WEIGHT GAIN ASSOCIATED WITH SMOKING CESSATION: A COHORT ANALYSIS AND FEASIBILITY TRIAL FOR DIETARY MANAGEMENT

by

DEBORAH ANNE LYCETT

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Behavioural Medicine
Primary Care Clinical Sciences
School of Health and Population Studies
College of Medical and Dental Sciences
University of Birmingham
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ABSTRACT

Background

Quitting smokers gain weight, this offsets some advantages of quitting and may increase risk of type 2 diabetes above that of continuing smokers. The extent of weight gain, the associated characteristics, and management that will not hinder quit success are unclear.

Method

Examination of weight gain in an 8year prospective cohort.

Feasibility trial of smoking cessation combined with a very low calorie diet(VLCD) or individualised diet and physical activity planning(IDAP) with usual care.

Results

Abstainers gained 9kg, 7kg more than smokers over 8years. Underweight and obese smokers gained most. Less weight gain (1.7kg) was associated with higher baseline alcohol consumption (14units/week vs. none).

Recruitment from general practices was difficult and limited by VLCD contraindications. Following training, primary care nurses competently delivered specialist dietary interventions. The control condition was generally unacceptable. Half those on the VLCD were non-adherent. Mean weight change was +0.7kg(control), -1.3kg(IDAP), -7.1kg(VLCD) and +0.4kg for abstinence. We found

lower cigarette cravings in the VLCD than control arm, but no difference in IDAP and unrelated to hunger. Relapse was greatest in the VLCD and least in the control.

Conclusion

Weight gain after cessation is important and IDAP but not VLCD is a feasible approach for tackling this.

DEDICATION

To my wonderful husband Tim, I couldn't have done it without you.

Thank you for taking over all the cooking, cleaning, homemaking and kid's taxi driving for the sake of my PhD!

STATEMENT OF CONTRIBUTION

This thesis is written in the first person using the editorial 'we'. The author of the thesis contributed the following:

Chapter 1.

The author conducted this literature review in its entirety.

Chapter 2.

The author received tutoring by Paul Aveyard on regression analysis of the 'Oxford patch data'. Following this, the author carried out analysis on an updated set of these data and developed the hypothesis for the analysis, which was informed by literature review.

Chapter 3.

The feasibility trial developed from the author's idea in collaboration with Paul Aveyard and Peter Hajek. The author was principal investigator and trial coordinator. She designed the intervention, wrote the trial resources and trained the clinicians. She obtained permissions necessary to run the trial within the NHS, she acquired and set up the research sites.

Chapter 4.

The author carried out the analysis of feasibility including the qualitative interviews and analysis. Codes and themes emerging from qualitative transcripts were discussed with colleagues Nicola Lindson and Rachna Begh who are experienced in qualitative methods.

Chapter 5.

The author developed and analysed the Healthy Choice Index (HCI) and Hunger Craving Score (HCS). Paul Aveyard suggested the analyses to use.

Chapter 6.

The author carried out all the analyses contained in this chapter following discussion with Paul Aveyard regarding which methods to use.

Chapter 7.

This chapter contains the author's own interpretations and conclusions.

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To my two beautiful daughters, Abigail and Isabel, thank you for understanding when I've needed to work and making my time off such fun.

"I will give you [God] thanks, for you answered me; you have become my salvation."

Psalm 118:21

CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

BMI	Body mass index
BMR	Basal metabolic rate
BOCF	Baseline observation carried forward
CI	Confidence interval
CO	Carbon monoxide
CRF	Case report form
CRP	C-reactive protein
DeMiST	Dietary Management in Smoker's Trial
EAR	Estimated average requirement
FEV1	Forced expiratory volume in 1 second
FFM	Fat free mass
FM	Fat mass
FVC	Forced vital capacity
HCI	Healthy choice index
HCS	Hunger craving score
HDL	High density lipoprotein
HR	Horne Russell (score)
IDAP	Individualised dietary and activity plan
ITT	Intention to treat
LDL	Low density lipoprotein
MEOS	Microsomal ethanol oxidising system
MPSS	Mood and physical symptoms score
MPSS-C	Mood and physical combined symptoms score
NHS	National Health Service
NRT	Nicotine replacement therapy
NSP	Non starch polysaccharide
OR	Odds ratio
PAL	Physical activity level

RNI	Reference nutrient intake
RR	Relative risk
SBS	Step by step
SD	Standard deviation
SOP	Standard operating procedure
TBW	Total body water
TC	Total cholesterol
VLCD	Very low calorie diet
WC	waist circumference
WHR	Waist hip ratio
WIs	Work instructions

1. BACKGROUND: WHY AND HOW SHOULD WE ADDRESS THE PROBLEM OF WEIGHT GAIN ASSOCIATED WITH SMOKING CESSATION?

This thesis begins with a review of the literature on post cessation weight gain, its causes and consequences. It then presents original analysis of weight gain from a prospective eight year cohort of continuous abstainers, smokers and 'relapsers'. It describes the protocol and presents the results of a randomised controlled feasibility trial designed to test dietary interventions to prevent smoking cessation related weight gain.

1.1. **The undisputed benefits of smoking cessation**

In the year 2000, 4·83 million premature deaths worldwide were attributable to smoking. Cardiovascular disease (1·69 million deaths), chronic obstructive pulmonary disease (0·97 million deaths), and lung cancer (0·85 million deaths) were the leading causes of death from smoking (Ezzati & Lopez, 2003).

The causal relationships between smoking and numerous diseases have been established in the 2004 US Surgeon General's review (Table 1). This clearly defined criteria for causality (Table 2) and incorporated 1600 key articles. Where evidence was insufficient to infer causality three further categories were defined on the strength of evidence. These were 'suggestive but not sufficient to infer a causal

relationship', 'inadequate to infer the presence or absence of a causal relationship' and 'suggestive of no causal relationship'.

Causality is bolstered by the removal of the factor of interest resulting in reduced risk of or improvement in a disease. In 1990, the US Surgeon General reviewed a large body of observational studies and clinical trials with respect to the health benefits of stopping smoking. The conclusions were as follows:

- Smoking cessation has major benefits for men and women of all ages, with and without smoking related diseases,
- Former smokers live longer than continuing smokers, those quitting before the age of 50 have half the risk of dying in the next 15 years,
- Smoking cessation decreases the risk of lung cancer, other cancers, heart attack, stroke, chronic lung disease and low birthweight babies.

Since then, evidence of the benefits of smoking cessation has continued to mount. A 50 year prospective cohort of British male doctors showed stopping smoking at age 60, 50, 40, or 30 years resulted in a gain of approximately three, six, nine and 10 years of life expectancy respectively. Among the men born around 1920, cessation at age 50 halved the risk of premature death, and cessation at age 30 avoided almost all of it (Doll et al., 2004).

A systematic review of smoking cessation in patients with coronary heart disease showed a 36% reduction in all cause mortality (relative risk (RR) 0.64, 95% CI (0.58,

0.71)) in quitting smokers compared to continuing smokers (Critchley & Capewell, 2003). However, this review only included studies where follow-up was 2 years or more so risk during the first two years of quitting was not assessed.

The increased risk of non fatal acute myocardial infarction in current smokers compared to never smokers (odds ratio (OR) 2·95, 95% CI (2·77, 3·14)) fell to 1·87 (1·55, 2·24) within three years of quitting. An excess risk remained 20 or more years after quitting (1·22 (1·09, 1·37)). In light smokers (1-9 cigarettes/day) the risk was elevated at one to three years post quit beyond that of current smokers, but reduced after 3 years (Teo et al., 2006).

Data from national statistics and case control studies showed the risks of developing lung cancer by the age of 75 were reduced from 16% in continuing smokers to 10%, 6%, 3%, and 2% for men who stopped at ages 60, 50, 40, and 30 respectively. In women, they reduced from 10% to 5% and 2% in those who stopped at age 60 and 50 respectively (Peto et al., 2000). The risk of lung cancer in a prospective cohort of women reduced with increasing duration of abstinence (Ebbert et al., 2003). Death from lung cancer reduced in those who quit smoking (Anthonisen et al., 2005).

The impact of smoking cessation on lung function was first clearly demonstrated in an eight year prospective study of 792 working men recruited in 1961, Fletcher and Peto found that forced expiratory volume in 1 second (FEV1) gradually falls over a lifetime. In most non smokers and in many smokers, clinically significant airflow obstruction never develops. However, in those susceptible to chronic obstructive

pulmonary disease (COPD), smoking causes permanent obstructive airway changes. Fletcher and Peto found that if susceptible smokers quit smoking, although their current reduced lung function was permanent, the average rate of decline in FEV1 thereafter, reverted to follow a normal trajectory (Fletcher and Peto, 1977). More recently, a prospective cohort in those with COPD who quit 11 years previously showed FEV1 declined by 30.2ml/year in men and 21.5ml/year in women. Whereas in those who continued to smoke, FEV1 declined by 60.1ml/year and 54.2ml/year, in men and women respectively (Anthonisen et al., 2002).

Evidence sufficient to infer causality	Suggestive but not sufficient to infer a causal relationship	Inadequate to infer the presence or absence of a causal relationship	Suggestive of no causal relationship
Chronic Obstructive Pulmonary disease (COPD) Ischaemic heart disease Stroke Aortic aneurism Atherosclerosis Peptic ulcer (Helicobactor (H.) Pylori positive) Pneumonia Osteoporosis (post menopausal) Hip fracture Periodontitis Cataract Reduced fertility Premature rupture of membranes Placenta previa Placental abruption Preeclampsia Foetal growth restriction low birth weight Sudden infant death syndrome Surgical complications Cancers: – Lung – Oral cavity/pharyngeal – Laryngeal – Oesophagus – Bladder – Kidney – Stomach – Pancreas – Cervical – Endometrial – Myeloid leukaemia	Acute respiratory infections Chronic respiratory disease in offspring (maternal smoking during pregnancy) Erectile dysfunction Ectopic pregnancy Peptic ulcer complications Oral clefts Dental caries (root surface) Macular degeneration Graves disease opthalmology Low bone density in older men Cancers: – Colorectal – Liver – Non cardia gastric cancers	Asthma Glaucoma Dental caries (coronal) Peptic ulcer (H. Pylori negative) Idiopathic pulmonary fibrosis Poor sperm quality Congenital malformations Childhood growth (maternal smoking) Childhood neurocognitive development (maternal smoking) Reduced bone pre-menopausal bone density Fractures at sites other than the hip Cancers: – Ovarian	Diabetic retinopathy Cancers: – Prostate – Adult brain – Breast

Table 1. Causal relationships between smoking and disease established in 2004 by the US Surgeon General's review

