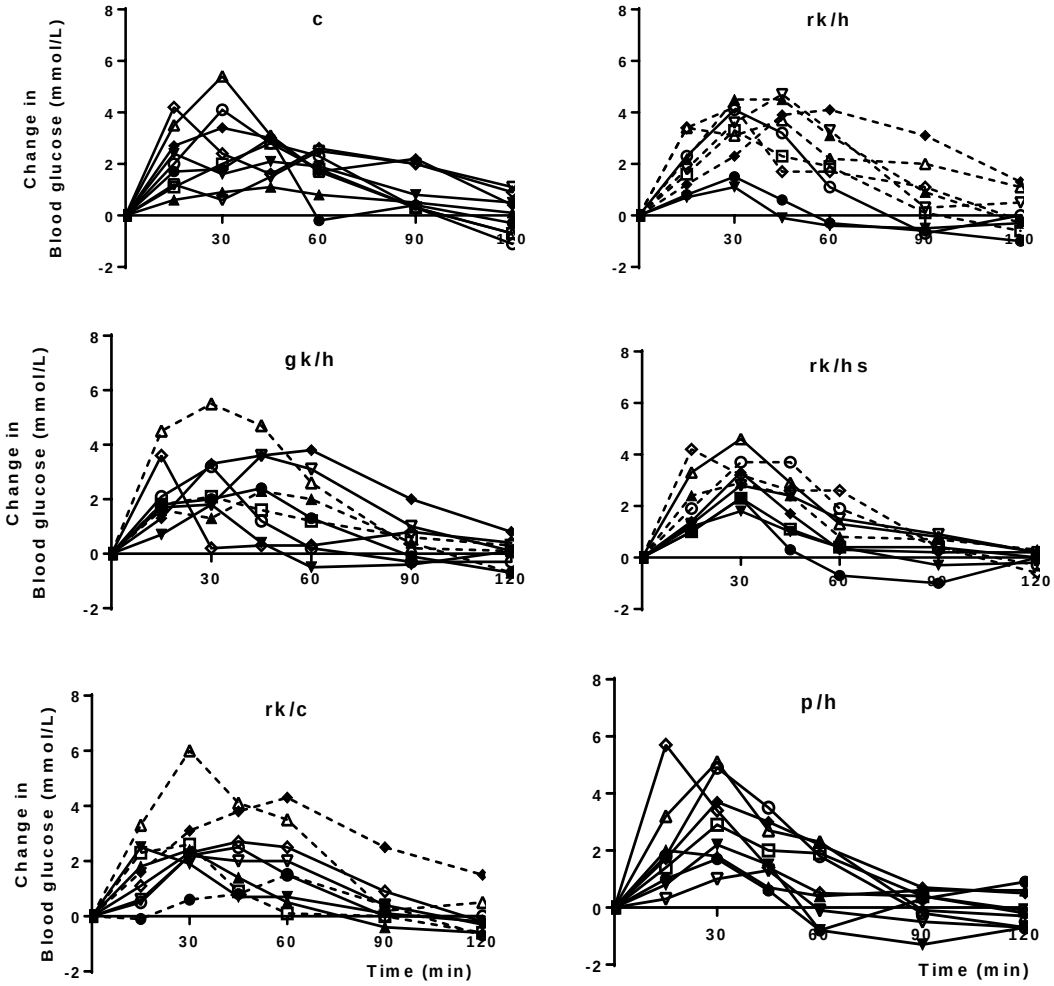


Figure 61: Mean BG delta change for each of the 6 test foods, n=9 individuals, test food greater than glucose curve (shown as per dotted line)

RW4111 (closed circle); AL4113 (closed triangle); KS4114 (closed inverted triangle); AW4115 (closed diamond); AZ4116 (open circle); NR4117 (open square); AT4118 (open triangle); FR4119 (open inverted triangle); SC4120 (open diamond)

The iAUC for blood glucose was calculated in the 9 participants using the delta change as shown in Table 48. The test was completed in a controlled and supervised environment. However, the mean iAUC showed considerable inter-individual variation, with 78% of the participants (7/9) with iAUC test food results greater than their respective glucose control.

Table 48: Incremental area under the glucose curve for the 9 participants at time 0-120 minutes

Participant no.	c	rk/h	gk/h	rk/hs	rk/c	p/h
1 (RW4111)	106.5	80.3	133	96.6	69.8	73.5
3 (AL4113)	135.2	262.5	137.9	159.0	109.6	103.5
4 (KS4114)	165.8	55.6	62.52	75.9	96.3	127.2
5 (AW4115)	246.8	315.8	280.5	111.8	321.8	204.0
6 (AZ4116)	203.7	176.9	111.9	193.6	111.8	204.6
7 (NR4117)	142.2	160.2	132.0	87.0	98.3	148.4
8 (AT4118)	231.5	279.0	286.5	218.3	293.3	221.4
9 (FR4119)	182.3	242.3	207.8	161.3	128.4	65.4
10 (SC4120)	255.0	208.7	98.3	222.3	172.8	179.8

c, glucose control; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot

Using the iAUC from Table 48 above, the GI was calculated as shown Figure 62. The kumara varieties are all in the H-GI range from mean of 95.2 to 102.2 units (Table 49). P/h is also in the H-GI range with a mean of 92.7units. The iAUC glucose is shown on Figure 62. Notably, rk/h had a trend towards a greater iAUC compared to the glucose control.

Table 49: GI (units) calculated using iAUC blood glucose in 9 participants

Participant no.	rk/h	gk/h	rk/hs	rk/c	p/h	P value
1 (RW4111)	75	125	91	66	69	
3 (AL4113)	194	102	118	81	77	
4 (KS4114)	34	38	46	58	77	
5 (AW4115)	128	114	45	130	83	
6 (AZ4116)	87	55	95	55	100	
7 (NR4117)	113	93	61	69	104	
8 (AT4118)	121	124	94	127	96	
9 (FR4119)	133	114	88	70	36	
10 (SC4120)	82	39	87	68	71	
Mean (n=9)	102.2	95.2	96.2	98.3	92.7	0.3019
SD	9.3	7.6	6.9	8.3	5.9	
SEM	3.1	2.5	2.3	2.8	2.0	

c, glucose control; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot. Mean±SEM; p-value, one way ANOVA

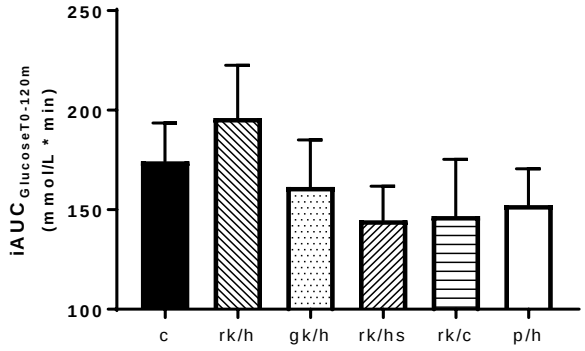


Figure 62: Incremental area under the glucose curve at time 0-120 repeated measures using one way ANOVA (ns), n=9 individuals, P=0.2125

c, glucose control; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot

Figure 63 presents the GI data for both KumaraGI$_{calculated}$ and KumaraGI$_{analysed}$. It is notable that the results from study 2 differ considerably from study 1. Two trends appear; (i) GI of all test foods tend to be consistently higher in KumaraGI$_{analysed}$, and (ii) variability within each test food is far lower as demonstrated by the smaller error bars.

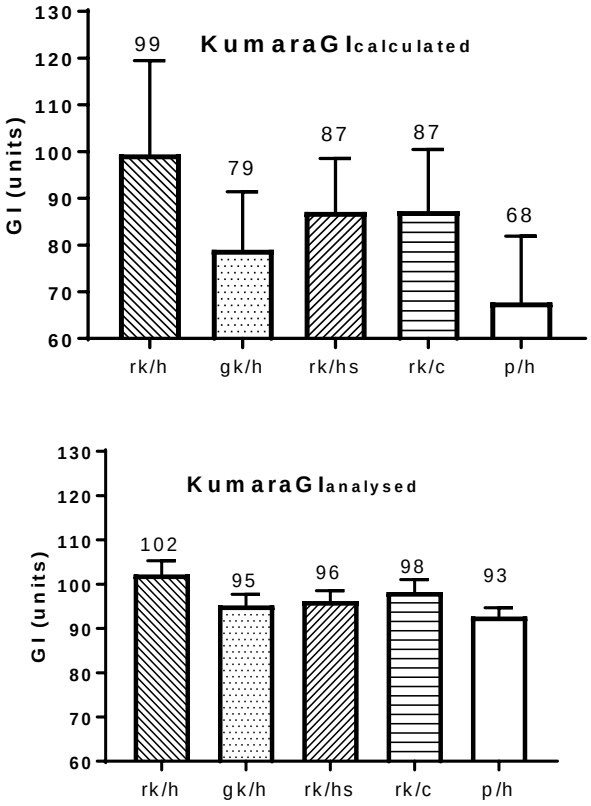


Figure 63: GI for the 2 studies KumaraGI$_{calculated}$ and KumaraGI$_{analysed}$, Mean (SEM). calculated, P=0.6333; analysed, P=0.3019

Despite these (between study) trends, there are several consistent findings;

(i) Kumara of all varieties had a GI>70units

(ii) (rk/h had the highest GI

(iii) p/h had the lowest GI; all kumara varieties and formats were higher GI than standard potato

(iv) There was considerable variation within and between participants; with a high percentage of test foods generating a higher peak and iAUC glucose than the 50g glucose control treatment in a high percentage of individuals.

Again, these effects did not reach statistical significance but may have importance in dietetic practice. There was no evidence from either study that kumara was moderate/L-GI.

Table 50 compares the 2 studies. Following analysis by AsureQuality Ltd, kumara presented with almost double the available CHO content in all varieties of kumara (27-29g CHO/100g) when compared to standard potato (14g/100g CHO/100g). Available CHO content also varied between all kumara types in both studies resulted in H-GI (>70 units). Potato had a lower GI than kumara in both studies. Notably, despite the lower weight of kumara test food consumed by participants in KumaraGI$_{analysed}$, there was a trend for the GI of these foods to be higher than for KumaraGI$_{calculated.}$ Comparison of Figure 55 and Figure 61 shows that the BG peak for the glucose control was much lower in KumaraGI$_{analysed}$. Clearly response was very different between different individuals confirming inter-individual variation.

Table 50: Combined KumaraGI$_{calculated}$ and KumaraGI$_{analysed}$ comparison

	rk/h	gk/h	rk/hs	rk/c	p/h
KumaraGI$_{calculated}$ (weight, g)	250	250	250	250	285
GI mean	99.4	79.0	87.1	87.3	67.7
SD	63.5	39.3	36.1	41.6	45.0
SEM	20.1	12.4	11.4	13.2	14.2
Composition Table (g available CHO/100g)	20	20	20	20	18
KumaraGI$_{analysed}$ (weight, g)	183	184	170	183	357
GI mean	102.2	95.2	96.2	98.3	92.7
SD	9.3	7.6	6.9	8.3	5.9
SEM	3.1	2.5	2.3	2.8	2.0
Analysed by AsureQuality (g available CHO/100g)	27	27	29	27	14

c, glucose control; rk/h, red kumara hot; gk/h, gold kumara hot; rk/hs, red kumara hot with skin; rk/c, red kumara cooled; p/h, potato hot; GI, Glycaemic Index; CHO, Carbohydrates; SD, standard deviation; SEM, standard error of the mean,

5.5 Discussion

Kumara is one of the oldest staple foods and is one of the top ten leading food crops with origins dating back to pre-historic Polynesians, 14th Century A.D (Woolfe, 1992) and has become a staple food for New Zealand (Yen, 1961). It was an important food item for the PREVIEW:NZ study. The 2 kumara and GI sub-studies assessed the GI of kumara and standard potato and resulted in some interesting findings, which whilst not statistically significant may be of relevance to dietetic practice. In summary, the GI of kumara was not significantly lower than standard potato, rather it was identified as a H-GI food item. Changes to the food matrix through heating and cooling and inclusion of the kumara skin, altering the fibre content of the test food, showed some reduction in GI but did not lower it sufficiently to change the GI category and hence it remained as a H-GI food. The standard potato had a lower GI than kumara and was classified in the medium GI category. The hypothesis that Kumara had a lower GI than standard potato was therefore rejected.

To review the outcomes in more detail, it was clear from both studies, KumaraGI$_{calculated}$ using calculated available CHO and KumaraGI$_{analysed}$ using analysed data, that kumara is a H-GI food, ranging from 79.0 to 99.4 units (H-GI) and 95.2 to 102.2 units (H-GI) for KumaraGI$_{calculated}$ and KumaraGI$_{analysed}$, respectively. Unexpectedly, study 2 gave a lower weight of test food to participants yet a higher GI was measured. Of course a direct comparison of GI between the 2 studies is not possible as study 1 and study 2 recruited 2 different sets of participants, yet this was still an unexpected finding. It highlights the difficulty in assigning GI (a physiological) response to a single food item. On the contrary, standard potato, previously perceived by many to be a less healthy food option with a higher GI factor than kumara (Atkinson et al., 2008; Atkinson et al., 2015; Foster-Powell & Miller, 1995), had a mean (SD) GI of 67.7(45.0)units (M-GI) and 92.7(5.9)units (H-GI) for KumaraGI$_{calculated}$ and KumaraGI$_{analysed}$, respectively. In this thesis, both study KumaraGI$_{calculated}$ and KumaraGI$_{analysed}$ showed standard potato to have a lower GI than all of the kumara test foods. Hence, potato has a lower GI than all varieties of kumara and is classified as the only test food with a medium GI (KumaraGI$_{calculated}$ study, ns).

The use of GI values for risk management for the development of T2D remains controversial with many factors affecting GI, such as food environment of production, food matrix, food preparation, mixed meals and individual variation between participants consuming the food (Jenkins. et al., 1988; Kataoka. et al., 2013; Matthan et al., 2016; Venn. & Green., 2007; Venn. et al., 2010; Williams. et al., 2008; Wolever. et al., 1986). Following the results from these 2 sub-studies, it is clear that using the GI concept may be more complex than expected and may lead to confusion when educating the public. GI is extremely variable. The guidelines in some countries encourage a L-GI diet and one of the dietary recommendations in the PREVIEW study also encouraged L-GI in the HP arm (Chapter 1.6). However, confusion around the classification of GI for foods arises, with GI for kumara ranging from 48 to 77 units, i.e. L-GI to H-GI (Foster-Powell & Miller, 1995; Foster-Powell et al., 2002). This inconsistency extends to the standard potato, with GI varying according to potato varieties, maturity level, starch structure, food processing techniques and

composition of the meal (Aldughpassi et al., 2012; Fernandes et al., 2005; Nayak et al., 2014). The GI for standard potato also appears to cross all three GI groups, from 47 to 70 units (Fernandes et al., 2005; Foster-Powell & Miller, 1995; Foster-Powell et al., 2002; Nayak et al., 2014). Modifiable factors around food matrix include food processes in the preparation/cooking method of test food can affect the GI, as extreme temperatures changes the starch structure as a fraction of the amylopectin changes to amylose affecting the overall GI (Åkerberg et al., 1998; Aldughpassi et al., 2012). Kim et al reported a lower GI due to a change in resistance starch of pasta during the cooling period (Kim et al., 2008); this result was confirmed in this chapter with a trend (although not statistically significant) towards L-GI for consumption of cooled test food vs. hot. This chapter did not test the mixed meal effect, with the addition of protein, fat and fibre reported to lower GI in previous research (Aldughpassi et al., 2012; Miller et al., 1992; Monro & Shaw, 2008), including a study conducted by myself and collaborators where rice mix with added fibre, protein and fat using wild rice, nuts and seeds lowered GI in Chinese participants with T2D (Zhang. et al., 2015).

Inter-individual variation results in inconsistency of use of GI for chronic disease risk management and prevention (Kataoka. et al., 2013; Matthan et al., 2016; Venn. et al., 2010; Williams. et al., 2008). Ethnic differences have raised increasing interest within recent research, with rice being lower GI for Caucasian women and higher GI when consumed by Chinese women (Kataoka. et al., 2013; Venn. et al., 2010). Matthan et al reported that differences in inter- and intra-individual absorptive factors alters the digestion in the small intestine changing the GI, with mean variation to be 20% and 25%, between intra- and inter-individual variations, respectively (Matthan et al., 2016). One of the notable findings in this current study was the high variability between individuals which, despite careful adherence to the International GI methodology and assessment guidelines (Atkinson et al, 2008; Wolever. et al., 1991) may have significantly influenced the outcome of the study. This demonstrated that assigning a single GI value to a food may be problematic as variation was seen when assessing 10 healthy and lean individuals, let alone individuals with IR and metabolic syndrome.

In this chapter, only inter-individual variation was investigated and was found to be high in both studies KumaraGI$_{calculated}$ and KumaraGI$_{analysed}$, with almost half of the participants in both studies having iAUC BG concentrations following the test foods greater than the glucose control. Also, unexpectedly in KumaraGI$_{analysed}$, one participant was classified as an outlier as the glucose control treatment generated no postprandial rise in blood glucose. This was difficult to explain as all tests were supervised to ensure all of the test food was consumed on each occasion in the time allowed, and it was confirmed that this individual (AD4112) did consume the full 50g glucose drink and hence compliance was 100%. The other possibility was gastrointestinal malabsorption. However, there was no report of adverse GI symptoms by the participant. This participant was identified as a statistical outlier and excluded from Study 2. Other possible reasons could include poor participant preparation (e.g. non-fasting on the test day, excessive exercise the day prior), and issues such as stress upon seeing the glucose control solution. Anxiety or stress has been hypothesised to cause delayed gastric emptying and/or insulin antagonistic effects on stress

hormones in turn affecting glycaemic response (Brouns et al., 2005). The final explanation may have been a simple failure of the handheld blood FP monitor, although all monitors were calibrated and shown to be in good working order each morning before the study was started.

In both studies, 33-34% of test foods generated a postprandial peak, greater than the glucose control. This was most unexpected. The International GI methodology mandates the inclusion of 10 participants to assess new foods (Brouns et al., 2005). However, Venn et al recommends enrolment of 26 participants for GI testing to reduce inter-individual variation (Venn et al, 2013). Matthan et al measured glucose and insulin response in 63 participants (Matthan et al., 2016) to investigate variability, however, Wolever has stated that increasing the number of participants from 10 to 63 has little or no effect on the mean or SD and that dietary recommendations using this GI analysis method of n=10 are valid and recommended (Wolever et al., 2017). Notably, both previous GI analyses (1995 and. 2002) followed the International GI methodology, yet reported differing results. Whether increasing the number of participants in the current kumara studies would have assisted with a more accurate determination of GI for these test foods is unknown, but of interest.

The reference food (control) used in these current studies was monosaccharide glucose drink, commonly used rather than the alternate standard of white bread in order to reduce variability that may be introduced during production of a commercial food product such as bread (, and in turn the intra- and inter-individual variation in GI (Brouns et al., 2005; Wolever et al., 2003).

Considering the wider concept and utility of GI, there is conflicting research around the benefits of L-GI and T2D in interventional and epidemiological studies (Augustin. et al., 2015; de Boer & Aiking, 2017; Du et al., 2009; Jenkins. et al., 1987; Jenkins. et al., 2002; Wolever. & Jenkins., 1986). The GI concept has been integrated in the dietary guidelines in Australia, France, Sweden, Canada and South Africa and recommended by the Food and Agricultural Organisation (FAO) and WHO that dietary CHO should be low in GI and high in fibre (FAO, 1998; Ludwig, 2002). New Zealand uses L-GI recommendations in combination with lower TE, modified macronutrients (Mann & Te Morenga, 2013; New Zealand Guidelines Group, 2011). DioGENES is an important study which conducted a 6-month intervention in 8 European countries involving 932 O/W participants on higher protein and L-GI diet (Goyenechea et al., 2011; Larsen et al., 2010; Ludwig & Ebbeling, 2010). L-GI was shown to be successful, where L-GI (HP) group had the lowest dropout and least weight regain (0.93kg less than M-GI, P=0.003) after 6 months and this was maintained for 12 months (Astrup et al., 2015; Larsen et al., 2010; Ludwig & Ebbeling, 2010). This was an important intervention that led to the design of the PREVIEW diabetes prevention study, with L-GI advice given for 1 study arm, higher protein lower GI diet group (HP:L-GI).

The results of the current kumara and GI substudies are relevant for the PREVIEW:NZ cohort due to the popularity of kumara consumption within New Zealand and the conflicting information on whether this sweet potato/kumara is L-GI or H-GI. Also, there are 3 varieties of kumara in New Zealand – red, golden and orange - but no validated data available on their respective GI content. The 2 substudies have shown that GI (a physiological rather than a food property) response is highly varied and difficult to predict. Even for a single food such as kumara consumed alone under highly standardised conditions, there is continued confusion around whether kumara and potato is L-GI or not. For the PREVIEW study, prior to these two sub-studies, we had advised participants that kumara is L-GI and should be encouraged in the HP:L-GI group. However, after conducting these two sub-studies, the results were contradictory and nutritional group advice for the HP:L-GI was changed.

The strengths for both $KumaraGI_{calculated}$ and $KumaraGI_{analysed}$ studies for this thesis, include the fact that the test foods were consumed in a clinical setting under direct surveillance to ensure standardisation of test food consumption; there was constant assessments, supervision and fingerprick was timed and accurate based on the International GI methodology protocol. Another strength of this study is that 10 participants, as recommended were assessed in study 1. A possible weakness is that 1 of the participant had to be excluded as an outlier in study 2. Even though n=10 was recommended in the International GI methodology, the inter-individual variation has resulted in significant variation in GI. Wolever states than a sample size of 63 or a sample size of 10 has no major effect on the group in mean and SD (Wolever et al., 2017). However, if all the GI testing followed the International GI methodology and resulted in highly variable data, how can we attribute a single GI value and/or classify foods which range from L-GI to H-GI. In this study, both $KumaraGI_{calculated}$ and $KumaraGI_{analysed}$ defined kumara as H-GI, higher than standard potato. Although this was just a trend, certainly there was no evidence that kumara should be recommended instead of standard potato due to a lower GI. Even though the International GI methodology was carefully followed, it was difficult to determine a consistent GI due to substantial variability in individual responses. Previously, there has been criticism of GI showing that the measurement lacks accuracy and precision and the clinical relevance has been questioned (Ludwig, 2002). For a food with a GI of 70 units and a SEM of 10, the GI of the population is estimated to between 50 to 90 units, i.e. an imprecise estimate ranging from L-GI to H-GI. Using this in a clinical context, should we raise the question as to whether GI is a good approach when guiding patients, particularly those at risk of or with T2D who have even greater glycaemic variations, on healthy food choices and in nutritional guidelines? The clinical significance of these findings shows that GI is complex and too complicated to be of practical use in a clinical setting and as part general health recommendations.

5.6 Conclusions

Even though the International GI methodology was used and followed, it was difficult to determine a consistent GI result for the different test foods due to substantial variability in individual responses between foods. KumaraGI$_{calculated}$ used 50g available CHO as calculated from the Concise New Zealand Food Composition Tables (Plant and Food Research Limited & Ministry of Health, 2016). The results from KumaraGI$_{calculated}$ suggested the need to have these food items analysed to measure actual CHO content, and then to repeat this study to determine the GI of varying kumara types and cooking method using an accurately measured weight of test food equivalent to 50g of available CHO.

Both studies showed that both types of kumara tended to have higher GI than standard potato. Kumara does not appear to be low in GI and therefore arguably not a better food choice than standard potato for T2D prevention. The difference between glycaemic response within an individual and the GI of a food using population data has been acknowledged. However, individual glycaemic response clearly leads to high variability between individuals and therefore is difficult to attribute a single GI value even for individual foods for the general population in dietary guidelines. The data from this thesis chapter adds to this weight of evidence. Clinical relevance using GI has previously been debated as the measurement has been criticised in that it lacks accuracy and precision; and also stated as too complicated to be practical. Using this in a clinical context, it is clear that GI is a complex physiological response which can be highly variable; and this must raise the question as to whether it is a useful and/or reliable index for guiding the general public and patients in their food choices. Dietary recommendations for the PREVIEW:NZ study were revised in light of these findings.

Chapter 6 General Discussion and Conclusions

This thesis investigated the effect of a novel higher protein, lower GI (HP/L-GI) and lower fat diet recommendation compared with current higher CHO, lower protein, moderate GI (LP/M-GI) and lower fat diet recommendations, for better maintenance of BW and glucose control following a period of rapid weight loss. The cohort was a subgroup of adults in the international PREVIEW study recruited in Auckland, New Zealand. At the time of data analysis for this thesis, data from the PREVIEW International Phase 2 maintenance phase was still 'blinded' (i.e. not available for analysis as per the randomised diet groups), and hence 2 statistical approaches were undertaken. Firstly, a categorical analysis where a high protein and low protein cut-off was set and data analysed over the initial 6 months of the trial, and secondly a continuous analysis where longer term data was analysed over 24 months. In addition, 2 short substudies were conducted to investigate the GI of a commonly eaten New Zealand food item, the sweet potato/kumara.

As hypothesised based on a large number of previous studies (Geiker. et al., 2018; Haywood et al., 2017; Hjelmesaeth. et al., 2018; Jebb et al., 2017; Lean et al., 2017; Leslie et al., 2017; Leslie et al., 2016; McCombie et al., 2017; Rudovich et al., 2016; Sellahewa et al., 2017; Taylor et al., 2017; Zhyzhneuskaya et al., 2017), the use of a meal replacement LED led to very successful BW loss in a large percentage of the cohort. Again as hypothesised, individuals with higher BW at baseline lost more weight and FM when following the 8-week fixed intake (4MJ/d) LED. Men were heavier at baseline and also lost more absolute BW then women during LED. Men however, did not have a greater FPG improvement.

This significant weight loss resulted in a major improvement in metabolic health for all individuals who achieved the cut off by 8 weeks of ≥8% of baseline BW. Again this was expected, based on previous studies. In this thesis, the anthropometric benefits from LED included a reduction of BW and WC. A reduction in absolute and percentage FM and absolute android fat and reduction in absolute FFM although an increase in percentage FFM. Loss of FFM is a concern as FFM has a direct effect on thermogenesis, resting metabolic rate and insulin sensitivity therefore improving glycaemia (Goodpaster et al., 1999; Segal et al 1989; Stiegler & Cunliffe, 2006). This study also shows that improvements to anthropometric changes resulted in improvements to several glycaemia endpoints (FPG and HbA_{1C}).

It was hypothesised that improvements in glycaemia may be related to ethnicity, since risk status at a given age and BW is known to differ in different ethnic groups. For example, Asian Chinese and Indian have been shown to be at a high risk even before they gain a lot of excess weight and body fat (Chandalia et al., 2007; Duncan et al., 2004; Lin et al., 2009; Møller et al., 2014; Rush et al., 2007; Rush et al., 2004; Rush et al., 2009; Venn. et al., 2010; Wang et al., 1994; Wuhan et al., 2010). This may be related to where on the body the fat is deposited. Even a small amount of fat deposited in the visceral region, or even worse deposited in the liver or pancreas, may cause this high risk in slim, lower BMI (~BMI 23kg/m^2) Asian individuals (Chandalia et al., 2007; Duncan et al., 2004; Liu. et al., 2018; Rush et al., 2004; Rush et al., 2009; Wang et al., 1994).

On the contrary, the body composition of Maori/Pacific comprise more FFM overall and less centrally distributed FM and visceral fat than Caucasian and Asians, which in turn should have a positive effect on insulin sensitivity and glycaemia (Duncan et al., 2004; Rush et al., 2007; Rush et al., 2004; Rush et al., 2009); yet Maori/Pacific have more than 3 times higher risk of developing T2D than Caucasians (Ministry of Health, 2016). Genetic factors may have an influence on fat deposit, body composition and insulin resistance/T2D risk (Duncan et al., 2004; Rush et al., 2007; Rush et al., 2004). This is explained by the high prevalence of obesity and morbid obesity in Maori/Pacific living in New Zealand. The findings of this thesis showed that Maori/Pacific had the highest CID1/Baseline BW and had slightly more weight loss during the LED phase. However, Maori/Pacific did not lose significantly more absolute BW when compared to Caucasian or Other groups. Maori/Pacific also did not have a greater FPG improvement.

An important point to consider in PREVIEW:NZ is the cohort recruited. Different intervention trials have defined pre-diabetes in different ways, and this can result in a range of glucose levels from very 'early' pre-diabetes to much more advance 'late' pre-diabetes which is bordering on T2D. There are currently 3 international recommendations to diagnose pre-diabetes. The ADA uses a lower cut-off of either IFG of 5.6 to 6.9mmol/l or IGT (2h-PPG) of 7.8 to 11mmol/l (American Diabetes Association, 2016; American Diabetes Association, 2017). WHO recommends using a higher FPG cut off from 6.1 to 6.9mmol/l, the IGT (2h-PPG) remains the same (7.8-11mmol/l) (International Diabetes Federation, 2013). The newest approach is the use of a longer term marker of high blood glucose concentration, HbA_{1C} (ADA: pre-diabetes 40-48mmol/mol vs New Zealand: pre-diabetes 41-49mmol/mol) (American Diabetes Association, 2018; Barry et al., 2017, NZSSD., 2011). However, there has been some considerable debate as to which diagnostic criteria is recommended. ADA has the lightest approach and would identify a group of lower risk population when compared to the WHO (higher FPG) and an even 'higher risk/sicker' group based on the HbA_{1C} cut-off (Braatvedt et al., 2012; Guo et al., 2014; Sequeira & Poppitt, 2017) to diagnose pre-diabetes. In the PREVIEW study and hence the PREVIEW:NZ cohort in this thesis, the diagnosis of pre-diabetes using the ADA guidelines was used (either FPG and/or IGT), which probably resulted in 'early'/lower risk pre-diabetics. Whilst, HbA_{1C} was analysed, it was not used as an inclusion criteria. The mean HbA_{1C} for the PREVIEW:NZ participants at CID1/Baseline was 36.6mmol/l, which confirms they were on average a lower risk group. Perhaps not requiring PREVIEW participants to have a both raised FPG and raised IGT was part of the cause of this low HbA1c.

In the 3 largest diabetes prevention RCTs, Da Qing recruited their pre-diabetic cohort using an OGTT and either raised FPG or IGT (not both); with urinary glucose and albumin excretion for confirmation (Pan et al., 1997). USDPP used an even lower cut-off for FPG of 5.3-6.9mmol/l and standard IGT cut-off of 7.8-11mmol/l, diagnosis was either FPG or IGT, not both (Diabetes Prevention Program (DPP) Research Group, 2002). Lastly, FDPS used IGT only (7.8-11mmol/l), the first positive result required confirmation by calculating the mean of the next 2 IGT (2h-PPG) readings (Lindstrom et al., 2008). In the PREVIEW study and hence the PREVIEW:NZ cohort in this thesis, the diagnosis of pre-diabetes using the ADA guidelines was used (FPG and IGT).

Whilst, HbA_{1C} was analysed, it was not used as an inclusion criteria. The mean HbA_{1C} for the PREVIEW:NZ participant at CID1/Baseline was 36.6mmol/l, which confirms they were on average a lower risk group.

HbA_{1C} is a simple and cost-effective method that has been adopted by the ADA for 10 years (American Diabetes Association, 2018). It is argued that treating those diagnosed using the ADA glucose cut-offs is early intervention as this includes a healthier cohort when compared to the use of HbA_{1C} where individuals have higher circulating glycaemia and at a much higher risk of developing T2D. Lifestyle intervention has been shown to improve health and reduce the risk of developing T2D. However, the argument is whether intervening early (i.e. ADA-healthier population based on glucose cut-offs) is more beneficial or is there a need to focus only on the higher risk or later population (i.e. HbA_{1C}-sicker population) due to limited health resources (Barry et al., 2017).

As PREVIEW:NZ used the ADA cut-off for FPG, and there were a very large number of participants recruited on FPG rather than IGT in PREVIEW:NZ. There was a surprisingly high percentage who were no longer classified as pre-diabetic based on the OGTT by the time the intervention started. This may be due to change in lifestyle between the screening/enrolment phase and the trial start date. Perhaps this was not completely unexpected, as there is evidence that information given to an individual about an adverse health event (e.g. high risk of T2D) may cause them to consider their diet and other lifestyle factors (Bandura, 2004; Barry et al., 2017). There was no way in PREVIEW:NZ to assess whether this did happen, but it was clear that many individuals improved their risk of T2D ahead of the acute weight loss phase.

There was a high rate of dropout in PREVIEW:NZ, particularly in the Maori/Pacific group. It might be hypothesised that this was because the intervention was focused on the individual and not the wider family/whanau. New Zealand public health policy is strongly focused towards a whole-family/whanau supportive approach to better health (Ministry of Health, New Zealand Health Strategy, 2016; Gittelsohn & Trude, 2017; Heymsfield & Wadden, 2017; Mann et al., 2017; Ministry of Health, 2017; Sweeting & Caterson, 2017). It was not possible to modify PREVIEW:NZ to follow this approach as it was part of a much larger international trial, and comparable methods had to be adhered to across all 8 intervention centres in Europe, Australia and New Zealand. New Zealand was the only study site that had a multi-ethnic population, and so was quite different to the other countries where the majority of the cohort was Caucasian/European (Fogelholm et al., 2017; Huttunen-Lenz. et al., 2018).

Whilst the data could not be analysed as per the diet randomisation groups in this thesis, there were still important findings from the analyses carried out. The categorical analysis of higher protein vs lower protein groups did not show any significant differences in maintenance of weight loss, or better improvement in glucose control. This was unexpected as the DioGENES study had led to the hypothesis that higher protein/lower GI would have a big effect on BW, and so also in turn on blood glucose. The continuous analysis allowed the effect of protein to be investigated

without splitting the groups into high and low protein consumers and showed a small, but statistically significant, effect on BW.

In PREVIEW:NZ, if a higher protein diet had been found to be efficacious, there are still some controversies to consider. The increased cost often associated with a higher protein diet is an important issue, as this might affect patient preference which could also lead to reduction in compliance. Increased protein intake would mean that there must be a reduction in another macronutrient, some research shows that this is usually fibre-rich carbohydrates, leading to some health implications surrounding the protective benefits from fibre intake (Murphy et al., 2012; Threapleton et al., 2013; Veronese et al., 2018), which would be lost. In PREVIEW, red meat and processed meat were not recommended due to the harmful health effects clearly shown on, for example, colon cancer (Pan. et al., 2012; Pan. & Hu, 2014). A higher protein diet, even with poultry, fish, egg, dairy and other plant based protein may have adverse health effects on kidney function (Møller. et al., 2018; Richter et al., 2015; Willett et al., 1990; Xu et al., 2013). In the PREVIEW international study, there is a substudy investigating colon cancer markers using faecal analysis and also kidney function (Møller et al., 2018). There was no evidence of worse kidney function after 12 months in higher protein consumers in PREVIEW (Møller et al., 2018) . The other issue surrounding recommending a higher protein diet is the effect this has on the 'Earth' and sustainability (de Boer & Aiking, 2017; Hartmann & Siegrist, 2017; Henchion et al, 2017). Meat production has a larger impact on sustainability when compared with the production of plant based protein. The world's future protein supply is only sustainable by a reduction in meat intake and a movement towards increase in plant protein intake or introducing alternative protein sources e.g. insects or cultured meat (Hartmann & Siegrist, 2017).

Importantly weight loss achieved by LED was still beneficial after 2 years of the trial, independent of which diet group they were in. The anthropometric and metabolic improvements did not return to pre-trial baseline by 2 years and only n=12 (3.9% incidence rate over 2 years) individuals were diagnosed with T2D. As there was no control arm in PREVIEW:NZ, comparison with the other studies is useful. USDPP had a lowered incidence rate of 4.8% in the intervention arm vs. 11% in the control arm after 3 years (Diabetes Prevention Program (DPP) Research Group, 2002). FDPS showed an incidence of 6% in the intervention arm vs. 14% in the control arm after 2 years of intervention and this increased to 11% in the intervention arm vs. 23% in the control arm after 4 years. Even though this thesis investigated only 2-years out of the 3-year study, the number of T2D diagnosed at the end of 3 years in PREVIEW:NZ was n=17 (5.6%), which is still lower than the previous trials (Raben et al, 2019). The PREVIEW 3 year results was presented at the 54th European Association for the Study of Diabetes (EASD) annual meeting conference in Berlin, Germany in October 2018. The results were similar showing the initial rapid weight loss showed beneficial health effects with no preference for either of the weight loss maintenance diet and exercise groups (Raben et al, 2019). The reason for this increased success may possibly be due to the use of an LED to achieve more rapid weight loss goal, as the other trials used lifestyle to induce weight loss; or the higher weight loss cut-off of ≥8% in PREVIEW:NZ, compared to ≥7% in the USDPP and ≥5% in the FDPS.

Weight loss maintenance involving regular clinic visits and support has been recommended by many studies (Anderson et al., 2001; Apfelbaum et al., 1999; Astrup & Rössner, 2000; Gogebakan et al., 2011; Lean. & Hankey., 2018; Leslie et al., 2017). The fading visit approached used in the PREVIEW:NZ study was a public health 'hands-off' fading approach where the group sessions in the maintenance phase decreased from 8 visits in year-1, to 3 visits in year-2 and only 2 visits in year-3. Compared to the other studies, USDPP had an intensive 16 one-on-one sessions during the first 24 weeks (6 months) followed by individualised monthly sessions thereafter (Diabetes Prevention Program (DPP) Research Group, 2002). The FDPS however also had a similar fading visit approach with 7 group sessions in the first year followed by 3-monthly (4 sessions per year) sessions thereafter (Lehtisalo et al., 2016).

It has been shown that absolute kg weight loss is a critical part in other weight loss trials. The greater the BW loss, the better the outcome in later years follow-up – whether this BW loss in achieved slowly or very quickly (Affuso et al., 2014; Geiker. et al., 2018; Hamman et al., 2006; Hong et al., 2005; Jackness et al., 2013; Jebb et al., 2017; Johansson et al., 2014; Leslie et al., 2017; Leslie et al., 2016; McCombie et al., 2017; Scheen, 2017; Sellahewa et al., 2017; Taylor et al., 2017; Williams et al., 2015). The best approach seems to be the beneficial LED weight loss phase plus some form of regular group support with individualised lifestyle intervention to ensure compliance, although perhaps LED alone with no follow-up may also be very successful.

The PREVIEW:NZ study was focused primarily on higher protein vs higher CHO/fibre diets, and as such GI was an important dietary message for the participants. GI is a complicated message for diet interventions, as it is both difficult to generate sufficient GI data on a wide range of food items, and it is also well known that GI varies greatly in different situations such as mixed meals, or hot and cold food items (Nayak et al., 2014; Zhang. et al., 2015). In the PREVIEW:NZ sub-studies reported in this thesis, a common NZ food was the focus of the GI investigation, comparing sweet potato/kumara in various states with standard potato. Although it was hypothesised that there may be some variation in GI response, the findings were very unexpected and made clear the fact that GI is a very difficult aspect of the diet to define and be sure that the advice given is correct. That is the case both in a study such as PREVIEW:NZ and also in more general dietetic practice. The data from this thesis added to the growing concern that GI, when measured in groups of 10 healthy individuals, may not represent reliable data. Foods can change from low-GI to high-GI just based on the participant variability, consuming the food item within a mixed meal, changing the cooking conditions – as well as many other factors such as different growing conditions. (Aldughpassi et al., 2012; Augustin. et al., 2015; Brand-Miller & Buyken, 2012; Larsen et al., 2010; Nayak et al., 2014; Wolever & Bhaskaran, 2012). The findings from the 2 sub-studies led to a change in advice given to the PREVIEW:NZ participants by the dietetics team as it was shown to be much higher and more variable than expected.

6.1 Conclusions

In conclusion, the 8-week LED weight loss intervention was very successful and produced health benefits during the 8 weeks of LED. However, O/W individuals cannot stay on this for many

years. The weight loss and health benefits were maintained to some extent through the weight loss maintenance phase, although with gradual rebound and worsening but at 2-years remained under the pre-trial baseline for both anthropometric and metabolic parameters. The primary hypothesis of PREVIEW:NZ that a higher protein, lower CHO/GI diet would be more successful for weight loss maintenance was however not supported by the data in this thesis. The difference in protein intake resulted in a very small but clinically insignificant effect, which may not be of practical use when educating high risk populations. The results from the GI substudy confirmed that it is extremely difficult to make recommendations and educate patients to use GI due to the results being highly variable with many factors influencing GI.

6.2 Future Directions / Research

Future direction for research following the results of this thesis emphasised the need for a longer follow-up with a larger population and use of the incidence of T2D as primary outcome, as used in the other 3 large diabetes prevention RCTs (Da Qing, USDPP and FDPS). A larger study allows diagnosis of T2D to be the primary endpoint of a study. The PREVIEW international study is a 3-year intervention study with 2,300 adults recruited from 8 countries worldwide. There is also a 5-year observational follow-up to assess ongoing progress, with incidence of T2D used as the primary outcome. There is strong evidence surrounding the benefits of diet and physical activity with both metabolic health and weight loss maintenance benefits. Physical activity was not assessed in this thesis but it is also very important. As the PREVIEW international study is a randomised 2x2 factorial, 2 diet and exercise groups will be analysed once the code is 'unlocked' later in 2018. There is also a need to monitor compliance to both diet and exercise, with dietary components validated using urinary nitrogen and physical activity validated using accelerometer data. This also is part of PREVIEW international study with results available following the 'breaking of the code' in late 2018.

6.3 Alternative Approaches / New Studies

Future research studies could be implemented using a weight loss phase with LED but with a maintenance phase that uses a different trial design. Considerable research supports the benefits of a higher protein approach to support weight loss probably due to factors such as increased satiety and higher energy costs of digestion and absorption. It does seem reasonable to continue to investigate higher protein diets. Trial designs that improve patient compliance may be more successful. Like the DiRECT study, where there was a 'rescue plan' which included the use of LED meal replacements to replace 1 to 2 meals for a set time period followed by education on meal recipes and food equivalence; and where weight loss medication (e.g. Orlistat) could also be used; once BW regain reached cut-off of 2kg and 4kg. The purpose of the 'rescue plan' is to prevent a 'back slide' of weight regain and also to ensure weight loss maintenance. During the

weight loss maintenance phase, there is a need for a more innovative approach to promote good efficacy. A novel approach would be to continue with the randomised weight loss maintenance group but if the patient is unhappy with their randomised group, this would have an impact on compliance and hence also their weight loss targets so the innovative plan would be to pilot a 'patient preference' diet. If efficacy and compliance during the long-term weight loss maintenance phase can be improved using strategies that have evidence of success, such as intermittent fasting diets, this may result in much better success for weight loss maintenance and T2D prevention.

Appendices

Appendix A: SOP instructions on how to follow the LED

Standard Operating Procedures (SOP): Guidelines to dietitian educators for instructing participants on how to use the LED (8-week weight loss phase)
Objectives: To ensure instructions given by the dietitian allow participants to correctly follow the LED plan.
Aim of the LED: Participants should follow the LED for the 8-week weight loss phase aiming to obtain the ≥8% weight loss goal from their initial BW.
Product description: The LED using a range of Cambridge Weight Plan products which are available in a variety of difference flavours. These include nutritionally complete shakes, soups and porridge.
The products are available in 40g sachets, and participants will be required to eat a total of 4 sachets per day. Three sachets should be dissolved in low fat milk (3 x 250ml = 750ml per day). One sachet should be dissolved in 250ml of water. This will provide 810kcal per day, 84 grams of protein per day, approx. 5 grams of essential fatty acids per day and the daily requirements of vitamins and minerals.
If a participant is lactose intolerant, there are lactose free products, which should be dissolved in soya milk.

Product preparation:

Cambridge Weight Plan powder shakes:

Mix 1 sachet with 250ml of cold low fat milk or water, as described earlier. Shake powder and milk/water in a container with a lid or use an electrical mixer. It is essential that the powder is being shaken/blended until the powder is totally dissolved. If a more watery powder drink is preferred, extra water should be added. The drink should be consumed cold and immediately.

Cambridge Weight Plan powder soups:

Mix 1 sachet with 250ml of water, blended and heated in the microwave. It is essential that the powder is being shaken/blended until the powder is totally dissolved. If a more watery powder drink is preferred, extra water should be added. Allowed vegetables can be used and mixed with the soup. The soup should be consumed warm and immediately.

Cambridge Weight Plan powder porridge:

Mix 1 sachet with 250ml of water, blended and heated in the microwave. It is essential that the powder is being shaken/blended until the powder is totally dissolved. If a more watery powder drink is preferred, extra water should be added. The drink should be consumed warm and immediately.

Additions to the LED for taste and variety. These can be added to the Cambridge Weight Plan products to assist with taste and flavour:-

- Calorie free lemonade
- Vanilla, cinnamon or cardamom
- Coffee or instant coffee
- Crushed ice or ice cubes
- Herbs and spices

Adverse effects

Constipation is a common side effect of using LED. The reason for this is the change in food consumed and the reduced overall portion of food consumed. If a participant has a history of gastrointestinal discomfort and constipation, he/she should be advised to add extra fibre to supplement the LED. This could be 2-3 teaspoons of psyllium fibre or Metamucil with 1-2 glasses of water. The supplementary fibre can be added to shakes or used separately.

Daily intake during the LED period:

Over the 8-week LED period subjects' daily food intake will consist of 4 Cambridge Weight Plan powders consumed at intervals distributed across the day to replace breakfast, lunch, dinner and one in-between meal. It is also possible to skip the in-between meal and take 2 powders at lunch or dinner instead, depending on when the participant is hungry. If necessary, one powder may be divided into 2 portions (each portion shaken with 125ml of water or milk) but nevertheless important to consume a total of 4 sachets per day.

In addition to the 4 powders participants are permitted without limitation to:

- Drink coffee and tea without milk and sugar
- Drink water and mineral water
- Drink artificially sweetened 'diet' soft drinks
- Chew sugar free chewing (no more than 10 pieces per day)

Furthermore, it is permitted to consume 2 cups of non-starchy vegetables such as tomatoes, lettuce and cucumber per day. It is important to drink sufficient quantities of water to ensure that thirst is not confusingly mistaken for hunger. For most people, 2 litres a day will generally suffice in addition to powder meals and permitted vegetables.

Inconveniences and complications to the diet:

The following complications and inconvenience may occur when consuming the LED. These complications may include tiredness, dizziness, headache, nausea, sensitivity to cold, dry skin, bad breath (subject to ketosis) or hair loss (for a short period of time). A more frequent occurrence of gallstones and gout attacks are associated with rapid weight loss in overweight people. As well as constipation as a possible side effect, diarrhoea is another gastrointestinal symptoms that may be experienced by participants. The use of psyllium fibre and consumption of adequate water is suggested.

For participants with ≥40kg/m^2 can have all 4 sachets made with low fat milk to supple additional protein (4 x 250ml = 1000ml). This additional milk will provide an extra 100kcal per day and 8.5 grams of protein per day.

Special precautions

The following participants should be monitored by their GP during weight loss as dosage of medication might need to be adjusted with weight loss:

- Participants that are prescribed anti-coagulant for a clotting disorder
- Participants using medication for hypertension or use of diuretics.

If a participant is experiencing mild adverse effects that may affect compliance, the dietitian can suggest methods to alleviate the symptoms such as lactose free milk, spreading out meals, eating slowly, and drinking insufficient fluid intake. If symptoms persist and participant is not able to tolerate the LED, the participant cannot continue the study and must be excluded. If a participant reacts towards a component in the LED, the intervention must be ended immediately.

Weight loss – A LED with a daily energy intake of approximately 800-950kcal may typically result in a weight loss of 1000 grams or more per week. Usually, the weight loss is larger in the first weeks but the opposite situation may also occur. The size of weight loss depends on the

participants' initial weight, gender, muscle mass, age, physical activity and compliance to the LED.
Participants who have been using the LED may experience gastrointestinal disturbances during re-feeding, in particular abdominal pain, reflux symptoms, nausea and early satiety. To minimize discomfort, the participants should be advised to pay attention to satiety signals, adjust their portion sizes and avoid returning to former larger portions.