Criteria for causality (USDHHR, 2004)
1. Consistency of evidence,
2. Strength of association,
3. A high degree of specificity,
4. Temporality (cause must precede effect)
5. Coherence, plausibility, and analogy such that a claim can be supported or refuted by plausible biological mechanisms,
6. A biological gradient or dose-response relationship
7. Evidence from conditions which might imitate a randomised 'natural' experiment

Table 2. Definition of causality used by US Surgeon General, 2004

1.2. **Weight gain as a consequence of smoking cessation**

The 1990 US Surgeon General's review also showed that approximately 80% of those who stop smoking will gain weight, but concluded that:

> *"The health benefits of smoking cessation far exceed any risks of the average 5-pound (2-3kg) weight gain or any adverse psychological effects that may follow quitting."*

However, while there continues to be overwhelming evidence that smoking cessation reduces morbidity and mortality despite weight gain, more recent evidence demonstrates post cessation weight gain may be considerably greater than this early estimate. This presents us with a challenge which needs addressing for several reasons which I will elucidate in detail in this chapter. Firstly, for some this weight gain presents a barrier to making a quit attempt and is a reason to relapse. Secondly, those who gain weight receive less health benefit from smoking cessation than those who do not. Thirdly, there is emerging evidence of some increased medium term health risks in those who quit compared to that those who continue to smoke. For some diseases there appears to be an adaptation period before the full benefits of cessation become apparent, when ill health and health risk may in fact increase

beyond that of continuing smokers. This may be due to weight gain. If this proves to be the case, strategies to prevent weight gain, provide treatment and reduce risk during this period of heightened susceptibility may maximise the benefits of quitting and help more smokers to quit.

The rest of this chapter discusses these issues more fully and provides the rationale for our investigations, a cohort analysis and a randomised controlled feasibility trial, during this period of doctoral study. These contribute to addressing the problem of smoking cessation related weight gain.

1.2.1. How much weight is gained?

To obtain a more recent estimate of the amount of weight typically gained on smoking cessation we searched Medline, Embase and PsycINFO from 1989 to present day for review articles. We did a title search and used the terms 'weight' AND ('smoking cessation' OR 'smoking'). We limited our search to articles in English. We excluded reviews where authors made no attempt to describe how they searched the literature or selected articles. We identified three eligible review articles and appraised them, together with the 1990 US Surgeon's General report. We used the critical appraisal skills programme (CASP) tool for systematic review articles.

We found that none of these reviews assessed the validity of included studies or addressed the heterogeneity between them adequately (Table 3). For example, in the Klesges review (Klesges et al., 1989) estimated mean weight gain was derived

from studies reporting it at anything from four days to 40 years post quit. Weight gain does not reach its full extent after four days and so this combined estimate is hard to interpret. In addition, estimates included both studies that measured abstinence by point prevalence (abstinence verified at a single point in time) and continuous abstinence (reported continuous abstinence verified at follow-up). A prospective cohort study has shown that continuously abstinent participants gained significantly more weight at one year (5.9kg compared to 3.0kg respectively) than those who were point prevalent abstinent at one year (Klesges et al. 1997). Estimates of weight gain that include variable length of abstinence and point prevalence abstinence may include those quit for too short a time to demonstrate the full extent of weight gain.

Therefore, we sought prospective cohort studies using continuous abstinence criteria to define smoking status from a common time point of abstinence. We searched the databases described above using terms: (weight gain AND smoking cessation) AND (cohort OR prospective). We also searched our own reference library that contained randomised controlled trials reporting on weight change during smoking cessation. For another project we had conducted a meta-analysis of weight gain at follow up in randomised controlled trials using continuous abstinence criteria, this showed weight gain after one year to be 4.8kg (Aubin et al. 2011, unpublished). We only found two longer term studies since the Klesges et al. review in 1989 which met these criteria. They showed four and five years post cessation weight gain to be 8.9kg (Daughten et al., 1999) and 8.1kg (O'Hara et al., 1998) respectively. A further analysis of the Lung Health Study (O'Hara et al., 1998) was done using an instrumental variable approach which takes into account unmeasured confounders between smokers and quitters,

raised this estimate to 9.7kg (Eisenberg & Quinn, 2006). Therefore, recent prospective studies over 4-5 years show a weight gain in quitters of 8-10kg, compared to 1.6kg in continuing smokers (O'Hara et al., 1998). However, these are the only long term prospective cohort studies which we found that reported weight gain in continuously abstinent smokers.

1.2.2. Does this weight gain continue indefinitely?

The Klesges review found reasonably consistent evidence from 24 out of 29 cross sectional studies that smokers weigh less than non smokers. Eight out of nine cross sectional studies showed smokers weigh less than ex-smokers. However, whether ex-smokers weigh more than non smokers is less clear (2 out of 3 cross sectional studies show that they do) (Klesges et al., 1989). Therefore, debate exists over whether weight gain in quitters is permanent or temporary. It has been hypothesised that weight gain in quitters only continues until it catches up with that of the never smoking population (this could be explained by the 'set point' theory of weight gain, which is discussed later in the section 1.3 of this chapter).

Study	Klesges et al.,1989	US Surgeon General., 1990	Froom et al.,1998	Pistelli et al, 2009
Was the question addressed?	Yes. Although the article did seek to answer several questions at once. We have taken the ones relevant to our discussion separately	Yes. Although other questions were addressed method for this question was clear	Yes. Article tried to answer several different questions	Yes. Article tried to answer several different questions
Is it likely that important relevant studies were missed?	Unclear. No method was described, although a large number of studies were identified	Unclear. Method of searching not described	Yes. Only searched medline, no attempt to obtain data from unpublished studies. Not all relevant MeSH terms were used i.e. used 'smoking' but this did not cover 'smoking cessation'	Yes. No systematic selection procedure was applied. Large, population studies or large clinical trials from United States and Europe were preferably selected.
Was inclusion criteria for studies appropriate?	Not defined	Yes. Prospective cohorts after 1970, with control of continuing smokers, at least 1 month of follow up and 10 participants. Excluded studies where weight loss interventions were used or relapsed subjects were included in analysis	Not defined	As above
Was validity of included studies addressed?	To a degree. Narrative discussion mostly as an explanation for those which did not provide consistent results. No evidence of each study being formally assessed or excluded on the basis of its validity	Not beyond inclusion/exclusion described above	No	No
Were the results homogeneous or was heterogeneity adequately addressed?	Discussed but not adequately addressed e.g. no sub-analysis	Variable length of follow up not addressed, but means adjusted for sample size	Not addressed	No. Cross sectional and longitudinal studies were considered with equal merit. Some different methodological issues were discussed
What were the results?	41 prospective studies involving 110,000 participants were included. 76% show smokers who quit gain weight. Studies ranged in follow-up from 4 days to 40 years, mean follow up 2 years 11 months. Mean weight gain 2.9kg (range 0.3kg – 8kg) 19% of these studied relied of self reported smoking status 46% were in a select sample 37% either had small samples or high attrition rates	15 prospective studies, median follow up of 2 years. Weight gain among smokers who quit was 2.1kg (range 0.7-5kg) compared to 0.4kg (range 0-1.6kg) in continuing smokers. Relative risk of weight gain 1.45, 95% CI [1.31, 1.75]. Weight gain >9kg is rare	Narrative cited nine prospective studies and concluded sustained quitters gain on average 5kg more than continuing smokers, although how this figure was reached and over what period of time this refers to is unclear.	No attempt was made to combine findings into a mean estimate of weight gain. Authors concluded "most smokers who quit experience a weight gain, particularly within one year, and it may persist up to 8 years after smoking cessation".

Table 3. Critical appraisal of systematic reviews addressing the amount of post cessation weight gain

The Froom review (Froom et al., 1998) attempted to answer this question concluding evidence was conflicting. However, the authors of this review did not appraise the validity of the studies or consider methodological differences between then. We considered the relevant studies cited in the Froom review and searched for recent ones in the databases described above. We did a keyword search, using the MeSH terms “weight AND (never-smokers OR non-smokers) AND (abstainers OR abstinence OR former OR ex-smokers OR quit*) AND (cross sectional) OR (prospective OR cohort OR longitudinal OR follow-up)”.

We found six large cross sectional studies with relevant data (Table 4). Five examined gender differences, four examined differences according to duration of abstinence and three provided combined data of their whole sample.

Two out of three of the studies reporting on combined data found BMI was similar in ex-smokers and never smokers (Klesges et al., 1991, Mizoue et al., 1998) one study found it was higher in ex-smokers than never smokers (Chen et al, 1993).

In three out of the five studies examining gender, women had a similar BMI to never-smokers, whereas men had a higher BMI (Klesges et al., 1991, Molarius et al., 1997, Travier et al, 2009). Although in one of these studies women who had been abstinent for less than one year, and only men who had been abstinent for more than

one year, had a higher BMI than never smokers. Men who had been abstinent for less than one year had a lower BMI than never smokers (Klesges et al., 1991).

One study showed that women who had been abstinent for less than 10 years had a higher BMI than never smokers, and women abstinent for more than 10 years had a lower one. The same study showed the opposite was true for men. Those abstinent for more than 10 years had a higher BMI, and those abstinent for less, had a lower BMI than never-smokers (Flegal et al., 1995).

The three studies showing a higher BMI in male ex-smokers compared to male never-smokers showed that this difference was between 0.4-0.6kg/m^2, which is clinically important (Klesges et al., 1991, Molarius et al., 1997, Travier et al, 2009).

Therefore, cross-sectional data suggests that the BMI of women who have been abstinent for a relatively long period is similar to that of never-smokers, but in short term abstainers it may be higher. Whereas men who have been abstinent for a long time have a BMI that exceeds never-smokers and those abstinent for a shorter period have a lower BMI than never-smokers.

Some of the inconsistencies in these cross sectional studies, in particular those that show BMI in abstainers does not exceed former smokers, may be due to the

inclusion of shorter periods of abstinence. Prospective studies that track change in BMI from a specific quit date may be more accurate.

We found five prospective studies, all of which gave consistent evidence that increase in weight and BMI during the first five years post cessation exceeds that of never smokers. In one study (Munafo et al., 2009) the increase in BMI after five years of abstinence was not statistically different to that of never smokers over the same period of time. However, the mean difference was 0.3kg/m^2, which is clinically relevant.

Two studies (Williamson et al., 1991, Munafo et al., 2009) reported on BMI at baseline and at the end of study. They both found that quitters at baseline had lower BMIs than never smokers, but BMIs after 13 years were not statistically significantly different but the study by Munafo, in men only, did show a clinically relevant mean difference of 0.6kg/m^2 (Table 5).