Instructions on how to prepare the Cambridge Meal Replacement Product were given to participants as follows:
To prepare the Cambridge Meal Plan shakes and soups you will need:
A drink shaker (supplied) OR stick blender and container
Cold OR warm (not boiling) water OR milk
Shakes:
Pour 250ml cold skim milk/water into a shaker or container.
Add 1 sachet of Cambridge shake powder and the wire-mixing ball.
Place the lid on the shaker and shake vigorously for 45-60 seconds OR mix shake powder and water using a stick blender.
Consume shake cold and within 15 minutes of making it for full nutritional benefit.
4, 3, 2, 1 → SUCCESS!!
The Cambridge Diet can be a little bit confusing, so just remember each day: **4, 3, 2, 1.**
4 = The number of Cambridge products and the 'units' of free vegetables per day.
3 = The number of sachets on skim milk per day.
2 = The litres of water you need per day.
1 = Take the diet 1 day at a time. It will be challenging, but remain positive and take focus on getting through it one day at a time. It will get easier as time goes on.
Hints: Remember to make sure the shaker lid is on tight and place your finger over the lid/opening when shaking to avoid spilling it.
Always carry a spare shake with you in case you spill one, or get caught without one when your next meal is due. Shakes can taste better when they are colder. To make your shake colder, add 1-2 ice cubes to it before shaking (this can also help break up any lumps of shake powder).
Shakes taste nicer when made with milk AND soup taste nicer when made with water.
Some varieties of shakes make a delicious warm drink – simply mix with warm (not boiling)milk/water. If making a warm shake please use a stick blender,
To increase variety you can flavour your shakes with: vanilla or other flavoured essence; Ground spices e.g. cinnamon, nutmeg; Coffee or instant coffee (mixed with little hot water)
Example LED day
Example 1: B: Apple and Cinnamon porridge (LED sachet) made with 250ml trim milk and cup of coffee
AM: 1 cup stir-fry mushrooms (spray oil), 1 cup of tea and glass of water
L: Leek and Potato soup (LED sachet), made with 250ml hot water, 1 cup of salad
PM: Chocolate Orange shake (LED sachet) made with 250ml trim milk, glass of water
D: Chocolate shake (LED sachet) made with 250ml trim milk, 1 cup of salad
S: 1 diet jelly and 1 piece chewing gum

Example 2 (lactose free)
B: Chocolate shake (LED sachet) made with 250ml soy milk, chewing gum
AM: 1 cup of tea and chewing gum
L: Leek and Potato soup (LED sachet), made with 250ml hot water
PM: 1 cup of stir-fry vegetables and Chocolate shake (LED sachet) (made with 250ml soy milk)
D: Chocolate shake (LED sachet) (made with 250ml soy milk), 1 cup of miso soup
S: 3 pieces of cucumber, 2 pieces of tomato, 1 cup of tea (little trim milk and 1 artificial sweetener)
You may chew **sugar-free** chewing gum and eat **sugar-free** breath mints (maximum 10 pieces/day). Some examples include: Extra, 5, Airwaves, or Eclipse Ice sugar-free chewing gum, or Eclipse sugar-free breath mints (maximum 10 pieces/day).

List of allowed or 'free' vegetables - 2 cups per day

	ALLOWED			NOT ALLOWED
Free  **Vegetables**	Alfalfa sprouts Asparagus Green beans Bok choy Broccoli Brussels sprouts Celery Cabbage Capsicum Carrot (max 1/d)	Cauliflower Cucumber Eggplant Fennel Garlic Lettuce Leek Mushrooms Onions Puha	Radish Rocket salad Shallots Silverbeet Snowpeas Spinach Tomato Watercress Zucchini	Green bananas Corn Peas Legumes (lentils, chickpeas) Potato Pumpkin Sweet potato / Kumara Taro Yams Beetroot
Herbs and  **Spices**	All spices Basil Celery flakes Chili Chives Cinnamon cloves Coriander Cumin	Curry powder Dill Garlic Ginger Mint Mustard seed Nutmeg Oregano	Paprika Parsley Pepper Rosemary Sage Thyme Turmeric Tarragon	
Condiments and Sweeteners	Lemon/lime juice Fish Sauce Vinegar Worcestershire / Soy sauce Tomato paste	Artificial sweeteners (e.g. Equal, Splenda, Stevia)		NO: Sugar, honey Oil/butter etc Mayonnaise Tomato sauce
Drinks	Aim for 2L of water per day in addition to the LED	Tea and coffee (black in small amounts) Water 6-8 g/d Diet cordial Diet fizzy (<2/d)		NO: Alcohol Fruit juice
Miscellaneous	Miso soup Chicken stock (Limit to one per day)	Artificial sweetener Unsweetened gum Diet jelly (<2/d)		

No meat, chicken, fish, eggs, dairy, bread, fat or cereals!

Appendix B: Nutritional information for Shakes from Cambridge Weight Plan (Corby, UK) LED

	Per 40g serving	% of RDA per 3 servings	Per 4 servings
Energy (kJ)	615		2461
Protein (g)	14.1		56.4
Carbohydrate (g)	14.4		57.6
Fat (g)	2.9		11.5
Saturated fat (g)	0.7		2.6
Fibre (g)	3.3		13.3
Vitamin A (μg)	266.7	100	1066.7
Vitamin D (μg)	1.7	100	6.7
Vitamin E (mg)	4.0	100	16.0
Vitamin C (mg)	26.7	100	106.7
Thiamine (mg)	0.4	100	1.5
Riboflavin (mg)	0.5	100	1.9
Niacin (mg)	5.3	100	21.3
Vitamin B6 (mg)	0.5	100	1.9
Folacin (μg)	66.7	100	266.6
Vitamin B12 (μg)	0.8	100	3.3
Biotin (μg)	16.7	100	66.7
Calcium (mg)	327.1	100	1308.5
Iron (mg)	4.7	100	18.6
Magnesium (mg)	125.0	100	500.0
Zinc (mg)	3.3	100	13.3

Appendix C: Nutritional information for Soups from Cambridge Weight Plan (Corby, UK) LED

	Per 40g serving	% of RDA per 3 servings	Per 4 servings
Energy (kJ)	576		2302
Protein (g)	13.5		53.9
Carbohydrate (g)	13.6		54.2
Fat (g)	2.5		9.9
Saturated fat (g)	0.4		1.6
Fibre (g)	3.3		13.3
Vitamin A (μg)	266.7	100	1066.7
Vitamin D (μg)	1.7	100	6.7
Vitamin E (mg)	4.0	100	16.0
Vitamin C (mg)	26.7	100	106.7
Thiamine (mg)	0.4	100	1.5
Riboflavin (mg)	0.5	100	1.9
Niacin (mg)	5.3	100	21.3
Vitamin B6 (mg)	0.5	100	1.9
Folacin (μg)	66.7	100	266.7
Vitamin B12 (μg)	0.8	100	3.3
Biotin (μg)	16.7	100	66.6
Calcium (mg)	266.7	100	1066.7
Iron (mg)	4.7	100	18.6
Magnesium (mg)	125.0	100	500.0
Zinc (mg)	3.3	100	13.3

Appendix D: Dropouts between CID1/Baseline and CID6/24m, gender and ethnicity differences

	CID1/ Baseline n=305	CID2/Post LED n=267 (attended)	CID2/Post LED n=249 (met ≥8%)	CID3/6m n=187 (attended)	CID4/12m n=144 (attended)	CID5/18m n=135 (attended)	CID6/24m n=113 (attended)
All	305	267	249	187	144	135	113
Male	73	65 (89%)	61 (88%)	43 (59%)	36 (49%)	36 (49%)	33 (45%)
Female	232	202 (87%)	188 (81%)	144 (62%)	108 (47%)	99 (43%)	80 (34%)
Caucasian	163	154 (94%)	151 (93%)	127 (78%)	100 (61%)	99 (61%)	81 (50%)
Maori/Pacific	112	89 (79%)	77 (69%)	45 (40%)	30 (27%)	23 (21%)	22 (20%)
Other	30	24 (80%)	21 (70%)	15 (50%)	14 (47%)	13 (43%)	10 (33%)

Appendix E: Multiple regression analysis of change in anthropometric and metabolic outcome variables and en% protein: unadjusted and adjusted (baseline, gender, ethnicity) models – LVCF data

Outcome variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value	Adjusted model (interaction) (SE)	P value
BW(kg)	-0.007(0.033)	**0.033**	-0.007(0.033)	0.9911		
BMI(kg/m^2)	-0.002(0.012)	**0.0882**	0.001(0.012)	0.9744		
WC(cm)	-0.010(0.045)	0.8237	0.002(0.045)	0.9698		
FM (kg)	-0.005(0.026)	0.8558	0.004(0.026)	0.8558		
FM (%)	-0.021(0.022)	0.3531	-0.015(0.023)	0.5039		
Android fat(kg)	-0.001(0.003)	0.7514	0.001(0.003)	0.9345		
FFM (kg)	-0.005(0.008)	0.5518	-0.006(0.008)	0.4831		
FFM (%)	-0.001(0.01)	0.9584	-0.002(0.01)	0.8536		
SBP(mmHg)	-0.031(0.092)	0.738	0.022(0.088)	0.8069		
DBP(mmHg)	-0.065(0.052)	0.2084	-0.069(0.05)	0.1653		
FPG(mmol/l)	0.001(0.003)	0.7241	0.001(0.002)	0.7011		
2h-PPG(mmol/l)	0.001(0.009)	0.9505	0.003(0.009)	0.7638		
$AUC_{GlucoseT0-120m}$	0.19(0.852)	0.8233	0.406(0.829)	0.6246		
HbA_{1C}(mmol/mol)	0.003(0.011)	0.7942	0.004(0.01)	0.7012		
Insulin(mU/l)	-0.019(0.022)	0.3841	-0.016 (0.022)	0.4616		
HOMA-IR	-0.004(0.006)	0.5345	-0.003(0.006)	0.6342		
C-Peptide(pmol/l)	-1.743 (1.058)	0.1009	-1.504(1.045)	0.1515		
hs-CRP (mg/l)	-0.014(0.025)	0.5677	0.004(0.024)	0.883		
TC(mmol/l)	0.01 (0.005)	0.0487	0.009(0.005)	0.0838		
HDL-C(mmol/l)	0.005(0.001)	**<0.001**	0.005(0.001)	**<0.001**		
LDL-C(mmol/l)	0.006(0.004)	0.1374	0.005(0.004)	0.2321		
TG(mmol/l)	-0.001(0.003)	0.5872	-0.001(0.003)	0.5675		
TC:HDL ratio	-0.007(0.003)	**0.0396**	-0.008(0.003)	0.0223		
GI (units)	-0.282(0.038)	**<0.001**	-0.284(0.036)	**<0.001**		
TE (kJ/d)	11.134(21.947)	0.6124	-27.725(20.092)	0.1689	-126.543(24.703)	<0.001
-12m vs. 6m					-4339.92(605.45)	<0.001
-24m vs. 6m					-3517.26(831.87)	<0.001
-Baseline TE					-0.573(0.041)	<0.001
- Male vs. Female					508.196(309.735)	0.1021
-Maori/Pacific vs. Caucasian					888.163(290.826)	0.0025
-Other vs. Caucasian					620.967(480.074)	0.1971

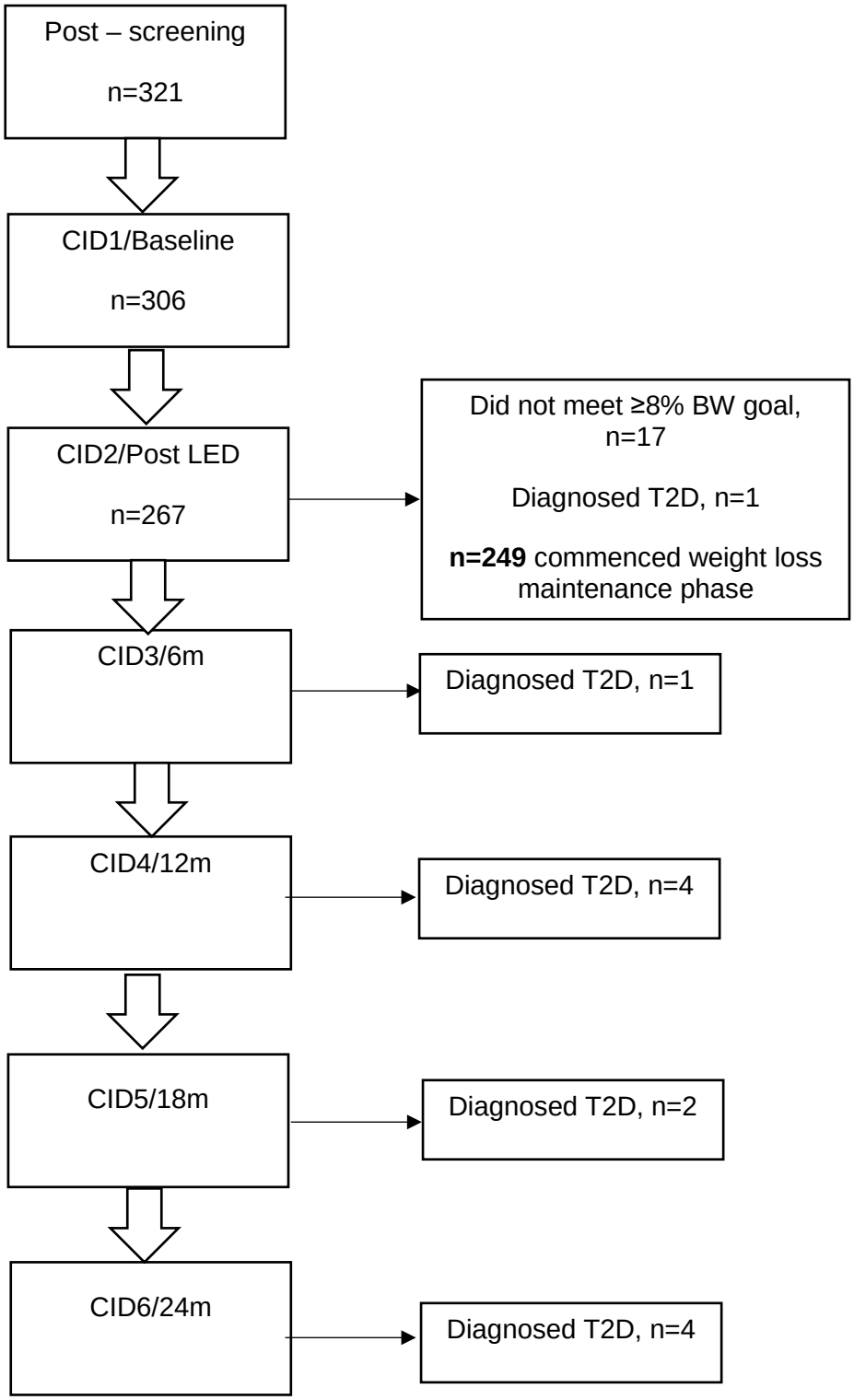
BW, body weight; BMI, Body Mass Index; WC, waist circumference; FM, Fat Mass; FFM, Fat Free Mass; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting Plasma Glucose; 2h-PPG, Postprandial Plasma Glucose at 2-hour timepoint; $AUC_{GlucoseT0-120}$, Area under the glucose curve time 0-120 min; HbA_{1c}, Glycated Haemoglobin; Insulin, Fasting serum insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; C-Peptide, serum connecting peptide; hs-CRP, high sensitivity C-reactive protein; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; TC:HDL ratio, Total cholesterol:high density lipoprotein ratio; TE, Total Energy 4 day diet record; GI, Glycaemic Index

Appendix F: Multiple regression analysis of change in anthropometric and metabolic outcome variables and en% protein: unadjusted and adjusted (baseline, gender, ethnicity)models – multiple imputation data

Outcome variables	Unadjusted coefficient (SE)	P value	Adjusted coefficient (SE)	P value
BW (kg)	-0.104(0.052)	**0.0706**	-0.101(0.051)	**0.0749**
BMI (kg/m^2)	-0.035(0.018)	**0.081**	-0.034(0.018)	**0.0876**
WC (cm)	-0.02(0.069)	0.7751	-0.011(0.072)	0.8771
FM (kg)	-0.043(0.043)	0.3372	-0.038(0.046)	0.4311
FM (%)	-0.049(0.037)	0.2185	-0.04(0.039)	0.3366
Android fat (kg)	-0.007(0.005)	0.1759	-0.007(0.005)	0.1994
FFM (kg)	-0.022(0.017)	0.2134	-0.027(0.017)	0.1357
FFM (%)	-0.027(0.02)	0.2076	-0.036(0.02)	0.1143
SBP (mmHg)	-0.091(0.135)	0.5159	-0.065(0.131)	0.6322
DBP (mmHg)	-0.06(0.072)	0.4241	-0.072(0.07)	0.3281
FPG (mmol/l)	0.00(0.004)	0.9347	0.00(0.004)	0.9192
2h-PPG (mmol/l)	0.001(0.009)	0.9505	0.003(0.009)	0.7638
$AUC_{GlucoseT0\text{-}120m}$	0.19(0.852)	0.8233	0.406(0.829)	0.6246
HbA_{1C} (mmol/mol)	-0.026(0.015)	0.1227	-0.023(0.015)	0.1396
Insulin (mU/l)	-0.037(0.046)	0.4477	-0.021(0.046)	0.6586
HOMA-IR	-0.007(0.011)	0.5834	-0.002(0.011)	0.8534
C-Peptide (pmol/l)	-3.333(1.96)	0.1312	-2.485(1.943)	0.2397
hs-CRP (mg/l)	0.035(0.041)	0.4064	0.042(0.037)	0.2755
TC (mmol/l)	-0.005(0.007)	0.5107	-0.007(0.007)	0.3928
HDL-C (mmol/l)	0.003(0.002)	0.2242	0.002(0.002)	0.2694
LDL-C (mmol/l)	-0.004(0.006)	0.5076	-0.005(0.006)	0.3941
TG (mmol/l)	-0.006(0.004)	0.1766	-0.006(0.004)	0.2089
TC:HDL ratio	-0.015(0.006)	**0.0432**	-0.015(0.006)	**0.0375**
GI (units)	-0.377(0.055)	**<0.001**	-0.39(0.05)	**<0.001**
TE (kJ/d)	46.592(31.307)	0.1671	41.944(26.001)	0.1348

BW, body weight; BMI, Body Mass Index; WC, waist circumference; FM, Fat Mass; FFM, Fat Free Mass; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting Plasma Glucose; 2h-PPG, Postprandial Plasma Glucose at 2-hour timepoint; $AUC_{GlucoseT0\text{-}120m}$, Area under the glucose curve time 0-120 min; HbA_{1c}, Glycated Haemoglobin; Insulin, Fasting serum insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; C-Peptide, serum connecting peptide; hs-CRP, high sensitivity C-reactive protein; TC, Total cholesterol; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; TC:HDL ratio, Total cholesterol:high density lipoprotein ratio; GI, Glycaemic Index; TE, Total Energy 4-day diet record; GI, Glycaemic Index

Appendix G: PREVIEW NZ flowchart - number of participants per CID and T2D diagnosis



References

Affuso, O., Kaiser, K. A., Carson, T. L., Ingram, K. H., Schwiers, M., Robertson, H., . . . Allison, D. B. (2014). Association of run-in periods with weight loss in obesity randomized controlled trials. *Obesity Reviews,* 15(1), 68.

Ahern, A. L., Olson, A. D., Aston, L. M., & Jebb, S. A. (2011). Weight watchers on prescription: An observational study of weight change among adults referred to weight watchers by the NHS. *BMC Public Health,* 11(1), 434.

Åkerberg, A., Liljeberg, H., & Björck, I. (1998). Effects of amylose/amylopectin ratio and baking conditions on resistant starch formation and glycaemic indices. *Journal of Cereal Science,* 28(1), 71-80.

Alberti, K. G., & Zimmet, P. Z. (2014). Diabetes: A look to the future. *The Lancet Diabetes & Endocrinology,* 2(1), e1-2.

Aldrich, N. D., Reicks, M. M., Sibley, S. D., Redmon, J. B., Thomas, W., & Raatz, S. K. (2011). Varying protein source and quantity do not significantly improve weight loss, fat loss, or satiety in reduced energy diets among midlife adults. *Nutrition Research,* 31(2), 104-112.

Aldughpassi, A., Abdel-Aal, e. M., & Wolever, T. M. (2012). Barley cultivar, kernel composition, and processing affect the glycemic index. *The Journal of Nutrition,* 142(9), 1666-1671.

Alibasic, E., Ramic, E., & Alic, A. (2013). Prevention of Diabetes in family medicine. *Materia Socio-Medica,* 25(2), 80-82.

American Diabetes Association. (2013). Economic costs of Diabetes in the US in 2012. *Diabetes Care,* 36(4), 1033-1046.

American Diabetes Association. (2016). Prevention or delay of Type 2 Diabetes. *Diabetes Care,* 39 (Suppl 1), S36-8.

American Diabetes Association. (2017). Standards of medical care in Diabetes—2017 abridged for primary care providers. *Clinical Diabetes,* 35(1), 5-26.

American Diabetes Association. (2018). Obesity management for the treatment of Type 2 Diabetes: Standards of medical care in Diabetes-2018. *Diabetes Care,* 41(Suppl 1), S65-S72.

An, Y., Zhang, P., Wang, J., Gong, Q., Gregg, E. W., Yang, W., . . . Li, G. (2015). Cardiovascular and all-cause mortality over a 23-year period among Chinese with newly diagnosed Diabetes in the Da Qing IGT and Diabetes study. *Diabetes Care,* 38(7), 1365-1371.

Anderson, G. H., & Moore, S. E. (2004). Dietary proteins in the regulation of food intake and body weight in humans. *The Journal of Nutrition,* 134(4), S974-979.

Anderson, G. H., Tecimer, S. N., Shah, D., & Zafar, T. A. (2004). Protein source, quantity, and time of consumption determine the effect of proteins on short-term food intake in young men. *Journal of Nutrition,* 134(11), 3011-3015.

Anderson, J. W., Konz, E. C., Frederich, R. C., & Wood, C. L. (2001). Long-term weight-loss maintenance: A meta-analysis of US studies. *The American Journal of Clinical Nutrition,* 74(5), 579-584.

Anderson, J. W., Kendall., C. W., & Jenkins., D. J. (2003). Importance of weight management in Type 2 Diabetes: Review with meta-analysis of clinical studies. *Journal of the American College of Nutrition,* 22(5), 331-339.

Apfelbaum, M., Fricker, J., & Igoin-Apfelbaum, L. (1987). Low-and very-low-calorie diets. *American Journal of Clinical Nutrition.*

Apfelbaum, M., Vague, P., Ziegler, O., Hanotin, C., Thomas, F., & Leutenegger, E. (1999). Long-term maintenance of weight loss after a very-low-calorie diet: A randomized blinded trial of the efficacy and tolerability of sibutramine. *The American Journal of Medicine,* 106(2), 179-184.

Araujo, T. G., de Oliveira., A. G., & Saad., M. J. (2013). Insulin-resistance-associated compensatory mechanisms of pancreatic beta cells: A current opinion. *Frontiers in Endocrinology,* 4, 146.

Arena, R., McNeil, A., Sagner, M., & Hills, A. P. (2017). The current global state of key lifestyle characteristics: Health and economic implications. *Progress in Cardiovascular Diseases,* 59(5):422-429.

Arvidsson-Lenner, R., Asp, N., Axelsen, M., Bryngelsson, S., Haapa, E., Järvi, A., . . . Thorsdottir, I. (2004). Glycaemic Index. *Scandinavian Journal of Nutrition,* 48(2), 84-94.

Ashley, J. M., Jeor, S. T., Perumean-Chaney, S., Schrage, J., & Bovee, V. (2001). Meal replacements in weight intervention. *Obesity,* 9(S11), 312S-320S.

Astrup, A., & Finer, N. (2000). Redefining Type 2 Diabetes: 'Diabesity' or 'Obesity Dependent Diabetes Mellitus'? *Obesity Reviews,* 1(2), 57-59.