Therefore, findings from prospective studies suggest initial rapid weight gain may eventually, after a decade or more, result in a BMI which is not statistically different to never-smokers, but sufficiently different to be of clinical relevance. This is consistent with the cross-sectional evidence of long term male abstainers. Observational data, at least for men, does not substantiate the set-point hypothesis.

Cross-sectional study	Klesges et al., 1991	Chen et al., 1993	Flegal et al., 1995	Molarius et al., 1997	Mizoue et al., 1998	Travier et al, 2009
Was the study sample clearly defined?	Yes. Second National Health and Nutrition Examination Survey (NHANES II)	Yes	Yes. NHANES III	Yes. 42 populations in the WHO MONICA project	Yes	Yes. European Prospective Investigation into Cancer and Nutrition (EPIC)
Was a representative sample achieved (e.g. was the response rate sufficiently high)?	Yes. 10,778 over 18 years old nationwide	1633 white Canadian men and women	Yes n=5837	69 000 men and women between 35 and 64 years	7324 working population of men	469, 543 men and women
Was exposure (smoking status) measured accurately?	Self reported recall	Self reported recall	Self reported recall up to 10 years previously	Self reported recall	Self reported recall	Self reported recall
Was outcome measured accurately?	Measured BMI	Measured BMI	Measured BMI	Measured BMI	Measured BMI	Measured BMI
Were confounders adjusted for?	Yes	Yes	Yes	Yes	Yes	Yes
What were the results and precision of these?	BMI in never smokers men: 25.5, women: 25.8 Quit< 1 year men: 25.2, women: 26.6 Quit >1year men 25.9, women: 25.8 Never and long term quitters BMI not significantly different.	Ex smokers (>6months) weighed more than never smokers. BMI less in women with greater duration of abstinence (significant association)	BMI in never smoker men: 29.6 (0.35) women: 27.2 (0.26) Quit <10years men: 27.9 (0.27) women: 27.7 (0.48) Quit>10years men: 27.3 (0.24) women: 26.7 (0.26)	Mean difference in BMI (95% CI) between never smokers and ex-smokers men: 0.5 (0.4, 0.6) women: 0.1 (-0.1, 0.3)	BMI of former smokers and never smokers not significantly different, 2-4 year quitters higher BMI than never smokers	Mean difference in BMI (95% CI) between never smokers and ex-smokers men: 0.55 (0.44, 0.65) women: -0.02 (-0.24, 0.19)

Table 4. Critical appraisal of cross sectional studies comparing BMI in quitters with never smokers

Cohort study	Williamson et al., 1991	Froom et al., 1999	Janzon et al., 2004	Reas et al., 2009	Munafo et al., 2009
Representative sample?	Yes N=9332	Males only N=1338	Females only All participating in the case control Malmo diet and cancer study N=10902	Yes N=1300	Males only N=2512
Common starting point?	For weight but not for smoking i.e. not from a set quit date	For weight but not for smoking i.e. not from a set quit date	Yes, actively smoking or never smoker	For weight but not for smoking i.e. not from a set quit date	For weight but not for smoking i.e. not from a set quit date
Adequate follow up (mean)?	13 years	2.6 years	11 years	11 years	13 years
Objective exposure?	Self report recall	Self report recall	Self reported recall	Self reported recall	Self report recall
Objective outcome?	Measured weight	Measured weight	Measured weight	Self reported BMI	Measured weight
Adjustment for confounding?	Yes	Yes	Not adjusted for case or control	yes	Yes
Results & precision of results?	Mean difference (95%CI) between weight gain (kg) in continuing smokers and: men / women Recent quitters (<1yr): 2(0.6-3.4) / 1.1(-0.4, 2.6) Sustained quitters > 1 year: 2.8 (2, 3.6) / 3.8(2.9, 4.7) Former smokers >12 years: 1.2(0.3, 1.6) / 1.6(0.8, 2.4) Never smokers: 0.9 (0.3, 1.5) / 1.4(0.9, 1.9) Smoking cessation had raised BMI from 25.7 to 27.7 in women and from 26.5 to 27.5 in men to never smokers 28.3 (women) and 27.6 (men)	Mean (SD) increase in BMI (kg/m^2) Quit after study entry: 0.99(0.18) Quit before study entry: 0.19(0,1) Never smokers: 0.07(0.06)	Mean (SD) increase in weight (kg) Quit < 1yr: 7.3 (0.63) Quit 1-2 yrs: 8.8 (0.77) Quit 2-5yrs: 7.9 (0.61) Quit 5-10yrs: 7.7 (0.73) Quit >10yrs: 6.2 (0.72) Never smokers: 3.9(0.1)	Mean (SD) increase in BMI (kg/m^2): men / women Recent quitters (<5yr): 2.6(0.30) / 2.4(0.34) Sustained quitters > 5 year: 1.9(0.22) / 2.1(0.22) Never smokers: 1.6(0.15) / 1.8(0.15) No significant differences between long term quitters and never smokers	BMI (kg/m^2) from: Quitters / Never smokers Baseline to <4 years post quit: 25.70 (3.64) / 26.96 (3.56) > 5 years: 27.13(3.64) / 27.08(3.60) >9 years: 27.46(3.90) / 27.12(3.64) 27.61(3.64) / 26.97(2.86)
Attrition adequately addressed?	No	Yes	Yes	No	Yes

Table 5. Critical appraisal of cohort studies comparing change in weight and BMI in quitters with never smokers

1.2.3. What characteristics are associated with this weight gain?

Although it has been reported that 80% of quitters gain weight (USDHHR, 1990), this leaves a potential 20% who do not, and there is a wide variation in the amount of weight gained. Several studies that follow biochemically validated continuous abstainers identify “supergainers”, quitters who gain an excessive amount. In a meta-analysis of one year follow-up of trial data (Aubin et al., unpublished) 13% of quitters gained more than 10kg. In a four year cohort, 7% gained more than 18kg (Daughten et al., 1999) and in a 5 year cohort 4% gained in excess of 20kg (O’Hara et al., 1998).

It is important to identify characteristics that are associated with greater weight gain for a couple of reasons. Firstly, on an individual level, preparing quitting smokers with realistic expectations of weight gain may be an important element of success. We know from weight loss interventions in obese participants that many people set themselves unrealistic expectations of weight loss, become disheartened when they fail to reach their target, and so give up (Foster et al., 1997). Also, there is some evidence that those who are counselled to accept weight gain have an increased chance of stopping smoking in the medium term. Increased abstinence rates were shown at 6 months (but not at 12 months) in a randomised controlled trial comparing cognitive behavioural therapy (CBT) to accept weight gain with usual care (Perkins et al., 2001). But a later study could not replicate these findings (Levine et al., 2010).

Secondly, those who put on the most weight will have a greater increase in health risks associated with weight gain such as diabetes and cardiovascular disease than those who gain less. Therefore, although smoking cessation independently reduces these risks, they rise again, although to a lesser extent, with post cessation weight gain. Therefore, in a climate of limited NHS resources, those who gain the most weight are the ones for who weight control interventions should be targeted.

Three of the reviews described in previous sections (Klesges et al., 1989, Froom et al., 1998, Pistelli et al., 2009) also examined factors associated with greater weight gain. They included cross sectional and longitudinal studies. We chose to pull out from these the longitudinal studies which measured weight change between two time points, rather than the cross-sectional studies, which may have recalled weight inaccurately. We did not include those factors, such as physical activity and dietary intake, which change over time following a quit attempt, as they are not fixed characteristics, identifiable at the time of quitting. Combining the findings showed the most consistent evidence, found in nine of 14 studies, was that higher smoking rates were associated with greater weight gain. The association between weight gain and age, baseline BMI and gender were all inconclusive (Table 6).

As discussed previously these reviews were not exhaustive, they did not appraise the studies they included or classify them according to those which relied on point prevalence or continuous abstinence. There is need for an updated systematic review of prospective studies to examine the characteristics associated with post

cessation weight gain. Such a review would need more inclusive search criteria, considered inclusion and exclusion study criteria, critical appraisal of studies and appropriate addressing of heterogeneity than the reviews to date. There is a need for more long term prospective studies with accurate classification of abstinence to contribute to such a review.

1.2.4. Our contribution to this knowledge

In the 1990s an influential randomised controlled trial examined the effects of nicotine patch versus placebo patch as an aid to smoking cessation within 19 general practices in Oxfordshire. Participants were treated for three months, followed up at six months, one year and eight years later. At these time points smoking status was verified by expired CO concentration and salivary cotinine (ICRF GPRG, 1993, ICRF GPRG,1994, Yudkin et al., 2003). Weight was recorded at baseline and at 8 years. We used these data (which we will refer to as the 'Oxford patch data' hereafter) to investigate weight change over this time by smoking status. We investigated the associations of baseline characteristics, recorded at the time of quitting in the Oxford patch data, with weight gain over eight years. These investigations are reported in chapter two of this thesis.

Baseline Characteristics	Associations with weight gain	Number of supporting cohort studies
Age	No association/inconsistent association	4
	Negative (older gain less e.g. greater if under 55 years old)	3
Genetic disposition	Greater concordance of weight among monozygotic than dizygotic twins	1
Self-rated health	Lower weight gain in quitters with lower self-rated health	1
Alcohol	Lower weight gain among social drinkers compared to those who do not drink alcohol at baseline	1
BMI	Positive (higher weight gain in quitters with higher baseline BMI)	1
	No association	3
	Negative (lower weight gain in quitters with higher baseline BM)	2
Smoking rate	Positive (greater weight gain in those who smoke more (e.g. greater than 25 cigs/day)	9
	n-shaped association with moderate smokers gaining most weight after smoking cessation	2
	No difference in weight gain with baseline smoking rate	3
Socioeconomic status (SES)	Lower weight gain in quitters with higher SES	2
Gender	Greater weight gain in women	3
	No association	2
	Greater weight gain in men	2
Ethnicity	Greater weight gain in African-Americans than European-Americans	2

Table 6. Baseline characteristics associated with weight gain

1.3. **What causes post cessation weight gain?**

Quitting smokers are faced with a number of weight promoting challenges associated with nicotine withdrawal, that tip the energy balance equation in favour of weight gain. As we have previously discussed (section 1.2.2) whether this means that weight exceeds that which would have been reached, if quitters had not smoked, or individuals reach their 'set point' is not entirely clear. Perkins in 1993 postulated the 'set-point' hypothesis in this context whereby smoking may suppress an individuals' set point; a homeostatically regulated predetermined weight regardless of whether this weight is in the ideal BMI range or not. Although we cannot confirm or refute this with current evidence, it does not detract from the health risks that post cessation weight gain poses. These are discussed in later sections of this chapter (section 1.4).