Astrup, A. (2001). The role of dietary fat in the prevention and treatment of obesity. Efficacy and safety of low-fat diets. *International Journal of Obesity,* 25(S1), S46.

Astrup, A., Buemann, B., Flint, A., & Raben, A. (2002). Low-fat diets and energy balance: How does the evidence stand in 2002? *Proceedings of the Nutrition Society,* 61(2), 299-309.

Astrup, A., & Rössner, S. (2000). Lessons from obesity management programmes: Greater initial weight loss improves long-term maintenance. *Obesity Reviews,* 1(1), 17-19.

Astrup, A. (2004). The effect of exercise and diet on glucose intolerance and substrate utilization? *Nestle Nutrition Workshop Series.Clinical & Performance Programme,* 9, 93-103.

Astrup, A. (2005). The satiating power of protein—a key to obesity prevention? *The American Journal of Clinical Nutrition,* 82(1), 1-2.

Astrup, A., Larsen, T. M., & Harper, A. (2004). Atkins and other low-carbohydrate diets: Hoax or an effective tool for weight loss? *Lancet,* 364(9437), 897-899.

Astrup, A., Raben, A., & Geiker, N. (2015). The role of higher protein diets in weight control and obesity-related comorbidities. *International Journal of Obesity,* 39(5), 721-726.

Astrup, A., Rossner, S., VanGaal, L., Rissanen, A., Niskanen, L., Al Hakim, M., . . . Lean, M. E. (2009). Effects of liraglutide in the treatment of obesity: A randomised, double-blind, placebo-controlled study. *Lancet,* 374(9701), 1606-1616.

Atkinson, R. L. (1989). Low and very low calorie diets. *Medical Clinics of North America,* 73(1), 203-215.

Atkinson, F. S., Foster-Powell, K., & Brand-Miller, J. C. (2008). International tables of Glycemic Index and glycemic load values: 2008. *Diabetes Care,* 31(12), 2281-2283.

Augustin, L., Kendall, C., Jenkins, D., Willett, W. C., Astrup., A., Barclay, A. W., . . . Buyken, A. E. (2015). Glycemic index, glycemic load and glycemic response: An international scientific consensus summit from the international carbohydrate quality consortium (ICQC). *Nutrition, Metabolism and Cardiovascular Diseases,* 25(9), 795-815.

Backholer, K., Mannan, H. R., Magliano, D. J., Walls, H. L., Stevenson, C., Beauchamp, A., . . . Peeters, A. (2012). Projected socioeconomic disparities in the prevalence of obesity among Australian adults. *Australian and New Zealand Journal of Public Health,* 36(6), 557-563.

Backholer, K., Peeters, A., Herman, W. H., Shaw, J. E., Liew, D., Ademi, Z., & Magliano, D. J. (2013). Diabetes prevention and treatment strategies: Are we doing enough? *Diabetes Care,* 36(9), 2714-2719.

Baecke, J. A., Burema, J., & Frijters, J. E. (1982). A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *The American Journal of Clinical Nutrition,* 36(5), 936-942.

Baetge, C., Earnest, C. P., Lockard, B., Coletta, A. M., Galvan, E., Rasmussen, C., . . . Koozehchian, M. (2017). Efficacy of a randomized trial examining commercial weight loss programs and exercise on metabolic syndrome in overweight and obese women. *Applied Physiology, Nutrition, and Metabolism,* 42(2), 216-227.

Baird, I. M., Parsons, R., & Howard, A. (1974). Clinical and metabolic studies of chemically defined diets in the management of obesity. *Metabolism,* 23(7), 645-657.

Barclay, A. W., Petocz, P., McMillan-Price, J., Flood, V. M., Prvan, T., Mitchell, P., & Brand-Miller, J. C. (2008). Glycemic index, glycemic load, and chronic disease risk - a meta-analysis of observational studies. *The American Journal of Clinical Nutrition,* 87(3), 627-637.

Barkeling, B., Rössner, S., & Björvell, H. (1990). Effects of a high-protein meal (meat) and a high-carbohydrate meal (vegetarian) on satiety measured by automated computerized monitoring of subsequent food intake, motivation to eat and food preferences. *International Journal of Obesity,* 14(9), 743-751.

Barry, E., Roberts, S., Oke, J., Vijayaraghavan, S., Normansell, R., & Greenhalgh, T. (2017). Efficacy and effectiveness of screen and treat policies in prevention of Type 2 Diabetes: Systematic review and meta-analysis of screening tests and interventions. *British Medical Journal (Clinical Research Ed),* 356, i6538.

Batsis, J. A., Gill, L. E., Masutani, R. K., Adachi-Mejia, A. M., Blunt, H. B., Bagley, P. J., . . . Bartels, S. J. (2016). Weight loss interventions in older adults with obesity: A systematic review of randomized controlled trials since 2005. *Journal of the American Geriatrics Society,* 65(2): 257-268.

Baum, J. I., Freund, G. G., Rahn, K. A., Nakamura, M. T., & Yudell, B. E. (2006). A reduced carbohydrate, increased protein diet stabilizes glycemic control and minimizes adipose tissue glucose disposal in rats. *The Journal of Nutrition,* 136(7), 1855-1861.

Bazzano, L. A., Hu, T., Reynolds, K., Yao, L., Bunol, C., Liu, Y., . . . He, J. (2014). Effects of low-carbohydrate and low-fat diets: A randomized trial. *Annals of Internal Medicine,* 161(5), 309-318.

Bellissimo, N., Desantadina, M. V., Pencharz, P. B., Berall, G. B., Thomas, S. G., & Anderson, G. H. (2008). A comparison of short-term appetite and energy intakes in normal weight and obese boys following glucose and whey-protein drinks. *International Journal of Obesity,* 32(2), 362-371.

Berger, S. E., Huggins, G. S., McCaffery, J. M., & Lichtenstein, A. H. (2017). Comparison among criteria to define successful weight-loss maintainers and regainers in the action for health in Diabetes (look AHEAD) and Diabetes Prevention Program trials. *The American Journal of Clinical Nutrition,* 106(6), 1337-1346.

Berglund, G., Nilsson, P., Eriksson, K. F., Nilsson, J. Å., Hedblad, B., Kristenson, H., & Lindgärde, F. (2000). Long-term outcome of the Malmö Preventive Project: Mortality and cardiovascular morbidity. *Journal of Internal Medicine,* 247(1), 19-29.

Bernstein, A. M., Sun, Q., Hu, F. B., Stampfer, M. J., Manson, J. E., & Willett, W. C. (2010). Major dietary protein sources and risk of coronary heart disease in women. *Circulation,* 122(9), 876-883.

Bianchi, C., Battini, L., Aragona, M., Lencioni, C., Ottanelli, S., Romano, M., . . . Mori, M. L. (2017). Prescribing exercise for prevention and treatment of gestational Diabetes: Review of suggested recommendations. *Gynecological Endocrinology,* 33(4), 254-260.

Blackstone, R. P. (2016). Epidemiology, measurement, and cost of obesity. *Obesity* (pp. 1-22) Springer.

Blom, W. A., Lluch, A., Stafleu, A., Vinoy, S., Holst, J. J., Schaafsma, G., & Hendriks, H. F. (2006). Effect of a high-protein breakfast on the postprandial ghrelin response. *The American Journal of Clinical Nutrition,* 83(2), 211-220.

Boaz, M., Raz, O., & Weinstein, J. (2015). Low fat vs. low carbohydrate diet strategies for weight reduction: A meta-analysis. *Journal of Obesity Weight Loss Therapy,* 5(273), 2.

Bolinger, R. E., Brown, R. W., Guevara, L., & Steinberg, R. (1966). Metabolic balance of obese subjects during fasting. *Archives of Internal Medicine,* 118(1), 3-8.

Bourn, D. M., Mann, J. I., McSkimming, B. J., Waldron, M. A., & Wishart, J. D. (1994). Impaired glucose tolerance and NIDDM: Does a lifestyle intervention program have an effect? *Diabetes Care,* 17(11), 1311-1319.

Bovell-Benjamin, A. C. (2007). Sweet potato: A review of its past, present, and future role in human Nutrition. *Advances in Food and Nutrition Research,* 52, 1-59.

Bowen, J., Noakes, M., & Clifton, P. M. (2007). Appetite hormones and energy intake in obese men after consumption of fructose, glucose and whey protein beverages. *International Journal of Obesity,* 31(11), 1696-1703.

Bowen, J., Noakes, M., & Clifton, P. M. (2006a). Appetite regulatory hormone responses to various dietary proteins differ by body mass index status despite similar reductions in ad libitum energy intake. *The Journal of Endocrinology and Metabolism,* 91(8), 2913-2919.

Bowen, J., Noakes, M., Trenerry, C., & Clifton, P. M. (2006b). Energy intake, ghrelin, and cholecystokinin after different carbohydrate and protein preloads in overweight men. *The Journal of Clinical Endocrinology and Metabolism,* 91(4), 1477-1483.

Braatvedt, G., Cundy, T., Crooke, M., Florkowski, C., Mann, J. I., Lunt, H., . . . Drury, P. L. (2012). Understanding the new HbA1c units for the diagnosis of Type 2 Diabetes. *New Zealand Medical Association,* 125(1362), 70-80.

Brand-Miller, J. C., Stockmann, K., Atkinson, F., Petocz, P., & Denyer, G. (2008). Glycemic index, postprandial glycemia, and the shape of the curve in healthy subjects: Analysis of a database of more than 1000 foods. *The American Journal of Clinical Nutrition,* 89(1), 97-105.

Brewin, C. R., & Bradley, C. (1989). Patient preferences and randomised clinical trials. *British Medical Journal (Clinical Research Ed.),* 299(6694), 313-315.

Brouns, F., Bjorck, I., Frayn, K. N., Gibbs, A. L., Lang, V., Slama, G., & Wolever, T. M. S. (2005). Glycaemic index methodology. *Nutrition Research Reviews,* 18(1), 145-171.

Buhler, S., Raine, K. D., Arango, M., Pellerin, S., & Neary, N. E. (2013). Building a strategy for obesity prevention one piece at a time: The case of sugar-sweetened beverage taxation. *Canadian Journal of Diabetes,* 37(2), 97-102.

Bullo, M., Cozar-Torrell, P., & Salas-Salvado, J. (2013). Dietary regulation of glucose metabolism in metabolic syndrome. *Current Vascular Pharmacology,* 11(6), 928-945.

Burch, E., Ball., L., Somerville., M., & Williams, L. T. (2018). Dietary intake by food group of individuals with Type 2 Diabetes mellitus: A systematic review. *Diabetes Research and Clinical Practice,* 137, 160-172.

Burton-Freeman, B. M. (2008). Glycomacropeptide (GMP) is not critical to whey-induced satiety, but may have a unique role in energy intake regulation through cholecystokinin (CCK). *Physiology & Behavior,* 93(1), 379-387.

Calle, E. E., Thun, M. J., Petrelli, J. M., Rodriguez, C., & Heath Jr, C. W. (1999). Body-mass index and mortality in a prospective cohort of US adults. *New England Journal of Medicine*, 341(15), 1097-1105.

Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *New England Journal of Medicine,* 348(17), 1625-1638.

Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Quantity and quality of sleep and incidence of Type 2 Diabetes: A systematic review and meta-analysis. *Diabetes Care, 33*(2), 414-420.

Carels, R. A., Selensky, J. C., Rossi, J., Solar, C., & Hlavka, R. A novel stepped-care approach to weight loss: The role of self-monitoring and health literacy in treatment outcomes. *Eating Behaviors,* 26: 76-82.

Carmienke, S., Freitag, M. H., Pischon, T., Schlattmann, P., Fankhaenel, T., Goebel, H., & Gensichen, J. (2013). General and abdominal obesity parameters and their combination in relation to mortality: A systematic review and meta-regression analysis. *European Journal of Clinical Nutrition,* 67(6), 573-585.

Cecchini, M., & Warin, L. (2016). Impact of food labelling systems on food choices and eating behaviours: A systematic review and meta-analysis of randomized studies. *Obesity Reviews,* 17(3), 201-210.

Cefalu, W. T., Buse, J. B., Tuomilehto, J., Fleming, G. A., Ferrannini, E., Gerstein, H. C., . . . Rosenstock, J. (2016). Update and next steps for real-world translation of interventions for Type 2 Diabetes prevention: Reflections from a Diabetes care editors' expert forum. *Diabetes Care,* 39(7), 1186-1201.

Chan, M. (2017). Obesity and Diabetes: The Slow-Motion disaster. *The Milbank Quarterly,* 95(1), 11-14.

Chan., J. M., Rimm., E. B., Colditz., G. A., Stampfer., M. J., & Willett., W. C. (1994). Obesity, fat distribution, and weight gain as risk factors for clinical Diabetes in men. *Diabetes Care,* 17(9), 961-969.

Chandalia, M., Lin, P., Seenivasan, T., Livingston, E. H., Snell, P. G., Grundy, S. M., & Abate, N. (2007). Insulin resistance and body fat distribution in south Asian men compared to Caucasian men. *PLoS One,* 2(8), e812.

Chapman, M. J., Assmann, G., Fruchart, J., Shepherd, J., & Sirtori, C. (2004). Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: The role of nicotinic acid–a position paper developed by the European consensus panel on HDL-C. *Current Medical Research and Opinion,* 20(8), 1253-1268.

Cheraghpour, M., Hosseini, S. A., Ashtary-Larky, D., Shirali, S., Ghanavati, M., & Alipour, M. (2017). Effects of high-protein, low-energy diet on body composition in overweight and obese adults: A clinical trial. *World Academy of Science, Engineering and Technology, International Journal of Medical, Health, Biomedical, Bioengineering and Pharmaceutical Engineering,* 11(3), 51-54.

Christensen, P., Bartels, E. M., Riecke, B. F., Bliddal, H., Leeds, A. R., Astrup, A., . . . Christensen, R. (2012). Improved nutritional status and bone health after diet-induced weight loss in sedentary osteoarthritis patients: A prospective cohort study. *European Journal of Clinical Nutrition,* 66(4), 504-509.

Christensen, P., Bliddal, H., Riecke, B. F., Leeds, A. R., Astrup, A., & Christensen, R. (2011). Comparison of a low-energy diet and a very low-energy diet in sedentary obese individuals: A pragmatic randomized controlled trial. *Clinical Obesity,* 1(1), 31-40.

Clement, K., Viguerie, N., Poitou, C., Carette, C., Pelloux, V., Curat, C. A., . . . Langin, D. (2004). Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 18*(14), 1657-1669.

Clifton, P. (2012). Effects of a high protein diet on body weight and comorbidities associated with obesity. *British Journal of Nutrition,* 108(2), S122-S129.

Clifton, P. M., Condo, D., & Keogh, J. B. (2014). Long term weight maintenance after advice to consume low carbohydrate, higher protein diets–a systematic review and meta-analysis. *Nutrition, Metabolism and Cardiovascular Diseases,* 24(3), 224-235.

Clifton, P. M., Keogh, J. B., & Noakes, M. (2008). Long-term effects of a high-protein weight-loss diet. *The American Journal of Clinical Nutrition, 87*(1), 23-29.

Colagiuri, R., Short, R., & Buckley, A. (2010). The status of national Diabetes programmes: A global survey of IDF member associations. *Diabetes Research and Clinical Practice, 87*(2), 137-142.

Comino, E. J., Harris, M. F., Shaw, J. E., & Jayasinghe, U. W. (2012). Detection of Type 2 Diabetes: What role for associated risk and protective factors and socioeconomic status? *Australian Health Review: A Publication of the Australian Hospital Association, 36*(3), 349-355.

Cope, M. B., Erdman, J. W. J., & Allison, D. B. (2008). The potential role of soyfoods in weight and adiposity reduction: An evidence-based review. *Obesity Reviews, 9*(3), 219-235.

Coppell, K. J., Mann, J. I., Williams, S. M., Jo, E., Drury, P. L., Miller, J. C., & Parnell, W. R. (2013). Prevalence of diagnosed and undiagnosed Diabetes and Pre-Diabetes in New Zealand: Findings from the 2008/09 Adult Nutrition Survey. *New Zealand Medical Journal, 126*(1370), 23-42.

Coppell, K. J., Tipene-Leach, D. C., Pahau, H. L., Williams, S. M., Abel, S., Iles, M., . . . Mann, J. I. (2009). Two-year results from a community-wide Diabetes prevention intervention in a high risk indigenous community: The Ngati and healthy project. *Diabetes Research and Clinical Practice, 85*(2), 220-227.

Coulston, A. M., Hollenbeck, C. B., Swislocki, A. L., & Reaven, G. M. (1987). Effect of source of dietary carbohydrate on plasma glucose and insulin responses to mixed meals in subjects with NIDDM. *Diabetes Care, 10*(4), 395-400.

Cowie, C. C., Rust, K. F., Ford, E. S., Eberhardt, M. S., Byrd-Holt, D. D., Li, C., . . . Saydah, S. H. (2009). Full accounting of Diabetes and pre-Diabetes in the US population in 1988–1994 and 2005–2006. *Diabetes Care, 32*(2), 287-294.

Crandall, J. P., Knowler, W. C., Kahn, S. E., Marrero, D., Florez, J. C., Bray, G. A., . . . Nathan, D. M. (2008). The prevention of Type 2 Diabetes. *Nature Reviews Endocrinology, 4*(7), 382-393.

Crapo, P. A., Insel, J., Sperling, M., & Kolterman, O. G. (1981). Comparison of serum glucose, insulin, and glucagon responses to different Types of complex carbohydrate in noninsulin-dependent diabetic patients. *The American Journal of Clinical Nutrition, 34*(2), 184-190.

Crapo, P. A., Reaven, G., & Olefsky, J. (1977). Postprandial plasma-glucose and -insulin responses to different complex carbohydrates. *Diabetes, 26*(12), 1178-1183.

Critchley, C. R., Hardie, E. A., & Moore, S. M. (2012). Examining the psychological pathways to behavior change in a group-based lifestyle program to prevent Type 2 Diabetes. *Diabetes Care, 35*(4), 699-705.

Dagogo-Jack, S. (2017). Primary prevention of Type 2 Diabetes: An imperative for developing countries. *Diabetes mellitus in developing countries and underserved communities* (pp. 7-31).

Dale, K. S., Mann, J. I., McAuley, K. A., Williams, S. M., & Farmer, V. L. (2009a). Sustainability of lifestyle changes following an intensive lifestyle intervention in insulin resistant adults: Follow-up at 2-years. *Asia Pacific Journal of Clinical Nutrition, 18*(1), 114-120.

Dale, K. S., McAuley, K. A., Taylor, R. W., Williams, S. M., Farmer, V. L., Hansen, P., . . . Mann, J. I. (2009b). Determining optimal approaches for weight maintenance: A randomized controlled trial. *Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne, 180*(10), E39-46.

Dansinger, M. L., Gleason, J. A., Griffith, J. L., Selker, H. P., & Schaefer, E. J. (2005). Comparison of the Atkins, Ornish, Weight watchers, and Zone diets for weight loss and heart disease risk reduction: A randomized trial. *The Journal of the American Medical Association, 293*(1), 43-53.

de Boer, J., & Aiking, H. (2017). Pursuing a low meat diet to improve both health and sustainability: How can we use the Frames that shape our meals? *Ecological Economics, 142*, 238-248.

de Boer., A. T., Herraets., I. J., Stegen., J., Roumen., C., Corpeleijn., E., Schaper., N. C., . . . Blaak, E. E. (2013). Prevention of the metabolic syndrome in IGT subjects in a lifestyle intervention: Results from the SLIM study. *Nutrition, Metabolism and Cardiovascular Diseases, 23*(11), 1147-1153.

de Boer, J., Helms, M., & Aiking, H. (2006). Protein consumption and sustainability: Diet diversity in EU-15. *Ecological Economics, 59*(3), 267-274.

de Graaf, C., Blom, W. A., Smeets, P. A., Stafleu, A., & Hendriks, H. F. (2004). Biomarkers of satiation and satiety. *The American Journal of Clinical Nutrition, 79*(6), 946-961.

Deng, Y., & Scherer, P. E. (2010). Adipokines as novel biomarkers and regulators of the metabolic syndrome. *Annals of the New York Academy of Sciences, 1212*(1), E1-E19.

Devaux, M., & Sassi, F. (2015). The labour market impacts of obesity, smoking, alcohol use and related chronic diseases. Retrieved from: https://www.oecd-ilibrary.org/social-issues-migration-health/the-labour-market-impacts-of-obesity-smoking-alcohol-use-and-related-chronic-diseases_5jrqcn5fpv0v-en

Diabetes Prevention Program (DPP) Research Group. (2002). The Diabetes Prevention Program (DPP): Description of lifestyle intervention. *Diabetes Care, 25*(12), 2165-2171.

Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of Type 2 Diabetes with lifestyle intervention or metformin. *New England Journal of Medicine, 2002*(346), 393-403.

Dixon, J. B., O'Brien, P. E., Playfair, J., Chapman, L., Schachter, L. M., Skinner, S., ... & Anderson, M. (2008). Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *The Journal of the American Medical Association*, *299*(3), 316-323.

Dixon, J. B., le Roux, C. W., Rubino, F., & Zimmet, P. (2012). Bariatric surgery for type 2 diabetes. *The Lancet*, *379*(9833), 2300-2311.

Dobbs, R., Sawers, C., Thompson, F., Manyika, J., Woetzel, J., Child, P., ... & Spatharou, A. (2014). How the world could better fight obesity. *McKinsey Global Institute.*

Dombrowski, S. U., Knittle, K., Avenell., A., Araujo-Soares., V., & Sniehotta., F. F. (2014). Long-term maintenance of weight loss with non-surgical interventions in obese adults: Systematic review and meta-analyses of randomised controlled trials. *British Medical Journal (Clinical Research Ed.), 348*, g2646.

Dong, J. Y., Zhang, Z. L., Wang, P. Y., & Qin, L. Q. (2013). Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in Type 2 Diabetes: Meta-analysis of randomised controlled trials. *British Journal of Nutrition, 110*(05), 781-789.

Drury, P. L., & Cundy, T. (2012). Glycemic management of Type 2 Diabetes mellitus. *The New England Journal of Medicine, 367*(2), 182.

Du, H., van der A, D. L., van Bakel, M. M., Slimani, N., Forouhi, N. G., Wareham, N. J., . . . Schulze, M. B. (2009). Dietary glycaemic index, glycaemic load and subsequent changes of weight and waist circumference in European men and women. *International Journal of Obesity, 33*(11), 1280-1288.

Duijzer, G., Haveman-Nies, A., Jansen, S. C., ter Beek, J., Hiddink, G. J., & Feskens, E. J. (2014). SLIMMER: A randomised controlled trial of Diabetes prevention in Dutch primary health care: Design and methods for process, effect, and economic evaluation. *BMC Public Health, 14*(1), 602.

Duncan, E., Schofield, G., Duncan, S., Kolt, G., & Rush, E. (2004). Ethnicity and body fatness in New Zealanders. *The New Zealand Medical Journal (Online), 117*(1195)

Duncan, G. G., Cristofori, F. C., Yue, J. K., & Murthy, M. (1964). The control of obesity by intermittent fasts. *Medical Clinics of North America, 48*(5), 1359-1372.

Dunkley, A. J., Bodicoat, D. H., Greaves, C. J., Russell, C., Yates, T., Davies, M. J., & Khunti, K. (2014). Diabetes prevention in the real world: Effectiveness of pragmatic lifestyle interventions for the prevention of Type 2 Diabetes and of the impact of adherence to guideline recommendations: A systematic review and meta-analysis. *Diabetes Care, 37*(4), 922-933.

Ebbeling, C. B., Swain, J. F., Feldman, H. A., Wong, W. W., Hachey, D. L., Garcia-Lago, E., & Ludwig, D. S. (2012). Effects of dietary composition on energy expenditure during weight-loss maintenance. *The Journal of the American Medical Association, 307*(24), 2627-2634.

Eckel, R. H., Kahn, S. E., Ferrannini, E., Goldfine, A. B., Nathan, D. M., Schwartz, M. W., . . . European Association for the Study of Diabetes. (2011). Obesity and Type 2 Diabetes: What can be unified and what needs to be individualized? *Diabetes Care, 34*(6), 1424-1430.

Engels, J. M., & Diehr, P. (2003). Imputation of missing longitudinal data: A comparison of methods. *Journal of Clinical Epidemiology, 56*(10), 968-976.

Eriksson, K. F., & Lindgärde, F. (1991). Prevention of Type 2 (non-insulin-dependent) Diabetes mellitus by diet and physical exercise. The 6-year Malmö feasibility study. *Diabetologia, 34*(12), 891-898.

Eriksson, K. F., & Lindgärde, F. (1998). No excess 12-year mortality in men with impaired glucose tolerance who participated in the malmö preventive trial with diet and exercise. *Diabetologia, 41*(9), 1010-1016.

Evans, F. A., & Strang, J. M. (1929). A departure from the usual methods in treating obesity. *Obesity, 177*, 339-348.

Faerch, K., Borch-Johnsen, K., Holst, J. J., & Vaag, A. (2009). Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: Does it matter for prevention and treatment of Type 2 Diabetes? *Diabetologia, 52*(9), 1714-1723.

Fang, Y., Li, T., & Chen, S. (2004). Effect of medicine and non-medicine intervention on the outcomes of patients with impaired glucose tolerance: 5-year follow-up. *Zhongguo Linchuang Kangfu, 8*, 6562-6563.

Fantuzzi, G. (2005). Adipose tissue, Adipokines, and Inflammation. *Journal of Allergy and Clinical Immunology,* 115(5), 911-919.

Farnsworth, E., Luscombe, N. D., Noakes, M., Wittert, G., Argyiou, E., & Clifton, P. M. (2003). Effect of a high-protein, energy-restricted diet on body composition, glycemic control, and lipid

concentrations in overweight and obese hyperinsulinemic men and women. *The American Journal of Clinical Nutrition, 78*(1), 31-39.

Feinman, R. D., Pogozelski, W. K., Astrup, A., Bernstein, R. K., Fine, E. J., Westman, E. C., . . . Dashti, H. M. (2015). Dietary carbohydrate restriction as the first approach in Diabetes management: Critical review and evidence base. *Nutrition, 31*(1), 1-13.

Feldman, A. L., Griffin, S. J., Ahern, A. L., Long, G. H., Weinehall, L., Fhärm, E., . . . Wennberg, P. (2017). Impact of weight maintenance and loss on Diabetes risk and burden: A population-based study in 33,184 participants. *BMC Public Health, 17*(1), 170-180.

Ferrannini, E. (2014). Definition of intervention points in pre-diabetes. *The Lancet Diabetes & Endocrinology, 2*(8), 667-675.

Flint, A., Raben, A., Rehfeld, J., Holst, J., & Astrup, A. (2000). The effect of glucagon-like peptide-1 on energy expenditure and substrate metabolism in humans. *International Journal of Obesity & Related Metabolic Disorders, 24*(3)

Fogelholm, M., Larsen, T. M., Westerterp-Plantenga, M., Macdonald, I., Martinez, J. A., Boyadjieva, N., . . . Sundvall, J. (2017). PREVIEW: Prevention of Diabetes through lifestyle intervention and population studies in Europe and around the world. Design, methods, and baseline participant description of an adult cohort enrolled into a three-year randomised clinical trial. *Nutrients, 9*(6), 632.

Fogelholm, M., Larsen, T. M., Westerterp-Plantenga, M., Macdonald, I., Martinez, J. A., Handjiev, S., . . . Raben, A. (2013). The PREVIEW intervention trial: Design and methods. *Annals of Nutrition & Metabolism, 63*, 96-97.

Folin, O., & Denis, W. (1915). On starvation and obesity, with special reference to acidosis. *Journal of Biological Chemistry, 21*(1), 183-192.

Fontaine, K. R., Cheskin, L. J., & Barofsky, I. (1996). Health-related quality of life in obese persons seeking treatment. *Journal of Family Practice, 43*(3), 265-271.

Foo, L. L., Vijaya, K., Sloan, R. A., & Ling, A. (2013). Obesity prevention and management: Singapore's experience. *Obesity Reviews, 14*(S2), 106-113.

Food and Drug Administration. (2015). United States Food and Drug Administration (FDA) International CODEX Standardization and Legislation - guidelines for vitamin and mineral food supplements. Retrieved from http://www.fao.org/fao-who-codexalimentarius/sh-proxy/ar/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCODEX%2BSTAN%2B203-1995%252FCXS_203e.pdf

Food and Drug Administration (2015). United States Department of Agriculture. The food guide pyramid, center for Nutrition policy and promotion. Retrieved from http://www.cnpp.usda.gov/sites/default/files/archived_projects/FGPPamphlet.pdf

Foster, G. D., Wyatt, H. R., Hill, J. O., Makris, A. P., Rosenbaum, D. L., Brill, C., . . . Rader, D. J. (2010). Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: A randomized trial. *Annals of Internal Medicine, 153*(3), 147-157.

Foster, G. D., Wadden, T. A., Peterson, F. J., Letizia, K. A., Bartlett, S. J., & Conill, A. M. (1992). A controlled comparison of three very-low-calorie diets: Effects on weight, body composition, and symptoms. *The American Journal of Clinical Nutrition, 55*(4), 811-817.

Foster, G. D., Wyatt, H. R., Hill, J. O., McGuckin, B. G., Brill, C., Mohammed, B. S., . . . Klein, S. (2003). A randomized trial of a low-carbohydrate diet for obesity. *New England Journal of Medicine, 348*(21), 2082-2090.

Foster-Powell, K., Holt, S. H., & Brand-Miller, J. C. (2002). International table of glycemic index and glycemic load values: 2002. *The American Journal of Clinical Nutrition*, *76*(1), 5-56.

Foster-Powell, K., & Miller, J. B. (1995). International tables of glycemic index. *The American Journal of Clinical Nutrition*, *62*(4), 871S-890S.

Franz, M. J., VanWormer, J. J., Crain, A. L., Boucher, J. L., Histon, T., Caplan, W., . . . Pronk, N. P. (2007). Weight-loss outcomes: A systematic review and meta-analysis of weight-loss clinical trials

with a minimum 1-year follow-up. *Journal of the American Dietetic Association, 107*(10), 1755-1767.

Franz, M. J. (2017). Nutrition therapy for the prevention and treatment of preDiabetes and Diabetes. *Nutrition in Lifestyle Medicine* (pp. 151-171).

Friedrich, N., Schneider, H. J., John, U., Dorr, M., Baumeister, S. E., Homuth, G., . . . Wallaschofski, H. (2013). Correlates of adverse outcomes in abdominally obese individuals: Findings from the five-year followup of the population-based study of health in pomerania. *Journal of Obesity, 2013*, 762012 (Epub Sep 26).

Friel, S., Hattersley, L., Snowdon, W., Thow, A. M., Lobstein, T., Sanders, D., . . . Walker, C. (2013). Monitoring the impacts of trade agreements on food environments. *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity, 14*(S1), 120-134.

Fromentin, G., Darcel, N., Chaumontet, C., Marsset-Baglieri, A., Nadkarni, N., & Tome, D. (2012). Peripheral and central mechanisms involved in the control of food intake by dietary amino acids and proteins. *Nutrition Research Reviews, 25*(1), 29-39.

Gangwisch, J. E., Malaspina, D., Boden-Albala, B., & Heymsfield, S. B. (2005). Inadequate sleep as a risk factor for obesity: Analyses of the NHANES I. *Sleep, 28*(10), 1289.

Garber, A. J. (2012). Obesity and Type 2 Diabetes: Which patients are at risk? *Diabetes, Obesity and Metabolism, 14*(5), 399-408.

Gardner, C. D., Kiazand, A., Alhassan, S., Kim, S., Stafford, R. S., Balise, R. R., . . . King, A. C. (2007). Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: The A TO Z weight loss study: A randomized trial. *The Journal of the American Medical Association, 297*(9), 969-977.

Gardner, C. D., Offringa, L. C., Hartle, J. C., Kapphahn, K., & Cherin, R. (2016). Weight loss on low-fat vs. low-carbohydrate diets by insulin resistance status among overweight adults and adults with obesity: A randomized pilot trial. *Obesity, 24*(1), 79-86.

Gasteyger, C., Larsen, T. M., Vercruysse, F., Pedersen, D., Toubro, S., & Astrup, A. (2009). Visceral fat loss induced by a low-calorie diet: A direct comparison between women and men. *Diabetes, Obesity and Metabolism, 11*(6), 596-602.

Geiker., N. R., Veller., M., Kjoelbaek., L., Jakobsen, J., Ritz, C., Raben, A., . . . Bügel, S. (2018). Effect of low energy diet for eight weeks to adults with overweight or obesity on folate, retinol, vitamin B 12, D and E status and the degree of inflammation: A post hoc analysis of a randomized intervention trial. *Nutrition & Metabolism, 15*(1), 24.

Genoni, G., Prodam, F., Marolda, A., Giglione, E., Demarchi, I., Bellone, S., & Bona, G. (2014). Obesity and infection: two sides of one coin. *European Journal of Pediatrics*, 173(1), 25-32.

Gilbert, J. A., Bendsen, N. T., Tremblay, A., & Astrup, A. (2011). Effect of proteins from different sources on body composition. *Nutrition, Metabolism and Cardiovascular Diseases, 21*(Suppl 2), 16-31.

Gillies, C. L., Abrams, K. R., Lambert, P. C., Cooper, N. J., Sutton, A. J., Hsu, R. T., & Khunti, K. (2007). Pharmacological and lifestyle interventions to prevent or delay Type 2 Diabetes in people with impaired glucose tolerance: Systematic review and meta-analysis. *British Medical Journal (Clinical Research Ed), 334*(7588), 299.

Gittelsohn, J., & Trude, A. (2017). Diabetes and obesity prevention: Changing the food environment in low-income settings. *Nutrition Reviews, 75* (suppl 1), 62-69.

Gogebakan, O., Kohl, A., Osterhoff, M. A., van Baak, M. A., Jebb, S. A., Papadaki, A., . . . DiOGenes. (2011). Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: The diet, obesity, and genes (DiOGenes) study: A randomized, controlled trial. *Circulation, 124*(25), 2829-2838.

Gong, Q., Zhang, P., Wang, J., An, Y., Gregg, E. W., Li, H., . . . Li, G. (2016). Changes in mortality in people with IGT before and after the onset of Diabetes during the 23-year follow-up of the Da Qing Diabetes prevention study. *Diabetes Care, 39*(9), 1550-1555.

Goodpaster, B. H., Kelley, D. E., Wing, R. R., Meier, A., & Thaete, F. L. (1999). Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes, 48*(4), 839-847.

Gordon, D. J., Probstfield, J. L., Garrison, R. J., Neaton, J. D., Castelli, W. P., Knoke, J. D., . . . Tyroler, H. A. (1989). High-density lipoprotein cholesterol and cardiovascular disease. four prospective American studies. *Circulation, 79*(1), 8-15.

Gougeon, R. (1992). The metabolic response to two very low energy diets (VLED) of differing amino acid composition during weight reduction. International Journal of Obesity and Related Metabolic Disorders : *Journal of the International Association for the Study of Obesity, 16*(12), 1005-1012.

Goyenechea, E., Holst, C., van Baak, M. A., Saris, W. H., Jebb, S., Kafatos, A., ... & Larsen, T. M. (2011). Effects of different protein content and glycaemic index of ad libitum diets on diabetes risk factors in overweight adults: the DIOGenes multicentre, randomized, dietary intervention trial. *Diabetes Metabolism Research and Reviews*, *27*(7), 705-716.

Graham, T. E., Sathasivam, P., Rowland, M., Marko, N., Greer, F., & Battram, D. (2001). Caffeine ingestion elevates plasma insulin response in humans during an oral glucose tolerance test. *Canadian Journal of Physiology and Pharmacology, 79*(7), 559-565.

Greenway, F. (2015). Physiological adaptations to weight loss and factors favouring weight regain. *International Journal of Obesity, 39*(8), 1188.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., . . . National Heart, Lung, and Blood Institute. (2005). Diagnosis and management of the metabolic syndrome: An American heart Association/National heart, lung, and blood institute scientific statement. *Circulation, 112*(17), 2735-2752.

Guariguata, L., Whiting, D. R., Hambleton, I., Beagley, J., Linnenkamp, U., & Shaw, J. E. (2014). Global estimates of Diabetes prevalence for 2013 and projections for 2035 for the IDF Diabetes atlas. *Diabetes Research and Clinical Practice, 103*(2), 137-149.

Guiducci, L., Denoth, F., Liistro, T., & Iozzo, P. (2013). Obesity: The epidemic of the new millennium between genetics and environment. [Obesita: l'epidemia del nuovo millennio tra genetica e ambiente] *Recenti Progressi in Medicina, 104*(9), 467-475.

Guo, F., Moellering, D. R., & Garvey, W. T. (2014). Use of HbA1c for diagnoses of Diabetes and preDiabetes: Comparison with diagnoses based on fasting and 2-hr glucose values and effects of gender, race, and age. *Metabolic Syndrome and Related Disorders, 12*(5), 258-268.

Gutch, M., Kumar, S., Razi, S. M., Gupta, K. K., & Gupta, A. (2015). Assessment of insulin sensitivity/resistance. *Indian Journal of Endocrinology and Metabolism, 19*(1), 160.

Hadaegh, F., Hasheminia, M., Lotfaliany, M., Mohebi, R., Azizi, F., & Tohidi, M. (2013). Incidence of metabolic syndrome over 9 years follow-up; the importance of sex differences in the role of insulin resistance and other risk factors. *PloS One, 8*(9), e76304.

Halkjær, J., Olsen, A., Overvad, K., Jakobsen, M. U., Boeing, H., Buijsse, B., . . . Tjønneland, A. (2011). Intake of total, animal and plant protein and subsequent changes in weight or waist circumference in European men and women: The DioGENES project. *International Journal of Obesity, 35*(8), 1104-1113.

Hall, W. L., Millward, D. J., Long, S. J., & Morgan, L. M. (2003). Casein and whey exert different effects on plasma amino acid profiles, gastrointestinal hormone secretion and appetite. *British Journal of Nutrition, 89*(2), 239-248.

Halton, T. L., & Hu, F. B. (2004). The effects of high protein diets on thermogenesis, satiety and weight loss: A critical review. *Journal of the American College of Nutrition, 23*(5), 373-385.

Hamman, R. F., Wing, R. R., Edelstein, S. L., Lachin, J. M., Bray, G. A., Delahanty, L., . . . Wylie-Rosett, J. (2006). Effect of weight loss with lifestyle intervention on risk of Diabetes. *Diabetes Care, 29*(9), 2102-2107.

Hansen, D., Dendale, P., Jonkers, R., Beelen, M., Manders, R., Corluy, L., . . . Van Loon, L. (2009). Continuous low-to moderate-intensity exercise training is as effective as moderate-to high-intensity exercise training at lowering blood HbA1c in obese Type 2 Diabetes patients. *Diabetologia, 52*(9), 1789-1797.

Harding, J. L., Backholer, K., Williams, E. D., Peeters, A., Cameron, A. J., Hare, M. J., . . . Magliano, D. J. (2014). Psychosocial stress is positively associated with body mass index gain over 5 years: Evidence from the longitudinal AusDiab study. *Obesity, 22*(1), 277-286.

Hartmann, C., & Siegrist, M. (2017). Consumer perception and behaviour regarding sustainable protein consumption: A systematic review. *Trends in Food Science & Technology, 61*, 11-25.

Haywood, C. J., Prendergast, L. A., Purcell, K., Le Fevre, L., Lim, W. K., Galea, M., & Proietto, J. (2017). Very low calorie diets for weight loss in obese older adults-A randomized trial. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences,*

Healton, C. G., Vallone, D., McCausland, K. L., Xiao, H., & Green, M. P. (2006). Smoking, obesity, and their co-occurrence in the United States: Cross sectional analysis. *British Medical Journal (Clinical Research Ed.), 333*(7557), 25-26.

Heilbronn, L. K., Noakes, M., & Clifton, P. M. (2001). Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. *Arteriosclerosis, Thrombosis, and Vascular Biology, 21*(6), 968-970.

Henchion, M., Hayes, M., Mullen, A. M., Fenelon, M., & Tiwari, B. (2017). Future protein supply and demand: Strategies and factors influencing a sustainable equilibrium. *Foods, 6*(7), 53.

Henwood, W. (2007). Māori knowledge: A key ingredient in Nutrition and physical exercise health promotion programmes for Maori. *Social Policy Journal of New Zealand, 32*(3), 155-164.

Herman, C. P., & Polivy, J. (1975). Anxiety, restraint, and eating behavior. *Journal of Abnormal Psychology,* 84(6), 666.

Herman, W. H. (2017). The global burden of Diabetes: An overview. *Diabetes mellitus in developing countries and underserved communities* (pp. 1-5)

Herman, W. H., Edelstein, S. L., Ratner, R. E., Montez, M. G., Ackermann, R. T., Orchard, T. J., . . . Brown, M. B. (2012). The 10-year cost-effectiveness of lifestyle intervention or metformin for Diabetes prevention: An intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care, 35*(4), 723-730.

Heymsfield, S. B., & Wadden, T. A. (2017). Mechanisms, pathophysiology, and management of obesity. *New England Journal of Medicine, 376*(3), 254-266.

Hjelmesaeth, J., Asberg, A., Andersson, S., Sandbu, R., Robertsen, I., Johnson, L. K., . . . Karlsson, C. (2018). Impact of body weight, low energy diet and gastric bypass on drug bioavailability, cardiovascular risk factors and metabolic biomarkers: Protocol for an open, non-randomised, three-armed single centre study (COCKTAIL). *British Medical Journal (Open), 8*(5), e021878.

Hong, K., Li, Z., Wang, H., Elashoff, R., & Heber, D. (2005). Analysis of weight loss outcomes using VLCD in black and white overweight and obese women with and without metabolic syndrome. *International Journal of Obesity, 29*(4), 436.

Howard, A. N., Grant, A. M., Edwards, O. M., Littlewood, E. R., & McLean, I. B. (1978). The treatment of obesity with a very-low-calorie liquid-formula diet: an inpatient/outpatient comparison using skimmed-milk protein as the chief protein source. *International Journal of Obesity*, *2*(3), 321-332.

Huttunen-Lenz, M., Hansen, S., Christensen, P., Larsen, T. M., Sandø-Pedersen, F., Drummen, M., ... & Navas-Carretero, S. (2018). PREVIEW study—influence of a behavior modification intervention (PREMIT) in over 2300 people with pre-diabetes: intention, self-efficacy and outcome expectancies during the early phase of a lifestyle intervention. *Psychology Research and Behavior Management*, 11, 383.

Jaacks, L. M., Ma, Y., Davis, N., Delahanty, L. M., Mayer-Davis, E. J., Franks, P. W., ... & Wylie-Rosett, J. (2014). Long-term changes in dietary and food intake behaviour in the Diabetes Prevention Program Outcomes Study. *Diabetic Medicine*, 31(12), 1631-1642.

Jackness, C., Karmally, W., Febres, G., Conwell, I. M., Ahmed, L., Bessler, M., . . . Korner, J. (2013). Very low-calorie diet mimics the early beneficial effect of roux-en-Y gastric bypass on insulin sensitivity and beta-cell function in Type 2 diabetic patients. *Diabetes, 62*(9), 3027-3032.

Jakubowicz, D., & Froy, O. (2013). Biochemical and metabolic mechanisms by which dietary whey protein may combat obesity and Type 2 Diabetes. *The Journal of Nutritional Biochemistry, 24*(1), 1-5.

Jarrett, R. J., Keen, H., & McCartney, P. (1984). The Whitehall study: Ten year follow-up report on men with impaired glucose tolerance with reference to worsening to Diabetes and predictors of death. *Diabetic Medicine, 1*(4), 279-283.

Jarrett, R. J., Keen, K., Fuller, J. H., & McCartner, M. (1979). Worsening to Diabetes in men with impaired glucose tolerance ("borderline Diabetes"). *Diabetologia,* 16, 25-30.

Jebb, S. A., Ahern, A. L., Olson, A. D., Aston, L. M., Holzapfel, C., Stoll, J., ... & Lau, N. S. (2011). Primary care referral to a commercial provider for weight loss treatment versus standard care: a randomised controlled trial. *The Lancet*, 378(9801), 1485-1492.

Jenkins., D. J., Wolever., T. M., Collier., G. R., Ocana., A., Rao., A. V., Buckley., G., . . . Thompson., L. U. (1987). Metabolic effects of a low-glycemic-index diet. *The American Journal of Clinical Nutrition,* 46(6), 968-975.

Jenkins., D. J., Wolever., T. M., & Jenkins., A. L. (1988). Starchy foods and glycemic index. *Diabetes Care,* 11(2), 149-159.

Jenkins., D. J., Wolever., T. M., Taylor., R. H., Barker., H., Fielden., H., Baldwin., J. M., . . . Goff, D. V. (1981). Glycemic index of foods: A physiological basis for carbohydrate exchange. *The American Journal of Clinical Nutrition,* 34(3), 362-366.

Jenkins., D. J. A., Jenkins., A. L., Wolever., T. M. S., Josse., R. G., & Wong., G. S. (1984). The glycaemic response to carbohydrate foods. *The Lancet,* 324(8399), 388-391.

Jenkins., D. J. A., Wolever., T. M. S., Jenkins., A. L., Thorne., M. J., Lee., R., Kalmusky., J., . . . Wong., G. S. (1983). The glycaemic index of foods tested in diabetic patients: A new basis for carbohydrate exchange favouring the use of legumes. *Diabetologia,* 24(4), 257-264.

Jensen, K. J., Alpini, G., & Glaser, S. (2013). Hepatic nervous system and neurobiology of the liver. *Comprehensive Physiology,* 3(2), 655-665.

Jeon, C. Y., Lokken, R. P., Hu, F. B., & van Dam, R. M. (2007). Physical activity of moderate intensity and risk of Type 2 Diabetes: A systematic review. *Diabetes Care,* 30(3), 744-752.

Jo, E. C., & Drury, P. L. (2015). Development of a virtual Diabetes register using information technology in New Zealand. *Healthcare Informatics Research,* 21(1), 49-55.

Johansson, K., Neovius, M., & Hemmingsson, E. (2013). Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: A systematic review and meta-analysis of randomized controlled trials–. *The American Journal of Clinical Nutrition,* 99(1), 14-23.

Johansson, K., Neovius, M., Lagerros, Y. T., Harlid, R., Rossner, S., Granath, F., & Hemmingsson, E. (2009). Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: A randomised controlled trial. *British Medical Journal (Clinical Research Ed.),* 339, b4609.

Johnston, C. S., Tjonn, S. L., & Swan, P. D. (2004). High-protein, low-fat diets are effective for weight loss and favorably alter biomarkers in healthy adults. *The Journal of Nutrition,* 134(3), 586-591.

Johnstone, A. M., Horgan, G. W., Murison, S. D., Bremner, D. M., & Lobley, G. E. (2008). Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum. *The American Journal of Clinical Nutrition,* 87(1), 44-55.

Johnstone, A. M., Lobley, G. E., Horgan, G. W., Bremner, D. M., Fyfe, C. L., Morrice, P. C., & Duthie, G. G. (2011). Effects of a high-protein, low-carbohydrate v. high-protein, moderate-carbohydrate weight-loss diet on antioxidant status, endothelial markers and plasma indices of the cardiometabolic profile. *British Journal of Nutrition,* 106(2), 282-291.

Joris, P. J., Plat, J., Kusters, Y. H., Houben, A. J., Stehouwer, C. D., Schalkwijk, C. G., & Mensink, R. P. (2016). Diet-induced weight loss improves not only cardiometabolic risk markers but also markers of vascular function: a randomized controlled trial in abdominally obese men. *The American journal of clinical nutrition*, 105(1), 23-31.

Josse, A. R., Atkinson, S. A., Tarnopolsky, M. A., & Phillips, S. M. (2011). Increased consumption of dairy foods and protein during diet- and exercise-induced weight loss promotes fat mass loss and lean mass gain in overweight and obese premenopausal women. *The Journal of Nutrition,* 141(9), 1626-1634.

Jung, S., Jung, C., Reaven, G. M., & Kim, S. H. (2018). Adapting to insulin resistance in obesity: Role of insulin secretion and clearance. *Diabetologia,* 61(3), 681-687.