The reviews described previously and a number of narrative reviews have discussed potential causes of post cessation weight gain. They cited research ranging from metabolic studies which measure metabolic rate in laboratory conditions to cohort studies measuring processes such as dietary change and change in physical activity levels. This has led to a variety of biologically plausible theories; each of which could be a contributing factor. However, the body of evidence shows findings that are inconsistent or samples that are too small to be conclusive. However, we have summarised the possible mechanisms below.

1.3.1. Reduced basal metabolic rate and energy expenditure during physical activity

A reduction in basal metabolic rate on smoking cessation has been seen in some but not all human laboratory studies. A pooling of these studies in the narrative review reported that metabolic rate may drop by 4% to 16% with smoking cessation, and could account for up to 40% of this weight gain (Filozof et al., 2004). From meta-analysis of weight gain in the controlled arms of smoking cessation trials (Aubin et al. 2011, unpublished) we know that there is approximately a 5kg increase in weight by one year post cessation. Therefore, if there was no other change, and quitters continued to eat and exercise at their pre-quitting level, they could expect to gain 2kg (40% of 5kg) in the first year after stopping smoking (solely as a result of a fall in metabolic rate). The fall in metabolic rate is thought to arise primarily from reduced excitation of the sympathoadrenal pathway due to withdrawal of nicotine (Perkins, 1992). Nicotine is a cholinergic agonist, which enhances the effects of acetylcholine on nicotinic receptors.

There is fairly consistent evidence from cohort studies as described in section 1.2.3 that those who smoke more cigarettes a day gain more weight on cessation (Table 6). One explanation could be that excitation of the sympathoadrenal pathway is greater in these smokers and withdrawal reduces metabolic rate further in those who smoke more. This dose response relationship may explain why different studies have shown different levels of change in metabolic rate (Perkins, 1992). However, empirical evidence refutes this. A laboratory study has shown

those who smoke less have a greater rise in energy expenditure after smoking than those who smoke more; who seem to exhibit tolerance (Arcavi et al., 1994).

Smoking also affects energy expenditure during physical activity. A laboratory study has shown that when 24 hour periods of equal physical activity and dietary intake are compared within individuals in abstinent and smoking states, total energy expenditure reduces in the abstinent state; but basal metabolic rate stays constant (Hofstetter et al., 1986). Another laboratory study showed that the energy expending effect of nicotine more than doubled during periods of physical activity than during periods of rest (Perkins et al. 1989). Therefore, energy expenditure during activity may be reduced further with nicotine withdrawal, than it is when at rest.

In summary, nicotine withdrawal may reduce basal metabolic rate, but it is unclear how this relates to smoking rate. Alternatively, energy expenditure during physical activity may be affected more than basal metabolic rate by nicotine withdrawal. The latter would suggest that those who are habitually more active would experience greater weight gain, but we are not aware of any epidemiological evidence to support this.

1.3.2. Increased fat storage

Smoking cessation may reduce fat oxidation leading to increased storage of body fat. A small study has shown that fat oxidation, measured by indirect calorimetry was positively associated with 24 hour urinary cotinine excretion in smokers

(Jensen et al., 1995). Yet another small study that measured fat oxidation (lipolysis) in adipose tissue did not find it reduced in quitting smokers. However, this study did show increased activity in the fat storage enzyme, adipose tissue lipoprotein lipase, in gluteal (but not abdominal) adipose tissue which was associated with four week post cessation weight gain (Fererra et al., 2001).

Therefore, increased storage of fat may be a factor contributed to post cessation weight gain. However, the metabolic mechanism and the adipose tissue sites involved are unclear.

1.3.3. Increased energy intake

Laboratory studies in rats have shown that nicotine suppresses food intake (Myiata et al., 2001) and hunger is well established as a withdrawal symptom from cigarette smoking (Hughes et al., 1986). Two human studies measured food intake in quitters after the first two to three months after stopping smoking and found daily energy intake increased. The mean value was shown as no more than 230kcal/day. This may account for 69% of post cessation weight gain (Stamford et al., 1986, Moffart and Owens, 1991). However, an increase in energy intake has not been found in all studies (Rodin et al., 1987).

An increase in food intake could arise from a number of mechanisms. We can group these loosely into a homeostatic response to food deprivation and a hedonic response to food reward (Saper et al., 2002, Blundell, 2006).

The first response is commonly perceived as an abdominal sensation and described as emptiness in the stomach. This occurs through feedback mechanisms acting in response to a starved state. For example, low levels of leptin (released from adipose tissue in the fed state) allow Neuropeptide Y (NPY) to bind to receptors in the hypothalamus and trigger the sensation of hunger.

There is some evidence from altered activity of NPY in rat studies to suggest that increased energy intake during nicotine withdrawal may be due to increased homeostatically regulated hunger (Li et al., 2000) but the mechanism is unclear. A few studies in humans have measured leptin levels in quitting smokers but the evidence shows no consistent decrease in leptin after cessation (Filozof et al., 2004).

There is also evidence that eating based on sensory properties may increase on cessation. A systematic review shows consistent evidence that during smoking cessation the rewarding value of food increases (Berlin, 2009). Studies in rats (Schroeder et al., 2001) and several studies in humans also suggest that both nicotine and food increase dopamine through activation of the ventral tegmental area (Volkow et al., 2008). It has been suggested that food used as a "substitutional reinforcer" for smoking may contribute to weight gain (Audrain-McGovern & Benowitz, 2011). Hedonistic eating and food craving is described in more detail in section 3.1.2. However, we are unaware of any empirical studies that have examined whether hedonistic eating increases during nicotine withdrawal and how this contributes to post cessation weight gain.

Thus, while there is consistent evidence that hunger increases during smoking cessation and increased energy consumption may account for a significant proportion of weight gain. There is no strong evidence that this is mediated by changes in neuropeptides or that hedonistic eating is responsible.

1.3.4. Decreased physical activity post cessation

A reduction in physical activity has been considered as another factor for smoking cessation related weight gain, however a review of cohort studies shows a similar number of studies report a rise in post cessation physical activity as those that report a fall (Chiolero et al., 2007). Thus, the evidence suggests that changes in physical activity after cessation are unlikely to be an important cause of post cessation weight gain.

1.4. The impact of the weight gain associated with smoking cessation

In this section we examine the impact that smoking related weight gain may have on attempts to quit smoking, relapse to smoking and the risks of chronic diseases.

1.4.1. Association of smoking related weight gain with quit attempts and relapse to smoking

Anecdotally, weight gain is a common reason reported in clinical practice for relapse to smoking. Some individuals report they cannot tolerate the weight they gain when they stop smoking and relapse to smoking in an attempt to return to

their previous weight. Others do not attempt to quit for fear that they will gain unwanted weight. However, the evidence is less clear.

1.4.1.1. *Is concern about anticipated weight gain positively associated with reduced attempts to quit?*

The UK Office of National Statistics 2008/9 report showed only 3% of smokers claim anticipated weight gain is the main reason not to quit (ONS, 2009). Given that 21% of adults in the UK smoke (ONS, 2010), this is approximately 32,000 people. Whether these claims are in fact associated with lower quit rates, in those who are weight concerned, needs to be explored independently in epidemiological studies. In our searching of the literature, described at the beginning of this chapter, we found one review (French & Jeffrey, 1995, Table 7) which addressed the influence of weight concern on attempts to quit. The authors reported that studies suggest greater smoking related weight concern was associated with fewer attempts to quit. However, this evidence came from cross-sectional studies showing higher prevalence of weight concern in current smokers than former smokers. While this might suggest that weight concern is associated with fewer quit attempts, other explanations are possible. Perhaps former smokers became less concerned about weight after they quit smoking as a response to having put weight on but were equally concerned beforehand. Without prospective evidence showing a temporal relationship we cannot suggest causality.

1.4.1.2. *Is concern about anticipated or concern about actual weight gain positively associated with relapse?*

The UK Office of National Statistics 2008/9 report showed 5% of smokers claim weight gain was the reason they relapsed in their last quit attempt; this is approximately 53,000 people. In our searching of the literature we found two reviews of studies addressing this (Klesges et al., 1989, French and Jeffery, 1995 (Table 7)). These both concluded that fear or concern about post cessation weight gain was positively associated with relapse. As described above, the cross sectional evidence for this was limited by comparing weight concern in current versus former smokers. Where relapsed smokers were compared with former smokers it was unclear whether weight concern preceded quitting or was a consequence of post quit weight gain (Table 7).

Klesges et al. reported on two prospective studies examining prequit weight concern, they found that in both of these higher weight concern prequit was associated with higher relapse rates in those enrolled in smoking cessation programmes. However, it is unclear whether these studies adjusted for the impact of actual weight gain on weight concern. Without concurrent exploration of changing attitudes to changing weight during smoking cessation we cannot make conclusions regarding the effects of weight concern on relapse.

A more recent review (2010) of prospective studies, carried out as a masters dissertation that I supervised, reported four out of nine studies showed a positive association of weight concern with relapse and five found no association.

However, the heterogeneity between these studies means these findings are hard to interpret. Four of the studies measured weight concern prequit, and two identified weight concern post quit, as a reason for relapse.

1.4.1.3. *Is actual weight gain associated with relapse back to smoking?*

Klesges et al. reviewed three prospective studies measuring actual weight gain and found a negative association between weight gain and relapse. This was determined largely by the observation that greater weight gain was seen in those achieving abstinence rather than in those that relapsed.

The masters dissertation reviewing more recent studies found two out of seven reported a negative association. Four of the seven studies reported a positive association, where greater weight gain was associated with a higher relapse rate and one reported no association. Therefore, findings are inconclusive; some of this may be accounted for by differences between the studies and sub group analysis of these is needed. For example, in two of the seven studies these data were derived from placebo controlled trials of bupropion, an effective cessation aid. Bupropion may also temporarily delay weight gain. Therefore lower relapse rates in those who gain less weight may be confounded by bupropion use.

So what can we conclude? Weight gain is not consistently associated with higher relapse rates. Where it is, it may be due to weight concern at the amount gained

or it may be due to other factors. The opposite may also be true, weight gain may be associated with lower relapse rates, this may reflect less concern about weight in those who quit or it may simply be a consequence of abstinence.

Return to smoking is often a response to cravings for cigarettes, an impulsive desire when faced with smoking cues. Whether a reasoned response dependent on weight gain can result in the same impulsive action is questionable, although it could undermine motivation to resist smoking urges. Weight gain may be an excuse given for returning to smoking or it may be an underlying factor contributing to relapse, but more research is needed before we can be certain.