Kahlert, D., Unyi-Reicherz, A., Stratton, G., Meinert Larsen, T., Fogelholm, M., Raben, A., & Schlicht, W. (2016). PREVIEW behavior modification intervention toolbox (PREMIT): A study protocol for a psychological element of a multicenter project. *Frontiers in Psychology,* 7, 1136.

Karhunen, L. J., Juvonen, K. R., Huotari, A., Purhonen, A. K., & Herzig, K. H. (2008). Effect of protein, fat, carbohydrate and fibre on gastrointestinal peptide release in humans. *Regulatory Peptides,* 149(1), 70-78.

Kataoka, M., Venn, B. J., Williams, S. M., Te Morenga, L. A., Heemels, I. M., & Mann, J. I. (2013). Glycaemic responses to glucose and rice in people of Chinese and European ethnicity. *Diabetic Medicine,* 30(3), e101-107.

Keen, H., Jarrett, R. J., & McCartney, P. (1982). The ten-year follow-up of the Bedford survey (1962–1972): Glucose tolerance and Diabetes. *Diabetologia,* 22(2), 73-78.

Keen, H., Jarrett, R. J., Ward, J. D., & Fuller, J. H. (1973). Borderline diabetics and their response to tolbutamide. *Advances in Metabolic Disorders,* 2(S2), 521-531.

Keller, U. (2011). Dietary proteins in obesity and in Diabetes. *International Journal for Vitamin and Nutrition Research,* 81(2), 125.

Khandelwal, S., & Reddy, K. S. (2013). Eliciting a policy response for the rising epidemic of overweight-obesity in India. *Obesity Reviews,* 14(S2), 114-125.

Khavandi, K., Amer, H., Ibrahim, B., & Brownrigg, J. (2013). Strategies for preventing Type 2 Diabetes: An update for clinicians. *Therapeutic Advances in Chronic Disease,* 4(5), 242-261.

Kim, E. H., Petrie, J. R., Motoi, L., Morgenstern, M. P., Sutton, K. H., Mishra, S., & Simmons, L. D. (2008). Effect of structural and physicochemical characteristics of the protein matrix in pasta on in vitro starch digestibility. *Food Biophysics,* 3(2), 229-234.

Knol, M., Twisk, J. W., Beekman, A. T., Heine, R., Snoek, F. J., & Pouwer, F. (2006). Depression as a risk factor for the onset of Type 2 Diabetes mellitus. A meta-analysis. *Diabetologia,* 49(5), 837.

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., . . . Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of Type 2 Diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine,* 346(6), 393-403.

Knowler, W. C., Fowler, S. E., Hamman, R. F., Christophi, C. A., Hoffman, H. J., Brenneman, A. T., . . . Nathan, D. M. (2009). 10-year follow-up of Diabetes incidence and weight loss in the Diabetes Prevention Program outcomes study. *Lancet,* 374(9702), 1677-1686.

Knowler, W. C., Pettitt, D. J., Savage, P. J., & Bennett, P. H. (1981). Diabetes incidence in pima Indians: Contributions of obesity and parental Diabetes. *American Journal of Epidemiology,* 113(2), 144-156.

Knox, E. M., & Ng, R. T. (1998). Algorithms for mining distance based outliers in large datasets. Paper presented at the *Proceedings of the International Conference on very Large Databases,* 392-403.

Kosaka, K., Noda, M., & Kuzuya, T. (2005). Prevention of Type 2 Diabetes by lifestyle intervention: A Japanese trial in IGT males. *Diabetes Research and Clinical Practice,* 67(2), 152-162.

Kossoff, E. H., Turner, Z., Bluml, R. M., Pyzik, P. L., & Vining, E. P. (2007). A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet. *Epilepsy & Behavior,* 10(3), 432-436.

Krebs, J., Parry-Strong, A., Gamble, E., McBain, L., Bingham, L., Dutton, E., . . . Smith, R. (2013). A structured, group-based Diabetes self-management education (DSME) programme for people, families and whanau with Type 2 Diabetes (T2DM) in New Zealand: An observational study. *Primary Care Diabetes,* 7(2), 151-158.

Krebs, J. D., Elley, C. R., Parry-Strong, A., Lunt, H., Drury, P. L., Bell, D. A., . . . Mann, J. I. (2012). The Diabetes excess weight loss (DEWL) trial: A randomised controlled trial of high-protein versus high-carbohydrate diets over 2 years in Type 2 Diabetes. *Diabetologia,* 55(4), 905-914.

Kreitzman, S., & Beeson, V. (1996). Obese patients in UK general practices lose 16 tonnes. *Obese Patients in UK General Practices Lose 16 Tonnes,* 3, 5-8.

Kukutai, T., & Callister, P. (2009). A “main” ethnic group? ethnic self-prioritisation among New Zealand youth. *Social Policy Journal of New Zealand,* 36, 16-31.

Kushner, R. F., & Doerfler, B. (2008). Low-carbohydrate, high-protein diets revisited. *Current Opinion in Gastroenterology,* 24(2), 198-203.

Kussmann, M., Morine, M. J., Hager, J., Sonderegger, B., & Kaput, J. (2013). Perspective: A systems approach to Diabetes research. *Frontiers in Genetics,* 4, 205.

Lang, V., Bellisle, F., Oppert, J. M., Craplet, C., Bornet, F. R., Slama, G., & Guy-Grand, B. (1998). Satiating effect of proteins in healthy subjects: A comparison of egg albumin, casein, gelatin, soy protein, pea protein, and wheat gluten. *The American Journal of Clinical Nutrition,* 67(6), 1197-1204.

Layman, D. K., & Baum, J. I. (2004). Dietary protein impact on glycemic control during weight loss. *The Journal of Nutrition,* 134(4), S968-973.

Lean, M. E., Leslie, W. S., Barnes, A. C., Brosnahan, N., Thom, G., McCombie, L., ... & Rodrigues, A. M. (2018). Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *The Lancet*, 391(10120), 541-551.

Lean, M., Brosnahan, N., McLoone, P., McCombie, L., Higgs, A. B., Ross, H., . . . Morrison, D. (2013). Feasibility and indicative results from a 12-month low-energy liquid diet treatment and maintenance programme for severe obesity. *British Journal of General Practice,* 63(607), e115-24.

Lean, M. E., Han, T. S., & Morrison, C. E. (1995). Waist circumference as a measure for indicating need for weight management. *British Medical Journal (Clinical Research Ed.),* 311(6998), 158-161.

Lean, M., & Hankey, C. (2018). Keeping it off: The challenge of weight-loss maintenance. *The Lancet Diabetes & Endocrinology,* 6(9): 681-683.

Lebot, V. (2010). Sweet potato - In *root and tuber crops*. *Root and tuber crops* (pp. 97-125).

Lee, K., Lee, S., Kim, Y., & Kim, Y. (2008). Waist circumference, dual-energy X-ray absortiometrically measured abdominal adiposity, and computed tomographically derived intra-abdominal fat area on detecting metabolic risk factors in obese women. *Nutrition,* 24(7), 625-631.

Lee, C., Colagiuri, R., Magliano, D. J., Cameron, A. J., Shaw, J., Zimmet, P., & Colagiuri, S. (2013). The cost of Diabetes in adults in Australia. *Diabetes Research and Clinical Practice,* 99(3), 385-390.

Lee, Y. J., Lee, A., Yoo, H. J., Kim, M., Kim, M., Jee., S., . . . Lee., J. H. (2018). Effect of weight loss on circulating fatty acid profiles in overweight subjects with high visceral fat area: A 12-week randomized controlled trial. *Nutrition Journal,* 17(1), 28.

Lehtisalo, J., Lindström, J., Ngandu, T., Kivipelto, M., Ahtiluoto, S., Ilanne-Parikka, P., . . . Tuomilehto, J. (2016). Association of long-term dietary fat intake, exercise, and weight with later cognitive function in the Finnish Diabetes prevention study. *The Journal of Nutrition, Health and Aging,* 20(2), 146-154.

Leidy, H. J., Clifton, P. M., Astrup, A., Wycherley, T. P., Westerterp-Plantenga, M. S., Luscombe-Marsh, N. D., . . . Mattes, R. D. (2015). The role of protein in weight loss and maintenance. *The American Journal of Clinical Nutrition,* 101(6), 1320S-1329S.

Lemieux, I., Lamarche, B., Couillard, C., Pascot, A., Cantin, B., Bergeron, J., . . . Després, J. (2001). Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men: The Quebec cardiovascular study. *Archives of Internal Medicine,* 161(22), 2685-2692.

Leslie, W. S., Ford, I., Sattar, N., Hollingsworth, K. G., Adamson, A., Sniehotta, F. F., . . . Mathers, J. C. (2016). The Diabetes remission clinical trial (DiRECT): Protocol for a cluster randomised trial. *BMC Family Practice,* 17(1), 20.

Leslie, W. S., Taylor, R., Harris, L., & Lean, M. E. (2017). Weight losses with low-energy formula diets in obese patients with and without Type 2 Diabetes: Systematic review and meta-analysis. *International Journal of Obesity,* 41(1), 96.

Levine, M. E., Suarez, J. A., Brandhorst, S., Balasubramanian, P., Cheng, C. W., Madia, F., . . . Longo, V. D. (2014). Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population . *Cell Metabolism,* 19(3), 407-417.

Leys, C., Ley, C., Klein, O., Bernard, P., & Licata, L. (2013). Detecting outliers: Do not use standard deviation around the mean, use absolute deviation around the median. *Journal of Experimental Social Psychology,* 49(4), 764-766.

Li, G., Zhang, P., Wang, J., An, Y., Gong, Q., Gregg, E. W., . . . Hong, J. (2014). Cardiovascular mortality, all-cause mortality, and Diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes prevention study: A 23-year follow-up study. *The Lancet Diabetes & Endocrinology,* 2(6), 474-480.

Li, G., Zhang, P., Wang, J., Gregg, E. W., Yang, W., Gong, Q., . . . Bennett, P. H. (2008). The long-term effect of lifestyle interventions to prevent Diabetes in the china Da Qing Diabetes prevention study: A 20-year follow-up study. *Lancet,* 371(9626), 1783-1789.

Li, R., Qu, S., Zhang, P., Chattopadhyay, S., Gregg, E. W., Albright, A., . . . Pronk, N. P. (2015). Economic evaluation of combined diet and physical activity promotion programs to prevent Type 2 Diabetes among persons at increased risk: A systematic review for the community preventive services task force. *Annals of Internal Medicine,* 163(6), 452-460.

Liang, X., Chen, X., Li., J., Yan, M., & Yang, Y. (2018). Study on body composition and its correlation with obesity: A cohort study in 5121 Chinese Han participants. *Medicine,* 97(21), e10722.

Liao, D., Asberry, P. J., Shofer, J. B., Callahan, H., Matthys, C., Boyko, E. J., . . . Fujimoto, W. Y. (2002). Improvement of BMI, body composition, and body fat distribution with lifestyle modification in Japanese Americans with impaired glucose tolerance. *Diabetes Care,* 25(9), 1504-1510.

Liebler, C. A., & Halpern-Manners, A. (2008). A practical approach to using multiple-race response data: A bridging method for publicuse microdata. *Demography,* 45(1), 143-155.

Liebman, M. (2014). When and why carbohydrate restriction can be a viable option. *Nutrition,* 30(7), 748-754.

Liese, A. D., Schulz, M., Fang, F., Wolever, T. M., D'Agostino, R. B.,Jr, Sparks, K. C., & Mayer-Davis, E. J. (2005). Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the insulin resistance atherosclerosis study. *Diabetes Care,* 28(12), 2832-2838.

Lim, E., Hollingsworth, K., Aribisala, B., Chen, M., Mathers, J., & Taylor, R. (2011). Reversal of Type 2 Diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia,* 54(10), 2506-2514.

Lin, W. Y., Wu, C. H., Chu, N. F., & Chang, C. J. (2009). Efficacy and safety of very-low-calorie diet in Taiwanese: A multicenter randomized, controlled trial. *Nutrition,* 25(11), 1129-1136.

Lindström, J., Peltonen, M., Eriksson, J. G., Louheranta, A., Fogelholm, M., Uusitupa, M., & Tuomilehto, J. (2006). High-fibre, low-fat diet predicts long-term weight loss and decreased Type 2 Diabetes risk: The Finnish Diabetes prevention study. *Diabetologia,* 49(5), 912-920.

Lindstrom, J., Eriksson, J. G., Valle, T. T., Aunola, S., Cepaitis, Z., Hakumaki, M., . . . Tuomilehto, J. (2003). Prevention of Diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes prevention study: Results from a randomized clinical trial. *Journal of the American Society of Nephrology,* 14(7 Suppl 2), S108-13.

Lindström, J., Ilanne-Parikka, P., Peltonen, M., Aunola, S., Eriksson, J. G., Hemiö, K., . . . Laakso, M. (2006). Sustained reduction in the incidence of Type 2 Diabetes by lifestyle intervention: Follow-up of the Finnish Diabetes prevention study. *The Lancet,* 368(9548), 1673-1679.

Lindström, J., Louheranta, A., Mannelin, M., Rastas, M., Salminen, V., Eriksson, J., . . . Tuomilehto, J. (2003). The Finnish Diabetes prevention study lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care,* 26(12), 3230-3236.

Lindström, J., Neumann, A., Sheppard, K. E., Gilis-Januszewska, A., Greaves, C. J., Handke, U., . . . Rissanen, A. (2010). Take action to prevent Diabetes-the IMAGE toolkit for the prevention of Type 2 Diabetes in Europe. *Hormone and Metabolic Research,* 42(Suppl 1), S37-55.

Lindstrom, J., Peltonen, M., Eriksson, J. G., Aunola, S., Hamalainen, H., Ilanne-Parikka, P., . . . Finnish Diabetes Prevention Study (DPS) Group. (2008). Determinants for the effectiveness of lifestyle intervention in the Finnish Diabetes prevention study. *Diabetes Care,* 31(5), 857-862.

Lindström, J., Peltonen, M., Eriksson, J. G., Ilanne-Parikka, P., Aunola, S., Keinänen-Kiukaanniemi, S., . . . Tuomilehto, J. (2013). Improved lifestyle and decreased Diabetes risk over 13 years: Long-term follow-up of the randomised Finnish Diabetes prevention study (DPS). *Diabetologia,* 56(2), 284-293.

Lindström, J., & Tuomilehto, J. (2003). The Diabetes risk score: A practical tool to predict Type 2 Diabetes risk. *Diabetes Care,* 26(3), 725-731.

Lingvay, I., Guth, E., Islam, A., & Livingston, E. (2013). Rapid improvement in Diabetes after gastric bypass surgery: Is it the diet or surgery? *Diabetes Care,* 36(9), 2741-2747.

Liu, A. Y., Silvestre, M. P., & Poppitt, S. D. (2015). Prevention of Type 2 Diabetes through lifestyle modification: Is there a role for higher-protein diets? *Advances in Nutrition,* 6(6), 665-673.

Liu, L., Feng., J., Zhang., G., Yuan, X., Li., F., Yang., T., . . . Lou, Q. (2018). Visceral adipose tissue is more strongly associated with insulin resistance than subcutaneous adipose tissue in Chinese subjects with pre-Diabetes. *Current Medical Research and Opinion,* 34(1), 123-129.

Logue, J., Thompson, L., Romanes, F., Wilson, D. C., Thompson, J., & Sattar, N. (2010). Guidelines: Management of obesity: Summary of SIGN guideline. *British Medical Journal,* 340(7744), 474-477.

Look AHEAD Research Group, & Wing, R. R. (2010). Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with Type 2 Diabetes mellitus: Four-year results of the look AHEAD trial. *Archives of Internal Medicine,* 170(17), 1566-1575.

López López, R., Fuentes García, R., González-Villalpando, M., & González-Villalpando, C. (2017). Diabetic by HbA1c, normal by OGTT: A frequent finding in the Mexico City Diabetes study. *Journal of the Endocrine Society,* 1(10), 1247-1258.

Ludwig, D. S. (2002). The glycemic index: Physiological mechanisms relating to obesity, Diabetes, and cardiovascular disease. *The Journal of the American Medical Association,* 287(18), 2414-2423.

Ludwig, D. S., & Ebbeling, C. B. (2010). Weight-loss maintenance — Mind Over Matter? *Weight-Loss maintenance—Mind Over Matter?, 363*, 22.

Madjd, A., Taylor, M. A., Delavari, A., Malekzadeh, R., Macdonald, I. A., & Farshchi, H. R. (2016). Beneficial effect of high energy intake at lunch rather than dinner on weight loss in healthy obese women in a weight-loss program: A randomized clinical trial. *The American Journal of Clinical Nutrition,* 104(4), 982-989.

Mahan, L. K., Escott-Stump, S., & Krause, M. V. (2007). *Krause's food & Nutrition therapy* Elsevier Saunders.

Maki, D. G. (2017). HbA1c has low accuracy for preDiabetes; lifestyle programs and metformin reduce progression to T2DM. *Annals of Internal Medicine,* 166(8)

Mann, J. I. (2010). Evidence-based Nutrition: Does it differ from evidence-based medicine? *Annals of Medicine,* 42(7), 475-486.

Mann, J. I., De Leeuw, I., Hermansen, K., Karamanos, B., Karlström, B., Katsilambros, N., . . . Slama, G. (2004). Evidence-based Nutritional approaches to the treatment and prevention of Diabetes mellitus. *Nutrition, Metabolism and Cardiovascular Diseases,* 14(6), 373-394.

Mann, J. I., Flint, R., Liu, A. Y., Murphy, R., Percival, T., Taylor, R., . . . Vause, J. (2017). Clinical guidelines for weight management in New Zealand adults, ministry of health. Retrieved from https://www.health.govt.nz/publication/clinical-guidelines-weight-management-new-zealand-adults

Mann, J. I., & Te Morenga, L. (2013). Diet and Diabetes revisited, yet again. *The American Journal of Clinical Nutrition,* 97(3), 453-454.

Mann, J. (2006). Nutrition recommendations for the treatment and prevention of Type 2 Diabetes and the metabolic syndrome: An evidenced-based review. *Nutrition Reviews,* 64(9), 422-427.

Mann, J., Cummings., J., Englyst., H., Key., T., Liu., S., Riccardi., G., . . . Venn, B. (2007). FAO/WHO scientific update on carbohydrates in human Nutrition: Conclusions. *European Journal of Clinical Nutrition,* 61, S132-S137.

Mars, M., Stafleu, A., & de Graaf, C. (2012). Use of satiety peptides in assessing the satiating capacity of foods. *Physiology & Behavior,* 105(2), 483-488.

Martens, E. A., Lemmens, S. G., & Westerterp-Plantenga, M. S. (2013). Protein leverage affects energy intake of high-protein diets in humans. *The American Journal of Clinical Nutrition,* 97(1), 86-93.

Martens, E. A., & Westerterp-Plantenga, M. S. (2014). Protein diets, body weight loss and weight maintenance. *Current Opinion in Clinical Nutrition & Metabolic Care,* 17(1), 75-79.

Martin, C. K., & Gadde, K. M. (2014). Weight loss: Slow and steady does not win the race. *The Lancet Diabetes & Endocrinology,* 2(12), 927-928.

Martinez, V. V., Canete Garcia-Prieto, J., Notario-Pacheco, B., & Sanchez-Lopez, M. (2013). Successful intervention models for obesity prevention: The role of healthy life styles. *Nutricion Hospitalaria,* 28(Suppl 5), 105-113.

Matthan, N. R., Ausman, L. M., Meng, H., Tighiouart, H., & Lichtenstein, A. H. (2016). Estimating the reliability of glycemic index values and potential sources of methodological and biological variability. *The American Journal of Clinical Nutrition,* 104(4), 1004-1013.

Matthews, D., Hosker, J., Rudenski, A., Naylor, B., Treacher, D., & Turner, R. (1985). Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia,* 28(7), 412-419.

McAuley, K. A., Hopkins, C. M., Smith, K. J., McLay, R. T., Williams, S. M., Taylor, R. W., & Mann, J. I. (2005). Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women. *Diabetologia,* 48(1), 8-16.

McCaffrey, A. M., Pugh, G. F., & O'Connor, B. B. (2007). Understanding patient preference for integrative medical care: Results from patient focus groups. *Journal of General Internal Medicine, 22*(11), 1500-1505.

McCombie, L., Leslie, W., Taylor, R., Kennon, B., Sattar, N., & Lean, M. E. J. (2017). Beating Type 2 Diabetes into remission. *British Medical Journal (Clinical Research Ed.),* 358, j4030.

McGregor, R. A., & Poppitt, S. D. (2013). Milk protein for improved metabolic health: A review of the evidence. *Nutrition & Metabolism,* 10(1), 46-59.

McKeown, N. M., Meigs, J. B., Liu, S., Saltzman, E., Wilson, P. W., & Jacques, P. F. (2004). Carbohydrate Nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham offspring cohort. *Diabetes Care,* 27(2), 538-546.

McLaren, L. (2007). Socioeconomic status and obesity. *Epidemiologic Reviews,* 29, 29-48.

McLean, R. M., Hoek, J. A., Buckley, S., Croxson, B., Cumming, J., Ehau, T. H., . . . Schofield, G. (2009). "Healthy eating - healthy action": Evaluating New Zealand's obesity prevention strategy. *BMC Public Health,* 9, 452.

McLean, R. M., Williams, S., Mann, J. I., Miller, J. C., & Parnell, W. R. (2013). Blood pressure and hypertension in New Zealand: Results from the 2008/09 adult Nutrition survey. *The New Zealand Medical Journal,* 126(1372), 66-79.

McManus, K., Antinoro, L., & Sacks, F. (2001). A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. *International Journal of Obesity,* 25(10), 1503.

Meigs, J. B., Wilson, P. W., Fox, C. S., Vasan, R. S., Nathan, D. M., Sullivan, L. M., & D'agostino, R. B. (2006). Body mass index, metabolic syndrome, and risk of Type 2 Diabetes or cardiovascular disease. *The Journal of Clinical Endocrinology & Metabolism,* 91(8), 2906-2912.

Meisinger, C., Döring, A., Thorand, B., Heier, M., & Löwel, H. (2006). Body fat distribution and risk of Type 2 Diabetes in the general population: Are there differences between men and women? the

MONICA/KORA Augsburg cohort study–. *The American Journal of Clinical Nutrition,* 84(3), 483-489.

Mensink, M., Feskens, E. J., Saris, W. H., De Bruin, T. W., & Blaak, E. E. (2003). Study on Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM): Preliminary results after one year. *International Journal of Obesity,* 27(3), 377-384.

Miller, J. B., Pang, E., & Bramall, L. (1992). Rice: A high or low glycemic index food? *The American Journal of Clinical Nutrition,* 56(6), 1034-1036.

Ministry of Health. (2006). Nutrient reference values for Australia and New Zealand. Retrieved from https://www.health.govt.nz/publication/nutrient-reference-values-Australia-and-new-zealand

Ministry of Health. (2011). *A focus on Nutrition: Key findings of the 2008/09 New Zealand Adult Nutrition Survey. Wellington: Ministry of Health and University of Otago.* Retrieved from https://www.health.govt.nz/publication/focus-Nutrition-key-findings-2008-09-nz-adult-Nutrition-survey

Ministry of Health. (2012). *New Zealand primary care handbook for management of Type 2 Diabetes*.

Ministry of Health. (2013). Diabetes in New Zealand. Retrieved from https://www.health.govt.nz/our-work/diseases-and-conditions/Diabetes

Ministry of Health. (2015). Diabetes surveillance: Population-based estimates and projections for New Zealand, 2001–2011. Retrieved from https://www.health.govt.nz/publication/Diabetes-surveillance-population-based-estimates-and-projections-new-zealand-2001-2011

Ministry of Health. (2015). *Living well with Diabetes: A plan for people at high risk of or living with Diabetes 2015–2020. Wellington: Ministry of Health*.