Study	Klesges et al.,1989	French & Jeffrey, 1995	Masters Dissertation, 2010
Was the question addressed?	Yes. Although the article did seek to answer several questions at once. We have taken the ones relevant to our discussion separately	Yes	Yes
Is it likely that important relevant studies were missed?	Unclear. No method was described, although a large number of studies were identified	Possibly due to database search limited by search engines of the time	No, thorough search terms
Was inclusion criteria for studies appropriate?	Not defined	Yes, cross sectional	Yes, prospective only
Was validity of included studies addressed?	To a degree. Narrative discussion mostly as an explanation for those which did not provide consistent results. No evidence of each study being formally assessed or excluded on the basis of its validity	Yes	Yes
Were the results homogeneous or was heterogeneity adequately addressed?	Discussed e.g. gender difference, but not adequately addressed e.g. no sub-analysis	Unclear	Heterogeneity was discussed in the narrative but little attempt was made to unpick it e.g. results not presented according to homogenous categories.
What were the results/conclusions?	Investigations finding a positive relationship between weight gain and relapse have assessed beliefs, concerns, and fears regarding post cessation weight gain, Investigations finding a negative relationship have assessed actual weight gain. Actual weight gain may have little relationship to participants' perceptions of their weight status. High degree of concern regarding post cessation weight gain and a small weight gain after cessation may confirm the fear and prompt relapse. Conclusions predominantly based on cross-sectional studies	Weight concerns specific to smoking may have a negative influence on both cessation and relapse. General weight concerns do not appear to have this influence	Seven prospective studies on actual weight gain. Four were found to be positively associated with relapse. Two negatively associated with relapse. One found no association. The positive association in one of the studies was valid in males but not in females. These associations were weakened by differing time points for assessment of the relationship, and by varying lengths of follow up for the studies. Nine studies identified regarding weight concern. Four studies found it to be positively associated with relapse. No study was identified where weight gain concern was associated with less relapse. Five studies showed no significant association between post cessation weight gain concern and relapse to smoking. Four studies presented the relationship between weight concern and relapse as the weight gain which participants identified prequit as the amount they would tolerate before relapsing. A range of 10 – 20 pounds was found to be the tolerable weight range, with women willing to tolerate less than men, and higher weight concerns correlating with less tolerable weight gain. Two studies reported the proportion of subjects who mentioned weight gain after quitting as a reason why they would relapse to smoking. Women were more likely to relapse for this reason than men, and higher weight concerns predisposed to the naming of weight gain as a potential reason for relapse.

Table 7. Appraisal of systematic reviews that examine associations between weight concern and weight gain with quit attempts and relapse

1.4.2. Impact on risks of chronic diseases

To examine recent evidence that smoking cessation may have an adverse risk on chronic disease we searched Medline, Embase and PsycINFO from 1989 to present day for review articles. We did a title search and used the following MeSH terms 'smoking cessation' AND 'lung function OR diabetes OR metabolic OR cardiovascular OR blood pressure OR waist OR body composition'. We limited our search to articles in English. We excluded reviews where authors made no attempt to describe how they searched the literature and selected articles. Where there was no review article available we searched for observational studies.

1.4.2.1. *Changes in body composition*

Abdominal obesity is independently associated with an atherogenic profile and increased risk of type 2 diabetes (Berlin, 2008). Most studies looking at post cessation weight gain have not measured change in waist circumference, waist to hip ratio, or body fat distribution. Therefore, it is not yet clear whether the usual pattern of post cessation fat deposition is gluteal or intra-abdominal. If intra-abdominal it carries a greater health risk than gluteal fat. The Berlin review (2008) indentified one prospective study that found waist circumference increased in quitting compared to continuing smokers. This was a nine year prospective study in 16,587 men (Koh-Banerjee et al., 2003). It reported a mean 2.0cm (SD 0.3) increase in quitters and a reduction of 0.7cm (0.3) in continuing smokers. These values were after adjustment for confounders at baseline and changes in diet and physical activity levels during the study. When change in BMI was also adjusted

for, waist circumference was still shown to have increased in quitters and reduced in smokers, but by a smaller amount, 0.8(0.3) and 0.4(0.2) respectively. However this study relied on self reported recall of smoking abstinence, and the group of abstainers contained those who had been quit for variable lengths of time.

We know of one study which has measured change in waist circumference in validated quitters. Mean difference (SD) in waist circumference between quitters and continuing smokers was 3.5cm (0.5) in men and 4.5cm (0.6) in women (Pisinger et al., 2007).

One cross sectional study using computerised tomography scanning has shown ex-smokers to have higher visceral fat area (124.0–132.0 cm^2) than nonsmokers (123.1 cm^2) and current smokers (120.4 cm^2)[1].Categorising these ex-smokers by length of reported abstinence showed that recent ex-smokers had higher visceral fat area than ex-smokers of longer duration (Matsushita et al. 2011). Prospective studies, using such precise measures of visceral fat, would help to confirm whether smoking cessation leads to the accumulation of visceral fat and its associated adverse health consequences.

Given there are few studies investigating post cessation fat distribution we included measurement of waist to hip ratio and percentage body fat assessed by

[1] Visceral fat areas from a single scan obtained at the level of the umbilicus are accepted as highly correlated with the total visceral fat volume (Yoshizumi et al., 1991)

bioelectrical impedence analysis (BIA) in our feasibility trial, but due to limited resources were unable to use more advanced BIA or imaging techniques to differentiate between visceral and subcutaneous fat.

1.4.2.2. *Impact on type two diabetes mellitus*

A review article by Tonstad in 2009 cited two population studies investigating the association between smoking status and the risk of type two diabetes. However, the search terms used to identify and include or exclude studies for this review were unclear. We considered the two cited articles together with another three prospective studies identified from our own reference library to examine the relative risk of developing type two diabetes associated with smoking cessation.

All five studies showed a higher relative risk of developing type two diabetes in recent abstainers (quit for less that 5-8 years) than in continuing smokers (reference category: never smokers) (Table 8). In comparing these relative risks, the risk of type two diabetes increased by 6% to 73% in quitting compared to continuing smokers. In one of these studies this was not seen in heavy smokers (smoking 2 or more packs per day) (Will et al., 2001). Three of the five studies investigated whether weight gain mediated this association. The evidence suggested that some but not all the increased incidence of type two diabetes was mediated by weight gain. (Wannamathee et al., 2001, Davey-Smith et al., 2005, Yeh et al., 2010). The incidence of type two diabetes in long term ex-smokers was investigated in three of the five studies. The incidence of diabetes in smokers who

had been abstinent for more than five , 10 and 12 years was similar to that of never smokers in three separate proespective studies (Wannamethee et al., 2001, Will et al., 2001 and Yeh et al., 2010).

Therefore prospective studies show consistently that risk of type two diabetes is elevated in the first five years post cessation beyond that of continuing smokers, and this may be explained in part by post cessation weight gain. These findings can be further confirmed with long term prospective studies using biochemically validated abstinence. To begin to collect some data on this we measured fasting blood glucose at the start and end of our feasibility trial, where continuous abstinence was measured by expired carbon monoxide of less than 10ppm.

Cohort study	Wannamethee et al., 2001		Will et al., 2001			Davey-Smith et al., 2005		Hur et al., 2006		Yeh et al., 2010	
Representative sample?	Men N=7,124		Yes N=709,827			Men N=11,827		Men N=27,635		Yes N=10,892	
Common starting point?	Ex-smokers variable duration of abstinence at start		Ex-smokers variable duration of abstinence at start			Smoking cessation any point during follow-up		Smoking cessation any point during follow-up		Ex-smokers at baseline categorised by self report length of abstinence	
Adequate follow up (mean)?	16.8years		13years			6-7years		8years		9years	
Objective exposure?	Self reported recall of smoking status		Self reported recall of smoking status			Self reported smoking status		Self reported smoking status		Self reported smoking status	
Objective outcome?	Yes (diabetes incidence self report confirmed by medical records or death certificate)		Self report and death certificates			Measured glucose, on anti-diabetic medication		Uncontrolled DM only (fasting blood glucose >7mmol/l)		fasting blood glucose, self report of diagnosis and on anti-diabetic medication	
Adjustment for confounding?	Yes		Yes			Yes		Yes		Yes	
Results & precision of results?	Ref: never smokers	Relative risk (95% CI)	Ref: never smokers	Incidence density ratio IDR (95%CI) Men	Women		Hazard ratio (95%CI)	Ref: never smokers	Risk Ratio (95%CI)	Ref: never smokers	Hazard Ratio (95%CI)
	Smokers	1.74(1.24, 2.43)	Smoker < 1pack/d	1.05 (0.98, 1.12)	0.98(0.93, 1.03)	smokers	1.27(1.10-1.46)	Smoker < 10cig/d	1.23(1.86*, 1.77)	Smoker	1.31(1.04, 1.65)
	Ex- smokers	1.33 (0.92, 1.90)	Smoker 1-2 pack/d	1.19(1.13, 1.26)	1.21(1.14, 1.29)	Quit in intervention	1.21(0.99, 1.47)	Smoker 10-20cig/d	1.60(1.28, 2.00),	Ex-smoker	1.22(0.99, 1.51)
	<5 yr quit	1.89 (1.16, 3.06)	Smoker >2pack/d	1.45(1.34, 1.57)	1.74(1.49, 2.03)	Quit in usual care	1.35(1.06, 1.72)	Smoker >20cig/d	1.75(1.35, 2.27)	<3yr quit	1.73(1.19, 2.53)
	5-10	1.20 (0.67, 2.15)	Ex-smoker	1.07(1.02, 1.13)	1.07(0.99, 1.15)			Ex-smoker	0.95(0.72, 1.25)	<6yrs quit	1.80(1.44, 2.25)
	11-19	1.42 (0.87, 2.31)	<5yr quit	1.20(1.09, 1.32)	1.19(1.04, 1.37)			<6yr quit	1.44(0.96, 2.15)	<8yrs quit	1.54(1.10, 2.14)
	>20	0.95 (0.54, 1.67)	5-10yr quit	1.12(1.03, 1.21)	0.99(0.86, 1.13)			6-8yr quit	2.13(1.51, 3.00)	<12yrs quit	1.21(0.89, 1.65)
			>10yr quit	0.99(0.92, 1.07)	1.02(0.91, 1.15)			* CI appear to be in error		>12yrs quit	1.16(0.99, 1.36)
Was risk attenuted by post cessation weight gain?	Partially		Not investigated			Partially		Unclear		Partially	
Attrition adequately addressed?	99% follow-up achieved		Unclear			Did not compare characteristics between analysed and excluded individuals		Did not compare characteristics between analysed and excluded individuals		Did not compare characteristics between analysed and excluded individuals	

Table 8.Review of prospective cohort studies assessing relative risk of type two diabetes in quitting smokers

1.4.2.3. *Impact on lung function*

Systematic review evidence of prospective studies consistently shows that compared to continuing smokers, smoking cessation halts the accelerated decline in lung function in those susceptible to COPD (Gratziou, 2009, Willemse et al., 2004). This benefit can be seen within one year after cessation (Gratziou, 2009).

Both these reviews showed evidence that weight gain limited this benefit. One large prospective study was cited and, from our own reference library, we knew of one more that followed smokers and quitters for 5 years and investigated the association between post cessation weight gain and change in lung function. Wise et al. (1998) found that FEV1 decreased by a mean 2.2ml/year in men and 1.1ml/year in women for every 1kg/year increase in post cessation weight. Chinn et al. (2005) found it decreased by 11.5ml/kg/year in men and 3.7ml/kg/year in women. In these models weight gain and decline in lung function was averaged over the five years with no detail of the trajectory of lung function decline. We might expect lung function to decline by a greater extent initially, given that weight gain is highest during the first year post cessation (O'Hara et al. 1998). Knowing this could help with monitoring and thus more rigorous management of pulmonary disease. With a view to adding to this knowledge we measured lung function at baseline and at follow-up in our feasibility trial.

1.4.2.4. *Impact on cardiovascular risk and hypertension*

A review of studies has concluded that the reduction in cardiovascular risk in quitters to that of never smokers takes between 2 and 20 years (Bolego et al., 2002). Differences between the time it takes for this risk to reduce may be due to different baseline characteristics between the studies and it may also depend on post cessation weight gain.

A systematic review examined the association between smoking cessation and the incidence of hypertension (Gratziou, 2009). Three of four prospective studies found the incidence of hypertension was higher in quitters compared to continuing smokers (relative risk was 80-350% higher and a greater risk was seen with longer duration of abstinence). In all three studies there was evidence that the increased incidence of hypertension was mediated by weight gain. One of these studies also showed increased risk regardless of weight gain (Lee et al., 2001). Nonetheless, given that weight gain is an independent risk factor for hypertension it seems reasonable to suggest that greater reduction in cardiovascular risk, through a reduced risk of hypertension, would be seen if post cessation weight gain could be prevented. To add to this knowledge we measured changes in blood pressure in our feasibility trial.

1.5. **How can we prevent this weight gain?**

1.5.1. **Pharmacotherapies**

The most comprehensive evidence to date comes from a Cochrane review investigating interventions to prevent weight gain during smoking cessation (Parsons

et al., 2009). This found that fluoxetine, bupropion, nicotine replacement therapy (NRT), naltrexone and varenicline all had a small significant effect, and this meant between 0.4-1.3kg less weight was gained at the end of treatment compared to placebo. This is a prevention of between 14% and 46% of the mean weight gain known to occur at this time (2.8kg at three months post quit, Aubin et al., 2011). None of these pharmacotherapies had a long term effect on weight gain, by 12 months there was no significant difference in weight gain between those who had received these treatments at quitting and those who had not.

There is some evidence from observational studies that NRT use for 12 months prevents almost half the expected weight gain at 12 months (Hajek et al., 1988, Sutherland et al., 1992). One study also showed that after 10 months of gum use, a gradual reduction did not result in rebound weight gain (Hughes et al., 1991). However, evidence of increased insulin resistance in long term users of NRT (Eliasson, 1996) limits its use for this purpose.

The Cochrane review found no evidence of a dose response relationship with those allocated to higher doses of NRT not significantly less likely to gain weight. However, there is some observational evidence that people actually using more gum gain less weight. Three prospective studies were identified in the Klesges review (Klesges et al., 1989) and one more recently (Ferguson et al., 2011) showed this. However, another study showed no difference in weight gain according to the amount of gum used (Hajek et al., 1988). Therefore, although we cannot be certain, the evidence

does suggest that the amount of NRT actually used, rather than the amount people are told to use, may be important for weight control.

1.5.2. Cognitive behavioural therapy (CBT) to accept weight gain

One early trial showed a paradoxical finding. CBT to encourage people to accept weight gain was associated with 5.2kg less weight gain at one year compared to standard care (Perkins et al., 2001). However, a replication study by the same research team found no evidence that CBT to appease weight concern reduced weight gain (Levine et al., 2009). Therefore, an effect is doubtful.

1.5.3. Exercise

Results from the Cochrane review showed that exercise does not appear to help prevent weight gain during the actual period of smoking cessation, although by 12 months post quit there was less weight gain in those who had received exercise interventions than those who had not (-2.07kg (-3.78, -0.36)) (Parsons et al., 2009). The inconsistencies between these findings at these two time points create uncertainty of the effects of these exercise intervention of preventing post cessation weight gain.

1.5.4. Dietary interventions

Dietary intervention at the time of quitting holds the most promise for preventing post cessation weight gain, although it is controversial. The main reason quit attempts fail is due to quitters succumbing to their cravings to smoke. Evidence suggests that

hunger increases urges to smoke. Laboratory studies have shown that participants on a low calorie diet (700kcal/day deficit) smoked 8% more cigarettes than those on a normal-calorie diet (2000-2800kcal/day) (Cheskin et al., 2005). Smokers abstinent for 18 hours when in a fasted state were more likely to smoke sooner than those who had not fasted (Leeman et al., 2010). Observational studies have shown that people who gain most weight are more likely to succeed in quitting smoking (Hall et al., 1992) and use of glucose tablets during smoking cessation has been shown to reduce cigarette cravings (McRobbie & Hajek, 2004). All these findings suggest that avoiding hunger and feeding cigarette cravings with food may enhance smoking abstinence. Therefore current smoking cessation advice is to avoid hunger and not to diet during a quit attempt.

However the hypothesis that dieting while quitting increases hunger and thereby increases urges to smoke in the early phases of a quit attempt has not been tested in smokers who are attempting to quit. Results from a Cochrane review (Parsons et al., 2009) suggested that not all types of dietary intervention were effective and some may affect quit rates differently. The reviewers reported that general dietary education to reduce energy intake through eating a low fat, healthy diet did not prevent weight gain compared to standard smoking cessation behavioural support. Furthermore, there was a statistically significant reduction in abstinence at 12 months (Table 9). An individually tailored dietary plan to reduce energy intake; with regular monitoring and adaptation of individual goals, reduced weight gain at 6 and 12 months; without a statistically significant reduction in abstinence rates (Table 9). Intermittent use of a very low calorie diet (VLCD) provided the greatest effect on

preventing weight gain at end of treatment, but the effect was no longer statistically significant at 12 months although the mean point estimate remained clinically important. The use of the VLCD showed a statistically significant increased abstinence rate to nearly double that of controls at end of treatment and long-term follow up (Table 9).

These findings left a number of questions unanswered; firstly, although the effect of the individually tailored dietary plan to prevent post cessation weight gain looked promising, there was insufficient power to allow us to conclude it did not reduce abstinence. A larger trial to do so was required.

Secondly, although the VLCD might have a neutral effect on post cessation weight gain in the long term, it might have the benefit of improving abstinent rates. To explore whether this is a causal finding, it helps to understand plausible mechanisms by which this may occur.

Thirdly, all these previous trials were run in specialist units, where there was considerable dietary expertise, the generalisability of these findings for NHS stop smoking clinics is therefore questionable.

Therefore, we designed the Dietary Management in Smokers Trial (DeMiST) to see if it was feasible train clinicians and provide these specialist dietary interventions in

primary care. If so, this could lead to an adequately powered trial which tests their effects on abstinence, in real clinical settings.

Another main objective of DeMiST was to test the hypothesis that hunger increases urges to smoke and ketosis reduces urges to smoke. As part of this we developed and tested a tool to measure hunger and food craving. We also developed and tested a tool to help non dietary experts assess and advise on diet, this tool also aimed to measure dietary change as a process by which weight change may have occurred.

Chapter three of this thesis describes the methods of DeMiST. Chapter four discusses the measures of feasibility. Chapter five discusses the process measures developed and tested for DeMIST. Chapter six describes the effects of dietary intervention on urges to smoke and short term measures of weight and other chronic disease risk factors.

Intervention compared to standard smoking cessation	Mean difference in weight change (Kg [95%CI])		Abstinence (RR [95%CI])	
	End of treatment	At 12 months	End of treatment	At 12 months
General lifestyle and calorie reducing dietary advice	-0.04 [-0.57, 0.50]	-0.21 [-2.28, 1.86]	0.90 [0.76, 1.06]	0.66 [0.48, 0.90]
Individually tailored dietary and lifestyle advice	-1.05 [-2.01, -0.09]	-2.58 [-5.11, -0.05]	1.11 [0.84, 1.46]	0.79 [0.47, 1.33]
VLCD compared to general calorie reducing dietary advice	-3.70 [-4.82, -2.58]	-1.30 [-3.49, 0.89]	1.40 [1.07, 1.85]	1.73 [1.10, 2.73]

Table 9. Effects of dietary interventions on weight change and abstinence during smoking cessation (Adapted from Parsons et al., 2009)

1.6. Overview of thesis

1.6.1. Aims of thesis

There are three aims of this thesis:

1. To report on the associations of potential predictors at the time of quitting with post cessation related weight gain eight years later in a cohort with well defined smoking status.
2. To report on the feasibility of trialling dietary interventions to prevent weight gain within NHS stop smoking clinics.
3. To report on testing the hypothesis that hunger and ketosis affect urges to smoke in free-living quitting smokers.

1.6.2. Objectives of thesis

These aims are met through achieving the objectives described below. Chapter numbers are given in brackets beside each objective showing where in the thesis these objectives were met.

1. To summarise and appraise literature to date on the potential predictors of post cessation weight gain (Chapter 1).
2. To discuss the methodology and results of examining potential predictors of post cessation related weight gain within the Oxford patch data (Chapter 2).
3. To discuss the design of a randomised controlled trial (DeMiST) to investigate the feasibility of dietary interventions to prevent weight gain within NHS stop smoking clinics and examine the effects of these dietary interventions on urges to smoke (Chapter 3).

4. To report on the feasibility of running DeMiST, including discussion of recruitment rates and experiences of the participants (Chapter 4).
5. To report on the development and validity of a dietary assessment tool for use within DeMiST consultations (Chapter 5).
6. To report on the development of a questionnaire to measure both hunger and food craving during quitting smoking (Chapter 5).
7. To report on the effects of the dietary interventions on urges to smoke and whether this is a result of change in desire for food or ketosis (Chapter 6).
8. To report on the effects of dietary interventions on body weight and chronic disease risk factors in quitting smokers (Chapter 6).
9. To discuss the implications of findings from this doctoral research to advance understanding in this field and lead to improved clinical practice.