Ministry of Health. (2016). *New Zealand health strategy: Future direction. Wellington: Ministry of Health*. Retrieved from http://www.health.govt.nz/publication/new-zealand-health-strategy-2016

Ministry of Health. (2016). Annual update of key results 2015/16: New Zealand Health Survey. Retrieved from http://www.health.govt.nz/publication/annual-update-key-results-2015-16-new-zealand-health-survey

Ministry of Health. (2018). Virtual Diabetes register (VDR) in New Zealand. Retrieved from https://www.health.govt.nz/our-work/diseases-and-conditions/diabetes/about-diabetes/virtual-diabetes-register-vdr.

Ministry of Health. 2016. New Zealand Health Strategy: Future Direction. Wellington: Ministry of Health. (2016). Retrieved from https://www.health.govt.nz/system/files/documents/publications/new-zealand-health-strategy-roadmapofactions-2016-apr16.pdf

Ministry of Social Development. (2016). The Social Report 2016. Retrieved from http://socialreport.msd.govt.nz/documents/2016/msd-the-social-report-2016.pdf

Mohanraj, R., & Sivasankar, S. (2014). Sweet potato *(ipomoea batatas* [L.] lam)-A valuable medicinal food: A review. *Journal of Medicinal Food,* 17(7), 733-741.

Møller, G., Sluik, D., Ritz, C., Mikkilä, V., Raitakari, O. T., Hutri-Kähönen, N., . . . Silvestre, M. P. (2017). A protein diet score, including plant and animal protein, investigating the association with HbA1c and eGFR—The PREVIEW project. *Nutrients,* 9(7), 763.

Moller, J. B., Pedersen, M., Tanaka, H., Ohsugi, M., Overgaard, R. V., Lynge, J., . . . Kadowaki, T. (2014). Body composition is the main determinant for the difference in Type 2 Diabetes pathophysiology between Japanese and Caucasians. *Diabetes Care,* 37(3), 796-804.

Møller., G., Rikardt Andersen., J., Ritz., C., Silvestre., M., Navas-Carretero., S. J.,Elli, Christensen, P., . . . Martinez, J. A. (2018). Higher protein intake is not associated with decreased kidney function in pre-diabetic older adults following a one-year Intervention—A PREVIEW sub-study. *Nutrients,* 10(1), 54.

Monro, J. A., & Shaw, M. (2008). Glycemic impact, glycemic glucose equivalents, glycemic index, and glycemic load: Definitions, distinctions, and implications. *The American Journal of Clinical Nutrition,* 87(1), 237S-243S.

Moore, L. L., Visioni, A. J., Wilson, P. W., D'agostino, R. B., Finkle, W. D., & Ellison, R. C. (2000). Can sustained weight loss in overweight individuals reduce the risk of Diabetes mellitus? *Epidemiology,* 11(3), 269-273.

Murphy, N., Norat, T., Ferrari, P., Jenab, M., Bueno-de-Mesquita, B., Skeie, G., . . . Tjønneland, A. (2012). Dietary fibre intake and risks of cancers of the colon and rectum in the European prospective investigation into cancer and Nutrition (EPIC). *PloS One,* 7(6), e39361.

Nathan, D. M., Davidson, M. B., DeFronzo, R. A., Heine, R. J., Henry, R. R., Pratley, R., . . . American Diabetes Association. (2007). Impaired Fasting Glucose and Impaired Glucose Tolerance: Implications for care. *Diabetes Care,* 30(3), 753-759.

Nathan, D. M., Knowler, W. C., Fowler, S. E., Hamman, R. F., Hoffman, H. J., Brenneman, A. T., . . . Venditti, E. (2013). (2013). Results from the Diabetes Prevention Program outcomes study: 1996-2013 *American Diabetes Association 74th Scientific Symposium, San Francisco, USA*.

NCD Risk Factor Collaboration. (2014). Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet,* 387, 1377-1396.

Nichols, M. S., Reynolds, R. C., Waters, E., Gill, T., King, L., Swinburn, B. A., & Allender, S. (2013). Community-based efforts to prevent obesity: Australia-wide survey of projects. *Health Promotion Journal of Australia,* 24(2), 111-117.

Nilsen, V., Bakke, P. S., & Gallefoss, F. (2011). Effects of lifestyle intervention in persons at risk for Type 2 Diabetes mellitus - results from a randomised, controlled trial. *BMC Public Health,* 11, 893.

Noakes, M. (2008). The role of protein in weight management. *Asia Pacific Journal of Clinical Nutrition,* 17(Suppl 1), 169-171.

Noakes, M., Foster, P. R., Keogh, J. B., & Clifton, P. M. (2004). Meal replacements are as effective as structured weight-loss diets for treating obesity in adults with features of metabolic syndrome. *The Journal of Nutrition,* 134(8), 1894-1899.

NZSSD, NZSSD Position Statement on the diagnosis of, and screening for Type 2 Diabetes (2011). Retrieved from http://www.nzssd.org.nz/HbA1c/1.%20NZSSD%20position%20statement%20on%20screening%20for%20type%202%20diabetes%20final%20Sept%202011.pdf

O'Brien, M. J., Moran, M. R., Tang, J. W., Vargas, M. C., Talen, M., Zimmermann, L. J., . . . Kandula, N. R. (2016). Patient perceptions about pre-diabetes and preferences for Diabetes prevention. *The Diabetes Educator,* 42(6), 667-677.

OECD Obesity Update, (2017). Organization for Economic Cooperation and Development (OECD),

Retrieved from http://www.oecd.org/health/health-systems/Obesity-Update-2017.pdf

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2013). Prevalence of obesity among adults: United States, 2011-2012. *NCHS Data Brief,* 131, 1-8.

Ohno, M., Miura, J., Arai, K., Tsukahara, S., & Ikeda, Y. (1989). The efficacy and metabolic effects of two different regimens of very low calorie diet. *International Journal of Obesity,* 13 (Suppl 2), 79-85.

Paddon-Jones, D., Westman, E., Mattes, R. D., Wolfe, R. R., Astrup, A., & Westerterp-Plantenga, M. (2008). Protein, weight management, and satiety. *The American Journal of Clinical Nutrition,* 87(5), S1558-1561.

Page, R. C., Harnden, K. E., Cook, J. T., & Turner, R. C. (1992). Can Life-styles of subjects with impaired glucose tolerance be changed? A feasibility study. *Diabetic Medicine,* 9(6), 562-566.

Palmo, A. (2013). Severe obesity: Introductory outlines and the conventional non surgical therapy. *Clinical Nutrition ESPEN,* 8(5), e216-e227.

Palou, A., & Bonet, M. L. (2013). Challenges in Obesity Research. *Nutricion Hospitalaria,* 28(Suppl 5), 144-153.

Pan, X. R., Li, G. W., Hu, Y. H., Wang, J. X., Yang, W. Y., An, Z. X., . . . Howard, B. V. (1997a). Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: The Da Qing IGT and Diabetes study. *Diabetes Care,* 20(4), 537-544.

Pan, X. R., Yang, W. Y., Li, G. W., Liu, J., & National Diabetes Prevention and Control Cooperative Group. (1997b). Prevalence of Diabetes and its risk factors in China. *Diabetes Care,* 20(11), 1664-1669.

Pan., A., & Hu, F. B. (2014). Can eating red meat increase the risk of developing Type 2 Diabetes? *Diabetes Management,* 4(1), 1-4.

Pan., A., Sun, Q., Bernstein, A. M., Schulze, M. B., Manson, J. E., Stampfer, M. J., . . . Hu, F. B. (2012). Red meat consumption and mortality: Results from 2 prospective cohort studies. *Archives of Internal Medicine,* 172(7), 555-563.

Pan., A., Sun, Q., Bernstein, A. M., Schulze, M. B., Manson, J. E., Willett, W. C., & Hu, F. B. (2011). Red meat consumption and risk of Type 2 Diabetes: 3 cohorts of US adults and an updated meta-analysis. *The American Journal of Clinical Nutrition,* 94(4), 1088-1096.

Parnell, W., Wilson, N., Thomson, C., Mackay, S., & Stefanogiannis, N. (2011). A focus on Nutrition: Key findings of the 2008/09 New Zealand Adult Nutrition Survey. *Ministry of Health: Wellington, New Zealand.*

Pawlak, D. B., Kushner, J. A., & Ludwig, D. S. (2004). Effects of dietary glycaemic index on adiposity, glucose homoeostasis, and plasma lipids in animals. *The Lancet,* 364(9436), 778-785.

Pedersen, B. K. (2009). The diseasome of physical inactivity–and the role of myokines in muscle–fat cross talk. *The Journal of Physiology,* 587(23), 5559-5568.

Penhoat, A., Mutel, E., Amigo-Correig, M., Pillot, B., Stefanutti, A., Rajas, F., & Mithieux, G. (2011). Protein-induced satiety is abolished in the absence of intestinal gluconeogenesis. *Physiology & Behavior,* 105(1), 89-93.

Penn., L., White, M., Lindstrom, J., den Boer, A. T., Blaak, E., Eriksson, J. G., . . . Tuomilehto, J. (2013). Importance of weight loss maintenance and risk prediction in the prevention of Type 2 Diabetes: Analysis of European Diabetes prevention study RCT. *PLoS One,* 8(2), e57143.

Penn., L., White., M., Oldroyd., J., Walker., M., Alberti., K. G., & Mathers., J. C. (2009). Prevention of Type 2 Diabetes in adults with impaired glucose tolerance: The European Diabetes Prevention RCT in Newcastle upon Tyne, UK. *BMC Public Health,* 9, 342.

Perez, R. C. (2013). Current mapping of obesity. *Nutricion Hospitalaria,* 28 (Suppl 5), 21-31.

Pesta, D. H., & Samuel, V. T. (2014). A high-protein diet for reducing body fat: Mechanisms and possible caveats. *Nutrition & Metabolism,* 11(1), 53.

Plant and Food Research. (2016). The concise New Zealand Food Composition Tables 12th edition 2012. Retrieved from http://www.foodcomposition.co.nz/concise-tables

Popkin, B., Monteiro, C., & Swinburn, B. (2013). Overview: Bellagio conference on program and policy options for preventing obesity in the low- and middle-income countries. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity,* 14 (Suppl 2), 1-8.

Poppitt, S. (2017). Hyperglycaemia, pre-Diabetes and diabesity: Can we choose who to 'fast-track'into Diabetes prevention?

Poppitt, S., Silvestre, M., & Liu, A. (2014). Etiology of obesity over the life span: Ecologic and genetic highlights from New Zealand cohorts. *Current Obesity Reports,* 3(1), 38-45.

Poppitt, S. D., McCormack, D., & Buffenstein, R. (1998). Short-term effects of macronutrient preloads on appetite and energy intake in lean women. *Physiology & Behavior,* 64(3), 279-285.

Poppitt, S. D., Strik, C. M., McArdle, B. H., McGill, A. T., & Hall, R. S. (2013). Evidence of enhanced serum amino acid profile but not appetite suppression by dietary glycomacropeptide (GMP): A comparison of dairy whey proteins. *Journal of the American College of Nutrition,* 32(3), 177-186.

Poppitt, S. D., Swann, D., Black, A. E., & Prentice, A. M. (1998). Assessment of selective under-reporting of food intake by both obese and non-obese women in a metabolic facility. *International*

Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity, 22(4), 303-311.

Porrini, M., Crovetti, R., Testolin, G., & Silva, S. (1995). Evaluation of satiety sensations and food intake after different preloads. *Appetite,* 25(1), 17-30.

Puhl, R. M., & Heuer, C. A. (2009). The stigma of obesity: A review and update. *Obesity,* 17(5), 941-964.

Purcell, K., Sumithran, P., Prendergast, L. A., Bouniu, C. J., Delbridge, E., & Proietto, J. (2014). The effect of rate of weight loss on long-term weight management: A randomised controlled trial. *The Lancet Diabetes & Endocrinology,* 2(12), 954-962.

Raben, A. (2002). Should obese patients be counselled to follow a low-glycaemic index diet? no. *Obesity Reviews,* 3(4), 245-256.

Raben, A., Fogelholm, M., Feskens, E., Westerterp-Plantenga, M., Schlicht, W., & Brand-Miller, J. (2013). PREVIEW: PREVention of diabetes through lifestyle Intervention and population studies in Europe and around the World: On behalf of the PREVIEW consortium. In 20th European Congress on Obesity, 6 (Suppl 1).

Raben, A., Fogelholm, M., Larsen, T., Westerterp-Plantenga, M., Macdonald, I., Christensen, P., . . . and the PREVIEW consortium. (2017). The PREVIEW intervention study - preliminary results from >2,000 subjects on body weight and risk factors for Type 2 Diabetes: IUNS 21st International Congress of Obesity (ICO)*,* Buenos Aires, Argentina. *,* 71 122.

Raben, A., Christensen, P., Brand-Miller, J., Hovi, E., Drummen, M., Simpson, L., Martinez, JA., Handijieva-Darlenska, T., Stratton, G., Lenz-Huttenen, M., Lam, T., Sundvall, J., Muirhead, R., Poppitt, S., Ritz, C., Pietilainen, K., Westernterp-Plantenga, M., Taylor, M., Carretero, SN., Handjiev, S., McNarry, M., Hansen, S., Raman, S., Brodie, S., Silvestre, M., Adam, T., Macdonald, I., San-Cristobal, R., Boyadjieva, N., Mackintosh, K., Schlicht, W., Liu, A., Larsen, TM., Fogelholm, M. PREVIEW – Lifestyle intervention for the prevention of type 2 diabetes in >2,300 high risk adults: Results from a 3-year multinational, multicentre, randomised trial comparing two diets and two exercise strategies. Presented at the EASD annual conference, Berlin, Germany, 6th October 2018 and submitted to British Medical Journal (2019); Feb/March

Ramachandran, A., Snehalatha, C., Mary, S., Mukesh, B., Bhaskar, A. D., & Vijay, V. (2006). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent Type 2 Diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia,* 49(2), 289-297.

Reeves, M. M., Healy, G. N., Owen, N., Shaw, J. E., Zimmet, P. Z., & Dunstan, D. W. (2013). Joint associations of poor diet quality and prolonged television viewing time with abnormal glucose metabolism in Australian men and women. *Preventive Medicine,* 57(5), 471-476.

Rehackova, L., Araújo-Soares, V., Adamson, A. J., Steven, S., Taylor, R., & Sniehotta, F. F. (2017). Acceptability of a very-low-energy diet in Type 2 Diabetes: Patient experiences and behaviour regulation. *Diabetic Medicine,* 34(11): 1554-1567.

Riecke, B. F., Christensen, R., Christensen, P., Leeds, A. R., Boesen, M., Lohmander, L. S., . . . Bliddal, H. (2010). Comparing two low-energy diets for the treatment of knee osteoarthritis symptoms in obese patients: A pragmatic randomized clinical trial. *Osteoarthritis and Cartilage,* 18(6), 746-754.

Rigby, N. (2013). Eating and obesity-the new world disorder. *Nutrients,* 5(10), 4206-4210.

Riissnerl, S., & Flatenz, H. (1997). VLCD versus LCD in long-term treatment of obesity. *International Journal of Obesity,* 21, 22-26.

Roberts, S., Barry, E., Craig, D., Airoldi, M., Bevan, G., & Greenhalgh, T. (2017). Preventing Type 2 Diabetes: Systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-Diabetes. *British Medical Journal (Open),* 7(11), e017184.

Rossel, G., Kriegner, A., & Zhang, D. (1999). From latin America to oceania: The historic dispersal of sweetpotato re-examined using AFLP. *CIP Program Report,* 2000, 315-321.

Rothberg, A. E., McEwen, L. N., Kraftson, A. T., Fowler, C. E., & Herman, W. H. (2014). Very-low-energy diet for Type 2 Diabetes: An underutilized therapy? *Journal of Diabetes and its Complications,* 28(4), 506-510.

Roumen, C., Corpeleijn, E., Feskens, E. J., Mensink, M., Saris, W. H., & Blaak, E. E. (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: The SLIM study. *Diabetic Medicine,* 25(5), 597-605.

Roumen, C., Feskens, E. J., Corpeleijn, E., Mensink, M., Saris, W. H., & Blaak, E. E. (2011). Predictors of lifestyle intervention outcome and dropout: The SLIM study. *European Journal of Clinical Nutrition,* 65(10), 1141-1147.

Ruan, Y., Mo, M., Joss-Moore, L., Li, Y. Y., Yang, Q. D., Shi, L., . . . Xu, W. H. (2013). Increased waist circumference and prevalence of Type 2 Diabetes and hypertension in Chinese adults: Two population-based cross-sectional surveys in Shanghai, China. *British Medical Journal (Open),* 3(10), e003408.

Rubino., F., Nathan., D. M., Eckel., R. H., Schauer, P. R., Alberti., K. G., Zimmet., P. Z., . . . Herman., W. H. (2017). Metabolic surgery in the treatment algorithm for Type 2 Diabetes: A joint statement by International Diabetes organizations. *Obesity Surgery,* 27(1), 2-21.

Rudovich, N., Bernigau, W., Pivovarova, O., Osterhoff, M., Sparwasser, A., Bergmann, A., . . . Alfredo, M. J. (2016). Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on circulating pro-neurotensin in the diet, obesity, and genes (DiOGenes) study: A randomized, controlled trial. *Endocrine Abstracts,* 41(12.3)

Rush, E. C., Goedecke, J. H., Jennings, C., Macclesfield, L., Dugas, L., Lambert, E. V., & Plank, L. D. (2007). BMI, fat and muscle differences in urban women of five ethnicities from two countries. *International Journal of Obesity,* 31(8), 1232-1239.

Rush, E. C., Freitas, I., & Plank, L. D. (2009). Body size, body composition and fat distribution: Comparative analysis of European, Maori, Pacific Island and Asian Indian adults. *British Journal of Nutrition,* 102(04), 632-641.

Rye, K. A., Bursill, C. A., Lambert, G., Tabet, F., & Barter, P. J. (2009). The metabolism and anti-atherogenic properties of HDL. *Journal of Lipid Research,* 50 Suppl, S195-200.

Saaristo, T., Peltonen, M., Lindström, J., Saarikoski, L., Sundvall, J., Eriksson, J. G., & Tuomilehto, J. (2005). Cross-sectional evaluation of the Finnish Diabetes risk score: A tool to identify undetected Type 2 Diabetes, abnormal glucose tolerance and metabolic syndrome. *Diabetes and Vascular Disease Research,* 2(2), 67-72.

Sacks, F. M., Bray, G. A., Carey, V. J., Smith, S. R., Ryan, D. H., Anton, S. D., . . . Laranjo, N. (2009). Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *New England Journal of Medicine,* 360(9), 859-873.

Saito, T., Watanabe, M., Nishida, J., Izumi, T., Omura, M., Takagi, T., . . . Nakamura, Y. (2011). Lifestyle modification and prevention of Type 2 Diabetes in overweight Japanese with impaired fasting glucose levels: A randomized controlled trial. *Archives of Internal Medicine,* 171(15), 1352-1360.

Sakane, N. (2005). Japan Diabetes Prevention Program. *Nippon Rinsho,* 63 (Suppl 2), 488-492.

Sakane, N., Sato, J., Tsushita, K., Tsujii, S., Kotani, K., Tsuzaki, K., . . . Japan Diabetes Prevention Program (JDPP) Research Group. (2011). Prevention of Type 2 Diabetes in a primary healthcare setting: Three-year results of lifestyle intervention in japanese subjects with impaired glucose tolerance. *BMC Public Health,* 11(1), 40-2458-11-40.

Salmeron., J., Ascherio., A., Rimm., E. B., Colditz., G. A., Spiegelman., D., Jenkins, D. J., . . . Willett, W. C. (1997). Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care,* 20(4), 545-550.

Saltiel, A. R., & Olefsky, J. M. (2017). Inflammatory mechanisms linking obesity and metabolic disease. *The Journal of Clinical Investigation,* 127(1), 1-4.

Samaha, F. F., Iqbal, N., Seshadri, P., Chicano, K. L., Daily, D. A., McGrory, J., . . . Stern, L. (2003). A low-carbohydrate as compared with a low-fat diet in severe obesity. *New England Journal of Medicine,* 348(21), 2074-2081.

Saris, W. H. (2001). Very-low-calorie diets and sustained weight loss. *Obesity Research,* 9(S11), 295S-301S.

Scheen, A. (2017). Aggressive weight reduction treatment in the management of Type 2 Diabetes. *Diabetes,* 110897(107387b)

Schutz, Y., Kyle, U., & Pichard, C. (2002). Fat-free mass index and fat mass index percentiles in caucAsians aged 18–98 y. *International Journal of Obesity,* 26(7), 953.

Schwingshackl, L., & Hoffmann, G. (2013). Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis. *Nutrition, Metabolism and Cardiovascular Diseases*, 23(8), 699-706.

Scottish Intercollegiate Guidelines Network. (2010). Management of obesity guidelines. Retrieved from

http://sign.ac.uk/sign-115-management-of-obesity.html

Segal, K. R., Lacayanga, I., Dunaif, A., Gutin, B., & Pi-Sunyer, F. X. (1989). Impact of body fat mass and percent fat on metabolic rate and thermogenesis in men. *The American Journal of Physiology,* 256(5 Pt 1), E573-9.

Sellahewa, L., Khan, C., Lakkunarajah, S., & Idris, I. (2017). A systematic review of evidence on the use of very low calorie diets in people with Diabetes. *Current Diabetes Reviews,* 13(1), 35-46.

Sequeira, I. R., & Poppitt, S. D. (2017). HbA1c as a marker of preDiabetes: A reliable screening tool or not. *Insights in Nutrition and Metabolism,* 1(1)

Silvestre, M. P., Poppitt, S. D., Liu, A. Y., Folgelholm, M., Freskens, E., Westerterp-Plantenga, M. S., . . . McGill, A. T. (2014). PREVIEW: PREVention of Diabetes through lifestyle intervention in Europe and around the World–Where are we now? *Obesity Research & Clinical Practice,* 8, 93-94.

Silvestre., M. P., Christensen., P., Poppitt., S. D., Liu, A. Y., Fogelholm, M., Westerterp-Plantega, M., . . . Brand Miller, J. (2017). (2017). Weight loss and its maintenance for Type 2 Diabetes prevention–the PREVIEW study. Paper presented at the *XVI Portuguese Food and Nutrition Congress,*

Silvestre., M. P., Goode., J. P., Vlaskovsky., P., McMahon., C., Tay., A., & Poppitt., S. D. (2018). The role of glucagon in weight loss-mediated metabolic improvement: A systematic review and meta-analysis. *Obesity Reviews,* 19(2), 233-253.

Singh, R. G., Yoon, H. D., Poppitt, S. D., Plank, L. D., & Petrov, M. S. (2017). Ectopic fat accumulation in the pancreas and its biomarkers: A systematic review and meta-analysis. *Diabetes/metabolism Research and Reviews,* 33(8): e2918.

Singleton, J. R., Smith, A. G., Russell, J. W., & Feldman, E. L. (2003). Microvascular complications of impaired glucose tolerance. *Diabetes,* 52(12), 2867-2873.

Sloth, B., Krog-Mikkelsen, I., Flint, A., Tetens, I., Björck, I., Vinoy, S., . . . Raben, A. (2004). No difference in body weight decrease between a low-glycemic-index and a high-glycemic-index diet but reduced LDL cholesterol after 10-wk ad libitum intake of the low-glycemic-index diet. *The American Journal of Clinical Nutrition,* 80(2), 337-347.

Smith, J., Papa, D., & Jackson, G. (2008). *Diabetes in CMDHB and Northern region: Estimation using routinely collected data* Counties Manukau District Health Board Manukau City, New Zealand.

Smith, C. F., & Wing, R. R. (2000). New directions in behavioral weight-loss programs. *Diabetes Spectrum,* 13(3), 142.

Sobal, J., & Stunkard, A. J. (1989). Socioeconomic status and obesity: A review of the literature. *Psychological Bulletin,* 105(2), 260.

Sofi, F., Macchi, C., Abbate, R., Gensini, G. F., & Casini, A. (2013). Mediterranean diet and health. *Biofactors,* 39(4), 335-342.