2. ASSOCIATIONS BETWEEN POTENTIAL PREDICTORS OF WEIGHT CHANGE OVER EIGHT YEARS IN A COHORT OF CONTINUING AND QUITTING SMOKERS

This chapter fulfils the aim of the thesis to report on weight change over eight years according to clearly defined groups of quitting and continuing smokers. It reports on associations of potential predictors of such weight change, namely baseline BMI, baseline alcohol consumption, patch or placebo use at the time of quitting, smoking rate, age, gender and socioeconomic status.

The investigation of baseline BMI was published in Addiction in January 2011 (Lycett et al., 2011, Appendix 1). An early version of the abstract was presented at the 2009 Society for Social Medicine Annual Conference and published in the Journal of Epidemiology and Community Health (Lycett et al., 2009, Appendix 2). The abstract was also presented at the 2010 Annual Society of Nicotine and Tobacco Research.

The investigation of baseline alcohol consumption was published in Nicotine and Tobacco Research (Lycett et al., 2011b, Appendix 3).

The investigation of placebo or patch treatment during quitting was published as an e-letter in the BMJ (Appendix 4). This was in response to Yudkin et al., 2003 who reported the odds of continuous abstinence at 8 years increase by 39% in those who used nicotine patch over placebo.

2.1. Introduction

As discussed in section 1.2.3, there are few studies providing long-term follow up of smokers and quitters to examine changes in body weight. Most are population-based studies, where smoking status is typically characterised as point prevalence abstinence and where the date of quitting is uncertain, usually lying between follow up occasions (Klesges et al., 1989). Using point prevalence abstinence underestimates weight gain (Kesges et al., 1997). The first aim of this study was to examine weight gain over eight years in a group with well-characterised smoking status.

2.1.1. Associations of weight gain over eight years with baseline body mass index (BMI)

Reviews of studies that have explored the characteristics associated with greater weight gain have found conflicting findings regarding the association between body mass index (BMI) at the time of quitting and weight gain (Klesges et al., 1989, Froom et al., 1998). One study showed higher baseline BMI was positively associated with subsequent weight gain. Three showed higher BMI was negatively associated with weight gain, and four found no association. No study looked for a curvilinear relationship of BMI and post cessation weight gain. The second aim was therefore to examine more fully the relationship of baseline BMI to change in weight in those who quit or continued to smoke.

2.1.2. Associations of weight gain over eight years with baseline alcohol consumption

Avoidance of alcohol is often advocated in smoking cessation support to reduce cues to smoking. People trying to lose weight are often advised to moderate or avoid alcohol because alcohol has a combustible energy value of 7kcal/g. (Fat contains 9kcal/g and carbohydrate contains 4kcal/g). However, there is contrary evidence on the effect of alcohol on weight gain in general, and very few investigations have examined its association with post cessation weight gain.

Laboratory studies of the metabolic effects of alcohol show three important effects on energy balance. First, alcohol increases energy intake (Tremblay et al., 1995, Westerterp-Plantenga & Verwegen, 1999, Buemann, 2002), particularly when consumed in combination with fat (Tremblay & St-Pierre, 1996) and the extra energy from alcohol is not compensated for by reducing subsequent food intake (Tremblay et al.,1995, Tremblay & St-Pierre, 1996, De Catro & Orozco, 1990, Yeomans, 2004). Second, alcohol suppresses fat oxidation, which increases fat storage (Suter et al., 1992). Third, alcohol increases 24 hour energy expenditure through inducing thermogenesis by up to 30%. Dietary induced thermogenesis from alcohol is greater than that from carbohydrate, fat, or protein (Suter et al., 1994, Raben et al., 2003, Schutz, 2000, Westerterp, 2004). The first two effects point towards alcohol promoting weight gain and the last effect works against it. So what causes the balance to tip one way or the other?

The answer may depend on the pathway by which alcohol is metabolised. The alcohol dehydrogenase (ADH) pathway produces adenosine triphosphate (ATP) more efficiently than the microsomal ethanol oxidising system (MEOS). It is thought that low levels of alcohol are metabolised by ADH, whereas a high blood concentration of alcohol induces MEOS; and it is this that accounts for a higher energy expenditure seen in people with alcohol dependence (Suter, 2005, Levine et al., 2000). The threshold level of alcohol for MEOS induction is unknown, but individual variation of body weight, smoking status, gender, and genetic variation in enzymes metabolising alcohol may explain the different effects of alcohol on body weight (Suter, 2005).

Cross sectional studies have shown inconsistent results, although this has been explained in part by gender effects, smoking status and drinking patterns. Lower alcohol intake has been associated with greater BMI in women, but less so, or with the opposite effect, in men (Hellerstedt et al., 1990, Golditz et al., 1991, Breslow & Smothers, 2005). This effect in men is not consistently seen among male smokers (Mannisto et al., 1996, Cooke & Frost, 1982). More frequent drinking has been associated with lower BMI independent of total alcohol consumption (Tolstrup et al. 2005, Mannisto et al., 1996, Tolstrup et al., 2008).

Prospective studies have demonstrated increasing alcohol consumption over time is not associated with an increase in waist circumference (Tolstrup et al., 2008), but it is associated with weight gain (Gordon & Kannel, 1983), particularly in men

(Gordon et al., 1986, Wannamethee & Shaper, 2003). These studies have not investigated effect modification by smoking status. Prospective studies in women have found a U shaped curve (Wannamethee et al., 2004) and a significant inverse relationship on weight gain which was not modified by smoking status (Wang et al., 2010).

In the few short-term randomised trials, alcohol consumption did not influence weight in obese people (Beulens, et al., 2006), but alcohol reduced weight in lean people (Clevidence, et al., 1984).

Three prospective studies have considered the effects of alcohol on body weight around the time of quitting smoking; these have all found an inverse effect of alcohol consumption and weight gain (Froom et al., 1999; Kawachi et al., 1996; Nides et al., 1994). However, these studies did not fully explore the association according to smoking status. The weight gain trajectory in quitting and continuing smokers is very different; the third aim of this study was to investigate the effect of alcohol consumption on post cessation weight gain in both continuously abstinent quitters and continuing smokers.

2.1.3. Associations of weight change over eight years with patch or placebo use during quitting.

The fourth aim of this study was to examine the association of weight change with patch or placebo use at the time of quitting. A Cochrane review (Parsons et al., 2009) showed nicotine replacement therapy (NRT), compared to placebo, significantly reduced weight gain at the end of treatment by a mean difference (95% confidence interval) of 0.46kg (-0.66, -0.27), and the point estimate for the effect size was similar at the end of one year: 0.44kg (-1.02, 0.14). However, this Cochrane review included no studies that reported weight gain more than one year from commencement of a quit attempt. We have used our data to examine, for the first time, the association of patch versus placebo use at the time of quitting with very long term (over eight years) post cessation weight gain.

2.1.4. Associations of weight change over eight years with age, gender, smoking rate and socioeconomic status at baseline

The final aim of this study was to examine the associations of age, gender, smoking rate and socioeconomic status (SES) with weight gain in quitters. Evidence so far from prospective studies for this is inconsistent and we sought to add to this with the results of our analysis.

2.1.4.1. *Age*

As discussed in section 1.2.3 the association between younger age and greater post cessation weight gain has previously been shown in three out of seven prospective studies, with four showing no association.

2.1.4.2. *Gender*

Three out of seven prospective studies have shown a greater weight gain in women than men. Two studies have shown no association and two studies have shown a greater weight gain in men than women (section 1.2.3).

2.1.4.3. *Smoking rate*

The most consistent finding in the literature so far has been that lower smoking rate is associated with less weight gain after stopping smoking. Nine out of 14 prospective studies found a positive association and two studies found a U-shaped curve (section 1.2.3).

2.1.4.4. *Socioeconomic status*

So far, two prospective studies have found greater weight gain in those with a lower socioeconomic status (section 1.2.3).

2.2. **Methods**

2.2.1. Participants

1686 participants, aged between 25 and 65 years, smoking 15 or more cigarettes a day enrolled in a clinical trial of a 21mg nicotine patch or placebo in 19 general practices in Oxfordshire, UK, between June 1991 and March 1992. They were invited to take part in a stop smoking study through a letter from their general practitioner (GP). They made an appointment with a nurse, who told them what

the study involved. Then they saw their GP one week later, this was when they were recruited, they were expected to quit completely from this day and given nicotine patches (ICRFGPRG, 1993). The patch was used for three months then stopped and participants were reviewed at four, eight and 12 weeks. Participants were followed up six and 12 months later (ICRFGPRG, 1993). Abstinence was confirmed by expired CO<10ppm when participants were using the nicotine patch and by salivary cotinine <20ng/ml after they had stopped using the patch. Cotinine is considered a more reliable measure of abstinence but, as it is a metabolite of nicotine, it cannot confirm abstinence during nicotine replacement therapy. An unplanned follow up took place eight years later, 1625 participants were living, we were able to trace and contact 1532 participants, 840 of these responded. Previous examination of this data showed baseline body mass index (BMI) was similar between responders and non-responders. However, responders were older (43.0 vs. 41.5 years p=0.010), more likely to be female (59% v 52% p<0.005) and have stopped smoking during the trial than non-responders (13% v 6% p<0.0001 quit for 1 year) (Yudkin et al., 2003). Ethical approval for this was granted by Anglia and Oxford Multicentre Research Ethics Committee, and 86 local research ethics committees (Yudkin et al., 2003).

2.2.2. Measures of height and weight

Height and weight were measured at trial entry, although this was self-reported in 19% of participants. At eight year follow up, weight was self-reported on a questionnaire completed by post.

2.2.3. Characterisation of smoking status

Participants completed questionnaires on smoking history and quit attempts that spanned the last eight years and smoking status was biochemically confirmed at each follow-up visit.

2.2.3.1. *Quitters*

Those who stopped smoking on or around quit day and declared continuous total abstinence from three months to one year and were still abstinent eight years later were defined as quitters. Abstinence was confirmed by salivary cotinine concentration at three and six months, one and eight years.

2.2.3.2. *Smokers*

Those who were smoking at three months, six months, one year and eight years were defined as smokers. People not attending follow up in the first year were also classed as smokers.

2.2.3.3. *Relapsers*

Relapsers were those who were biochemically confirmed abstinent at three months, six months and one year but relapsed by eight years.