Sorensen, D., Jensen, S., Rigamoto, M. & Pritchard, M. (2015). Pasifika people in New Zealand - how are we doing? Retrieved from http://pasifikafutures.co.nz/wp-content/uploads/2015/06/PAF0018-Pasifika-People-in-NZ.pdf

Statistics New Zealand. (2016). Statistics New Zealand - obesity snapshots. Retrieved from http://www.stats.govt.nz/browse_for_stats/snapshots-of-nz/nz-social-indicators/Home/Health/obesity.aspx

Stegenga, H., Haines, A., Jones, K., Wilding, J., & Guideline Development Group. (2014). Identification, assessment, and management of overweight and obesity: Summary of updated NICE guidance. *British Medical Journal (Clinical Research Ed.),* 349, g6608.

Steven, S., Hollingsworth, K. G., Al-Mrabeh, A., Avery, L., Aribisala, B., Caslake, M., & Taylor, R. (2016). Very low-calorie diet and 6 months of weight stability in Type 2 Diabetes: Pathophysiological changes in responders and nonresponders. *Diabetes Care,* 39(5), 808-815.

Stevens, G. A., Singh, G. M., Lu, Y., Danaei, G., Lin, J. K., Finucane, M. M., . . . Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). (2012). National, regional, and global trends in adult overweight and obesity prevalences. *Population Health Metrics,* 10(1), 22.

Stiegler, P., & Cunliffe, A. (2006). The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. *Sports Medicine,* 36(3), 239-262.

Sundborn, G., Metcalf, P., Scragg, R., Schaaf, D., Dyall, L., Gentles, D., . . . Jackson, R. (2007). Ethnic differences in the prevalence of new and known Diabetes mellitus, impaired glucose tolerance and impaired fasting glucose. Diabetes heart and health survey (DHAH) 2002-2003, Auckland New Zealand. *The New Zealand Medical Journal (Online),* 120(1257)

Sweeting, A. N., & Caterson, I. D. (2017). Approaches to obesity management. *Internal Medicine Journal,* 47(7), 734-739.

Swinburn, B.A., Sacks, G., Vandevijvere, S., Kumanyika, S., Lobstein, T., Neal, B., . . . INFORMAS. (2013). INFORMAS (international network for food and Obesity/non-communicable diseases research, monitoring and action support): Overview and key principles. *Obesity Reviews,* 14 (Suppl 1), 1-12.

Swinburn, B.A., & Wood, A. (2013). Progress on obesity prevention over 20 years in Australia and New Zealand. *Obesity Reviews,* 14 (Suppl 2), 60-68.

Swinburn, B. A., Sacks, G., Hall, K. D., McPherson, K., Finegood, D. T., Moodie, M. L., & Gortmaker, S. L. (2011). The global obesity pandemic: Shaped by global drivers and local environments. *The Lancet,* 378(9793), 804-814.

Swinburn, B. A., Ley, S. J., Carmichael, H. E., & Plank, L. D. (1999). Body size and composition in polynesians. *International Journal of Obesity,* 23(11), 1178-1183.

Tao, L. L., Deng, Y. B., Fan, X. B., & Bao, Q. D. (2004). Effect of exercise training in patients with impaired glucose tolerance. *Zhongguo Linchuang Kangfu,* 8, 2912-2913.

Taylor, M. (2018). The globesity epidemic. *The Obesity Epidemic: Why a social justice perspective matters.* (pp. 1-20).

Taylor, R., Leslie, W. S., Barnes, A. C., Brosnahan, N., Thom, G., McCombie, L., . . . Zhyzhneuskaya, S. V. (2017). Clinical and metabolic features of the randomised controlled Diabetes remission clinical trial (DiRECT) cohort. *Diabetologia,* , 1-10.

Taylor, R. W., Brooking, L., Williams, S. M., Manning, P. J., Sutherland, W. H., Coppell, K. J., . . . Mann, J. I. (2010). Body mass index and waist circumference cutoffs to define obesity in indigenous New Zealanders. *The American Journal of Clinical Nutrition,* 92(2), 390-397.

Te Morenga, L., Mallard, S., & Mann, J. (2012). Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies. *British Medical Journal (Clinical Research Education),* 346, e7492.

Te Morenga, L., & Mann, J. (2012). The role of high-protein diets in body weight management and health. *British Journal of Nutrition,* 108 (Suppl 2), S130-138.

Te Morenga, L. A., Levers, M. T., Williams, S. M., Brown, R. C., & Mann, J. (2011). Comparison of high protein and high fiber weight-loss diets in women with risk factors for the metabolic syndrome: A randomized trial. *Nutrition Journal,* 10, 40.

Te Morenga, L. T., Williams, S., Brown, R., & Mann, J. (2010). Effect of a relatively high-protein, high-fiber diet on body composition and metabolic risk factors in overweight women. *European Journal of Clinical Nutrition,* 64(11), 1323-1331.

Teow, C. C., Truong, V., McFeeters, R. F., Thompson, R. L., Pecota, K. V., & Yencho, G. C. (2007). Antioxidant activities, phenolic and β-carotene contents of sweet potato genoTypes with varying flesh colours. *Food Chemistry,* 103(3), 829-838.

Thom, G., & Lean, M. (2017). Is there an optimal diet for weight management and metabolic health*?. Gastroenterology*, 152(7), 1739-1751.

Thomas, D., Elliott, E. J., & Baur, L. (2007). Low glycaemic index or low glycaemic load diets for overweight and obesity. *The Cochrane Library,* 3.

Thomas, J. G., Bond, D. S., Phelan, S., Hill, J. O., & Wing, R. R. (2014). Weight-loss maintenance for 10 years in the national weight control registry. *American Journal of Preventive Medicine,* 46(1), 17-23.

Thornley, S., Wright, C., Marshall, R., Jackson, G., Drury, P. L., Wells, S., . . . Jackson, R. (2011). Can the prevalence of diagnosed Diabetes be estimated from linked national health records? the validity of a method applied in New Zealand. *Journal of Primary Health Care,* 3(4), 262-268.

Threapleton, D. E., Greenwood, D. C., Evans, C. E., Cleghorn, C. L., Nykjaer, C., Woodhead, C., . . . Burley, V. J. (2013). Dietary fibre intake and risk of cardiovascular disease: Systematic review and meta-analysis. *British Medical Journal (Clinical Research Ed.),* 347, f6879.

Tipene-Leach, D. C., Coppell, K. J., Abel, S., Pahau, H. L., Ehau, T., & Mann, J. I. (2013). Ngati and healthy: Translating Diabetes prevention evidence into community action. *Ethnicity & Health,* 18(4), 402-414.

Tjonna, A. E., Lee, S. J., Rognmo, O., Stolen, T. O., Bye, A., Haram, P. M., . . . Wisloff, U. (2008). Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: A pilot study. *Circulation,* 118(4), 346-354.

Tobias, D. K., Chen, M., Manson, J. E., Ludwig, D. S., Willett, W., & Hu, F. B. (2015). Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: A systematic review and meta-analysis. *The Lancet Diabetes & Endocrinology,* 3(12), 968-979.

Tobias, M. (2011). Global control of Diabetes: Information for action. *Lancet, 378*(9785), 3-4.

Tsai, A. G., & Wadden, T. A. (2005). Systematic review: An evaluation of major commercial weight loss programs in the United States. *Annals of Internal Medicine,* 142(1), 56-66.

Tuomilehto, J., Lindström, J., Eriksson, J. G., Valle, T. T., Hämäläinen, H., Ilanne-Parikka, P., . . . Rastas, M. (2001). Prevention of Type 2 Diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine,* 344(18), 1343-1350.

Tuomilehto, J., Schwarz, P., & Lindström, J. (2011). Long-term benefits from lifestyle interventions for Type 2 Diabetes prevention time to expand the efforts. *Diabetes Care,* 34 (Suppl 2), S210-214.

Unick, J. L., Neiberg, R. H., Hogan, P. E., Cheskin, L. J., Dutton, G. R., Jeffery, R., . . . Wing, R. R. (2015). Weight change in the first 2 months of a lifestyle intervention predicts weight changes 8 years later. *Obesity,* 23(7), 1353-1356.

University of Sydney. (2017). Alphabetic table of carbohydrate foods, giving their glycæmic index and average carbohydrate concentration per 100g. Retrieved from www.glycaemicindex.com

Unwin, N., Shaw., J., Zimmet., P., & Alberti., K. G. (2002). Impaired glucose tolerance and impaired fasting glycaemia: The current status on definition and intervention. *Diabetic Medicine,* 19(9), 708-723.

Uusitupa, M. (2017). Remission of Type 2 Diabetes: Mission not impossible. *The Lancet,* 391(10120), 515-516.

Uusitupa, M. (2002). Lifestyles matter in the prevention of Type 2 Diabetes. *Diabetes Care,* 25(9), 1650-1651.

Uusitupa, M., Lindi, V., Louheranta, A., Salopuro, T., Lindström, J., & Tuomilehto, J. (2003). Long-term improvement in insulin sensitivity by changing lifestyles of people with impaired glucose tolerance: 4-year results from the Finnish Diabetes prevention study. *Diabetes,* 52(10), 2532-2538.

Van Achterberg, T., Huisman-de Waal, G. G., Ketelaar, N. A., Oostendorp, R. A., Jacobs, J. E., & Wollersheim, H. C. (2010). How to promote healthy behaviours in patients? an overview of evidence for behaviour change techniques. *Health Promotion International,* 26(2), 148-162.

Vazquez, G., Duval, S., Jacobs, D. R.,Jr, & Silventoinen, K. (2007). Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident Diabetes: A meta-analysis. *Epidemiologic Reviews,* 29, 115-128.

Vega-Lopez, S., Ausman, L. M., Griffith, J. L., & Lichtenstein, A. H. (2007). Interindividual variability and intra-individual reproducibility of glycemic index values for commercial white bread. *Diabetes Care,* 30(6), 1412-1417.

vegetables.co.nz. (2018). Kumara (sweet potato) has a long history of cultivation in New Zealand. Retrieved from http://www.vegetables.co.nz/vegetables-a-z/kumara

Veldhorst, M. A., Nieuwenhuizen, A. G., Hochstenbach-Waelen, A., vanVught, A. J., Westerterp, K. R., Engelen, M. P., . . . Westerterp-Plantenga, M. S. (2009a). Dose-dependent satiating effect of whey relative to casein or soy. *Physiology & Behavior,* 96(4-5), 675-682.

Veldhorst, M. A., Nieuwenhuizen, A. G., Hochstenbach-Waelen, A., Westerterp, K. R., Engelen, M. P., Brummer, R. M., . . . Westerterp-Plantenga, M. S. (2009b). A breakfast with alpha-lactalbumin, gelatin, orgelatin + TRP lowers energy intake at lunch compared with a breakfast with casein, soy, whey, or whey-GMP. *Clinical Nutrition,* 28(2), 147-155.

Veldhorst, M. A., Nieuwenhuizen, A. G., Hochstenbach-Waelen, A., Westerterp, K. R., Engelen, M. P., Brummer, R. M., . . . Westerterp-Plantenga, M. S. (2009c). Effects of high and normal soyprotein breakfasts on satiety and subsequent energy intake, including amino acid and 'satiety' hormone responses. *European Journal of Nutrition,* 48(2), 92-100.

Veldhorst, M. A., Westerterp, K. R., & Westerterp-Plantenga, M. S. (2012). Gluconeogenesis and protein-induced satiety. *British Journal of Nutrition,* 107(04), 595-600.

Venn, B., & Green., T. (2007). Glycemic index and glycemic load: Measurement issues and their effect on diet–disease relationships. *European Journal of Clinical Nutrition,* 61, S122-S131.

Venn, B., & Mann, J. I. (2004). Cereal grains, legumes and Diabetes. *European Journal of Clinical Nutrition,* 58(11), 1443.

Venn, B., Perry, T., Green, T. J., Skeaff, C. M., Aitken, W., Moore, N. J., . . . Williams, S. (2010). The effect of increasing consumption of pulses and wholegrains in obese people: A randomized controlled trial. *Journal of the American College of Nutrition,* 29(4), 365-372.

Venn, B., Wallace, A. J., Monro, J. A., Perry, T., Brown, R., Frampton, C., & Green, T. J. (2006). The glycemic load estimated from the glycemic index does not differ greatly from that measured using a standard curve in healthy volunteers. *The Journal of Nutrition,* 136(5), 1377-1381.

Venn, B., Williams, S., & Mann, J. I. (2010). Comparison of postprandial glycaemia in Asians and caucAsians. *Diabetic Medicine,* 27(10), 1205-1208.

Vergnaud, A. C., Norat, T., Romaguera, D., Mouw, T., May, A. M., Travier, N., . . . Peeters, P. H. (2010). Meat consumption and prospective weight change in participants of the EPIC-PANACEA study. *The American Journal of Clinical Nutrition,* 92(2), 398-407.

Veronese, N., Solmi, M., Caruso, M. G., Giannelli, G., Osella, A. R., Evangelou, E., . . . Tzoulaki, I. (2018). Dietary fiber and health outcomes: An umbrella review of systematic reviews and meta-analyses. *The American Journal of Clinical Nutrition,* 107(3), 436-444.

Wadden, T. A., Sternberg, J. A., Letizia, K. A., Stunkard, A. J., & Foster, G. D. (1989). Treatment of obesity by very low calorie diet, behavior therapy, and their combination: A five-year perspective. *International Journal of Obesity,* 13 (Suppl 2), 39-46.

Wadden, T. A., Stunkard, A. J., & Brownell, K. D. (1983). Very low calorie diets: Their efficacy, safety, and future. *Annals of Internal Medicine,* 99(5), 675-684.

Wadden, T. A., & Stunkard.A.J. (1993). The treatment of obesity: An overview. in obesity theory and therapy. (pp. 197-218)

Wang, J., Thornton, J. C., Russell, M., Burastero, S., Heymsfield, S., & Pierson Jr, R. N. (1994). Asians have lower body mass index (BMI) but higher percent body fat than do whites: Comparisons of anthropometric measurements. *The American Journal of Clinical Nutrition,* 60(1), 23-28.

Weigle, D. S., Breen, P. A., Matthys, C. C., Callahan, H. S., Meeuws, K. E., Burden, V. R., & Purnell, J. Q. (2005). A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. *The American Journal of Clinical Nutrition,* 82(1), 41-48.

Wein, P., Beischer, N., Harris, C., & Permezel, M. (1999). A trial of simple versus intensified dietary modification for prevention of progression to Diabetes mellitus in women with impaired glucose tolerance. *Australian and New Zealand Journal of Obstetrics and Gynaecology,* 39(2), 162-166.

Westerterp-Plantenga, M. S., Lejeune, M. P., Nijs, I., Van Ooijen, M., & Kovacs, E. M. (2004). High protein intake sustains weight maintenance after body weight loss in humans. *International Journal of Obesity,* 28(1), 57-64.

Westerterp-Plantenga, M. S., Lemmens, S. G., & Westerterp, K. R. (2012). Dietary protein – its role in satiety, energetics, weight loss and health. *British Journal of Nutrition,* 108 (Suppl 2), S105-112.

Westerterp-Plantenga, M. S., Nieuwenhuizen, A., Tome, D., Soenen, S., & Westerterp, K. R. (2009). Dietary protein, weight loss, and weight maintenance. *Annual Review of Nutrition,* 29, 21-41.

Whiting, D. R., Guariguata, L., Weil, C., & Shaw, J. (2011). IDF Diabetes atlas: Global estimates of the prevalence of Diabetes for 2011 and 2030. *Diabetes Research and Clinical Practice,* 94(3), 311-321.

WHO, & IDF. (2006). Definition and diagnosis of Diabetes mellitus and intermediate hyperglycaemia - report of a WHO/IDF consultation. Retrieved from http://www.who.int/Diabetes/publications/diagnosis_Diabetes2006/en/

Willett, W. C., Stampfer, M. J., Colditz, G. A., Rosner, B. A., & Speizer, F. E. (1990). Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *New England Journal of Medicine,* 323(24), 1664-1672.

Williams, S. M., Venn, B. J., Perry, T., Brown, R., Wallace, A., Mann, J. I., & Green, T. J. (2008). Another approach to estimating the reliability of glycaemic index. *British journal of nutrition*, 100(2), 364-372.

Williams, R., Wood, L., Collins, C., & Callister, R. (2015). Effectiveness of weight loss interventions–is there a difference between men and women: A systematic review. *Obesity Reviews,* 16(2), 171-186.

Williams, E. D., Magliano, D. J., Tapp, R. J., Oldenburg, B. F., & Shaw, J. E. (2013). Psychosocial stress predicts abnormal glucose metabolism: The Australian Diabetes, obesity and lifestyle (AusDiab) study. *Annals of Behavioral Medicine,* 46(1), 62-72.

Williamson, D. F., Madans, J., Anda, R. F., Kleinman, J. C., Giovino, G. A., & Byers, T. (1991). Smoking cessation and severity of weight gain in a national cohort. *New England Journal of Medicine*, *324(11), 739-745.*

Wing, R. R., Bray, G., & Bouchard, C. (2004). Behavioral approaches to the treatment of obesity. *Handbook of Obesity: Clinical Applications,* 2, 147-167.

Wing, R. R., Goldstein, M. G., Acton, K. J., Birch, L. L., Jakicic, J. M., Sallis, J. F.,Jr, . . . Surwit, R. S. (2001). Behavioral science research in Diabetes: Lifestyle changes related to obesity, eating behavior, and physical activity. *Diabetes Care,* 24(1), 117-123.

Wing, R. R., & Phelan, S. (2005). Long-term weight loss maintenance. *The American Journal of Clinical Nutrition,* 82 (Suppl 1), 222S-225S.

Wirth, A., & Steinmetz, B. (1998). Gender differences in changes in subcutaneous and Intra-abdominal fat during weight reduction: An ultrasound study. *Obesity,* 6(6), 393-399.

Wisse, B. E. (2004). The inflammatory syndrome: The role of adipose tissue cytokines in metabolic disorders linked to obesity. *Journal of the American Society of Nephrology,* 15(11), 2792-2800.

Withrow, D., & Alter, D. (2011). The economic burden of obesity worldwide: A systematic review of the direct costs of obesity. *Obesity Reviews,* 12(2), 131-141.

Wolever, T. M., Augustin, L. S., Brand-Miller, J. C., Delport, E., Livesey, G., Ludwig, D. S., & Sievenpiper, J. L. (2017). Glycemic index is as reliable as macronutrients on food labels. *The American Journal of Clinical Nutrition,* 105(3), 768-769.

Wolever, T. M., & Bhaskaran, K. (2012). Use of glycemic index to estimate mixed-meal glycemic response. *The American Journal of Clinical Nutrition,* 95(1), 256-257.

Wolever, T. M., & Bolognesi, C. (1996). Prediction of glucose and insulin responses of normal subjects after consuming mixed meals varying in energy, protein, fat, carbohydrate and glycemic index. *The Journal of Nutrition,* 126(11), 2807-2812.

Wolever, T. M. S., Vorster, H. H., Björck, I., Brand-Miller, J., Brighenti, F., Mann, J. I., . . . Perry, T. L. (2003). Determination of the glycaemic index of foods: Interlaboratory study. *European Journal of Clinical Nutrition,* 57(3), 475-482.

Wolever, T. M., & Jenkins, D. J. (1986). The use of the glycemic index in predicting the blood glucose response to mixed meals. *The American Journal of Clinical Nutrition,* 43(1), 167-172.

Wolever, T. M., Jenkins, D. J., Jenkins, A. L., & Josse, R. G. (1991). The glycemic index: Methodology and clinical implications. *The American Journal of Clinical Nutrition,* 54(5), 846-854.

Wolever, T. M., Jenkins, D. J., Kalmusky, J., Giordano, C., Giudici., S., Jenkins., A. L., . . . Josse., R. G. (1986). Glycemic response to pasta: Effect of surface area, degree of cooking, and protein enrichment. *Diabetes Care,* 9(4), 401-404.

Wolever., T. M., Nuttall., F. Q., Lee., R., Wong., G. S., Josse., R. G., Csima., A., & Jenkins., D. J. (1985). Prediction of the relative blood glucose response of mixed meals using the white bread glycemic index. *Diabetes Care,* 8(5), 418-428.

Woolfe, J. A. (1992). *Sweet potato: An untapped food resource* Cambridge University Press.

World Health Organization. (1998). Carbohydrates in human Nutrition: Report of a joint FAO/WHO expert consultation, Rome, 14-18 April 1997. *Carbohydrates in Human Nutrition: Report of a joint FAO/WHO expert consultation, Rome,* 14-18 April 1997.

World Health Organization. (2000). The Asia-Pacific perspective: Redefining obesity and its treatment.

World Health Organization. (2017). Obesity and overweight fact sheets (WHO). Retrieved from http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight

Wuhan, S. N., Westerterp, K. R., & Plasqui, G. (2010). Ethnic differences in body composition and the associated metabolic profile: A comparative study between Asians and CaucAsians. *Maturitas,* 65(4), 315-319.

Wycherley, T. P., Buckley, J. D., Noakes, M., Clifton, P. M., & Brinkworth, G. D. (2013). Comparison of the effects of weight loss from a high-protein versus standard-protein energy-restricted diet on strength and aerobic capacity in overweight and obese men. *European Journal of Nutrition,* 52(1), 317-325.

Xu, X., Yu, E., Gao, X., Song, N., Liu, L., Wei, X., . . . Fu, C. (2013). Red and processed meat intake and risk of colorectal adenomas: A meta-analysis of observational studies. *International Journal of Cancer,* 132(2), 437-448.

Xydakis, A. M., Case, C. C., Jones, P. H., Hoogeveen, R. C., Liu, M., Smith, E. O., . . . Ballantyne, C. M. (2004). Adiponectin, inflammation, and the expression of the metabolic syndrome in obese individuals: The impact of rapid weight loss through caloric restriction. *The Journal of Clinical Endocrinology & Metabolism,* 89(6), 2697-2703.

Yaggi, H. K., Araujo., A. B., & McKinlay., J. B. (2006). Sleep duration as a risk factor for the development of Type 2 Diabetes. *Diabetes Care,* 29(3), 657-661.

Yamaoka, K., & Tango, T. (2005). Efficacy of lifestyle education to prevent Type 2 Diabetes: A meta-analysis of randomized controlled trials. *Diabetes Care,* 28(11), 2780-2786.

Yen, D. E. (1961). The adaptation of kumara by the New Zealand Maori. *The Journal of the Polynesian Society*, 338-348.

Zhang, J., Shi, X. M., & Liang, X. F. (2013). Economic costs of both overweight and obesity among Chinese urban and rural residents, in 2010. *Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Zazhi,* 34(6), 598-600.

Zhang, Z., Kane., J., Liu., A. Y., & Venn., B., J. (2015). Benefits of a rice mix on glycaemic control in Asian people with Type 2 Diabetes: A randomised trial. *Nutrition & Dietetics,* 73(2), 125-131.

Zhyzhneuskaya, S. V., Al-Mrabeh, A., Peters, C., Hollingsworth, K. G., Pilkington, H., Lean, M., & Taylor, R. (2017). Liver fat content is the greatest abnormality in early Type 2 Diabetes: Baseline metabolic and imaging data from the Diabetes remission controlled trial (DiRECT). *Diabetic Medicine,* 34, 15

Zimmet, P. Z., Magliano, D. J., Herman, W. H., & Shaw, J. E. (2014). Diabetes: A 21st century challenge. *Lancet Diabetes & Endocrinology,* 2(1), 56-64.

Zimmet, P., & Baba, S. (1990). Central obesity, glucose intolerance and other cardiovascular disease risk factors: An old syndrome rediscovered. *Diabetes Research and Clinical Practice,* 10, S167-S171.

Zimmet, P. Z., & Alberti, K. G. (2016). Epidemiology of Diabetes-status of a pandemic and issues around metabolic surgery. *Diabetes Care,* 39(6), 878-883.

Zócalo, Y., Marotta, M., García-Espinosa, V., Curcio, S., Chiesa, P., Giachetto, G., & Bia, D. (2017). Children and adolescents macrovascular reactivity level and dynamics, but not the microvascular response, is associated with body mass index and arterial stiffness levels. *High Blood Pressure & Cardiovascular Prevention,* 24(4), 371-386.

Zomer, E., Gurusamy, K., Leach, R., Trimmer, C., Lobstein, T., Morris, S., . . . Finer, N. (2016). Interventions that cause weight loss and the impact on cardiovascular risk factors: A systematic review and meta-analysis. *Obesity Reviews,* 17(10), 1001-1011.