2.2.3.4. *Late quitters*

Late quitters were those who smoked during the first year but were confirmed abstinent at eight years.

2.2.4. Measure of alcohol intake

Baseline data on weekly units of alcohol was collected by a trained nurse interviewer. Alcohol consumption was assessed by asking participants to report daily consumption of beer, lager or cider (pints), wine (glasses), sherry, vermouth or port (glasses), and spirits or liqueurs (single tots). Total weekly consumption was then converted to UK units (equivalent to 8g ethanol) per week.

2.2.5. Baseline characteristics

Baseline questionnaires included questions on age, gender, ethnicity, socioeconomic status, number of cigarettes smoked per day and the Horne Russell score as a measure of smoking addiction.

2.3. Statistical Methods

2.3.1. Weight change according to smoking status

All statistical tests were carried out using Statistical Package for Social Sciences version 15 for windows software (SPSS 15.0). The characteristics of each of the four groups defined by smoking status were summarised with means and SDs or proportions. Chi squared tests and one-way ANOVA with Games-Howell post hoc testing were used to identify differences between the groups. Differences were taken into account in multivariate regression analysis (see below). Means, SDs and 95% confidence intervals (95% CI), were calculated for weight change within

each smoking status. We compared self reported weight and BMI data with measured weight and BMI data.

We calculated the percentage of quitters that gained more weight than the average continuing smoker. We compared the proportion of smokers that were in each of the groups defined by the World Health Organisation (WHO) categories of BMI (underweight <18.5kg/m^2, ideal 18.5 to 24.9, overweight 25 to 29.9, and obese 30kg/$m^2$and above (WHO, 2000) at baseline and at eight years using Mann-Whitney-U tests.

Linear regression analysis was used to investigate the differences in weight change (from baseline to eight year follow-up) according to the four groups defined by smoking status. This was adjusted for potential confounders using multiple linear regression. Potential confounders were identified from the reviews on predictors of post cessation weight gain weight gain. These have been discussed in section 1.2.3. Categorical variables (treatment allocation, gender, ethnic group (white European/non-white European), and socio-economic status measured by the Registrar General's classification of occupational status (Drudy, 1991) were recoded into dummy variables. Continuous variables (BMI, height, age, number cigarettes/day, smoking dependence measured by the Horn Russell (HR) score (Russell et al., 1974) and weekly units of alcohol consumed at baseline (1 unit defined as 8g of ethanol) were centred around the mean. These were entered stepwise (to avoid overfitting the model) and considered potentially

important if the association between them and the outcome had a p value of <0.2 (Rothman & Greenland, 1998).

2.3.2. Association with baseline BMI

To investigate whether the effect of BMI depended upon smoking status linear regression was carried out in the combined sample of smokers and quitters. This analysis was conducted on smokers and quitters only for simplicity (excluding late quitters and relapsers). Terms indicating smoking status, baseline BMI in kg/m^2 and a multiplicative interaction term between the two were included. Potential confounders were added as above.

There was evidence that the association of BMI with weight change was dependent on smoking status and so separate models for quitters and smokers examined these relationships further. In both models, we looked for curvilinear relations between BMI and weight change by sequentially adding linear, quadratic, and cubic terms for BMI. Ninety five percent prediction intervals were calculated from the best fitting models to estimate the likely weight gain of most quitters or smokers. In sensitivity analysis, the analysis was repeated including relapsed smokers within the smokers group and late quitters within the quitters group. Outliers defined by extreme baseline BMI and extreme weight change were removed and the models re-run to examine whether the coefficients changed.

2.3.3. Association with baseline alcohol intake

To investigate the effect of baseline alcohol intake on weight change linear regression analysis was used first with the combined cohort of smokers and quitters. We used higher order terms to investigate curvilinear relationships. We investigated effect modification by gender, baseline BMI and smoking status using these terms and the appropriate multiplicative interaction terms. As smoking status modified the effect of alcohol on weight change, separate regression equations were used for smokers and quitters. In both sets of equations confounding was controlled as described above. We used Cook's distance as a measure of influential cases; if Cook's distance exceeded one we considered that outliers had the potential to influence our findings.

2.3.4. Associations of weight change over eight years with patch or placebo use during quitting; age, gender, smoking rate and socioeconomic status at baseline

We calculated mean difference in weight change (kg) and 95% confidence intervals (CI) between quitters who had received nicotine patch and those who had received placebo.

We carried out a regression analysis of weight change over eight years in quitters. We forced age, gender, heaviness of smoking (measured here in cigarettes per day and as a measure of addiction using the Horne Russell score) and socioeconomic status, along with treatment group, alcohol consumption and

baseline BMI into a multivariable model. We did not use a stepwise analysis here as we were interested in the size of the coefficients of all these variables, regardless of their statistical significance. We did not include ethnicity as there was no ethnic variation within our quitters. We included a quadratic term for cigarettes per day and Horn Russell score, given that some studies have previously demonstrated a U-shaped association with smoking rate and weight gain (see section 1.2.3).

2.4. Results

2.4.1. Baseline characteristics

Baseline characteristics of the smoking status groups differed modestly and significantly in age, treatment allocation, and Horn Russell Score ($p<0.05$) (Table 10). Baseline weight data did not differ much or significantly between those whose weight was measured and those who self-reported. A t-test showed a mean difference of -0.58kg (-2.91, 1.75).

Variable	smokers	quitters	relapsed	Late quitter
N*	613	85	26	116
SES (%)				
I (professional)	3	1	0	4
II (managerial/technical)	31	33	54	34
III (skilled, non-manual)	22	17	19	27
III (skilled, manual)	21	27	15	15
IV (partially skilled)	17	16	8	16
V (unskilled)	6	5	4	5
Horn Russell score [#$](mean(SD))	15 (5)	14 (4)	16 (3)	14 (4)
Cigs per day	24 (7)	23 (7)	27 (12)	23 (7)
Weekly units alcohol	10.1 (13.0)	9.2 (9.6)	13.6 (19.9)	11.8 (11.6)
Height (cm)	168 (9)	169 (9)	171 (9)	168 (9)
Age[#&](mean(SD))	42 (10)	46 (11)	43 (11)	43 (11)
BMI (mean(SD))	25 (4)	24 (4)	25 (4)	26 (5)
Ethnicity (%):				
White	98.2	100	100	100
Asian	1.0	0	0	0
South East Asian	0	0	0	0
Afro-caribbean	0	0	0	0
Other	0.7	0	0	0
Not stated	0.2	0	0	0
Active patch treatment (%)[#]	49	58	65	41
Women (%)	59	59	50	60

*data was not available in all categories for every person. #ANOVA/Chi $p<0.05$ $Post hoc analysis: smokers v quitters p=0.089, relapsed v quitters p=0.067, smokers v late quitters p=0.093. &Post hoc analysis: smokers v quitters p=0.057

Table 10. Baseline characteristics by smoking status

2.4.2. Weight change over eight years

Weight change in those who self reported at both points in time did not differ significantly from those who were measured at baseline and self reported at 8 years. The mean difference (95% confidence interval) was -0.40kg (-1.67, 0.87). There was no significant difference between measured or self-reported baseline BMI. The mean difference was 0.47kg/m^2 (-0.15, 1.09). Eighty three percent of quitters gained more weight than the average smoker (Figure 1). Over the eight years, 15% of quitters became obese compared to 2% of smokers, while 18% of quitters became overweight compared to 5% of smokers (Figure 2).

2.4.3. Mean weight and BMI change according to smoking status

Quitters gained 8.79kg (SD 6.36) and BMI increased by 3.26kg/m^2 (SD 2.94). This was 6.55kg more than smokers; who gained on average 2.24kg (SD 6.65) in weight and a 0.94kg/m^2 (SD 2.92) in BMI. Late quitters, who were not continuously abstinent during the first year but quit before eight years had a mean weight gain of 8.33kg (SD 8.84), and this was not significantly different to those who had been quit from the end of treatment. Those who had quit smoking for the whole of the first year and subsequently relapsed gained a mean of 3.28kg (SD 7.16); this was not significantly different to smokers. Adjustment for potential confounders did not change these estimates (Table 11).

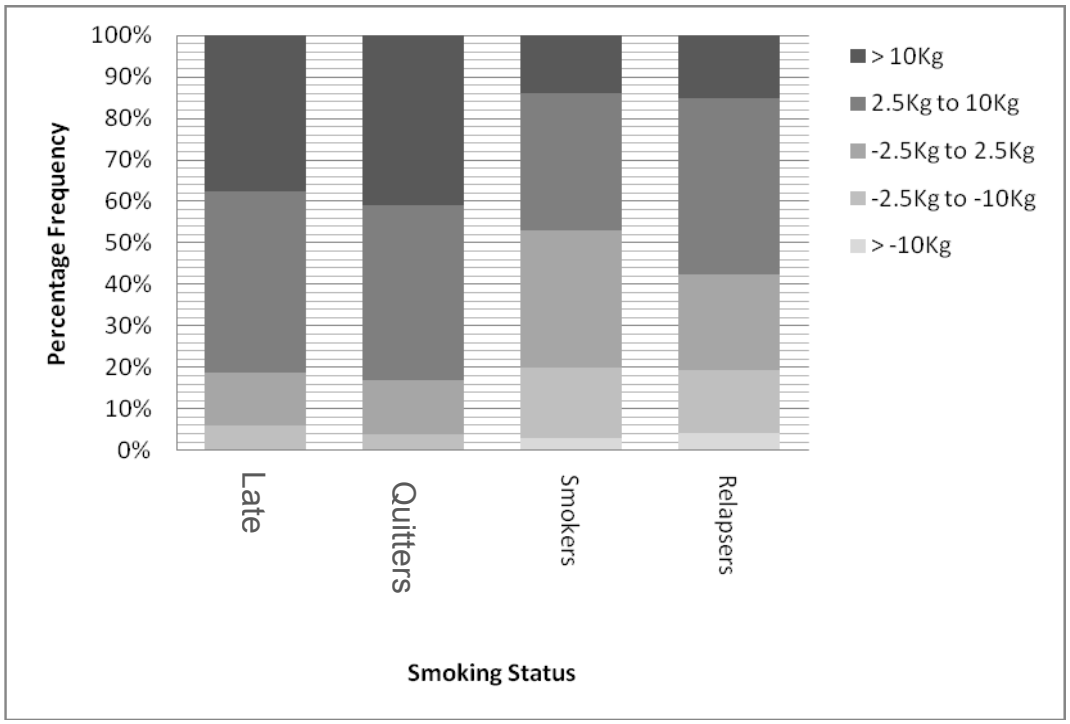


Figure 1. Percentage frequency of weight change according to smoking status

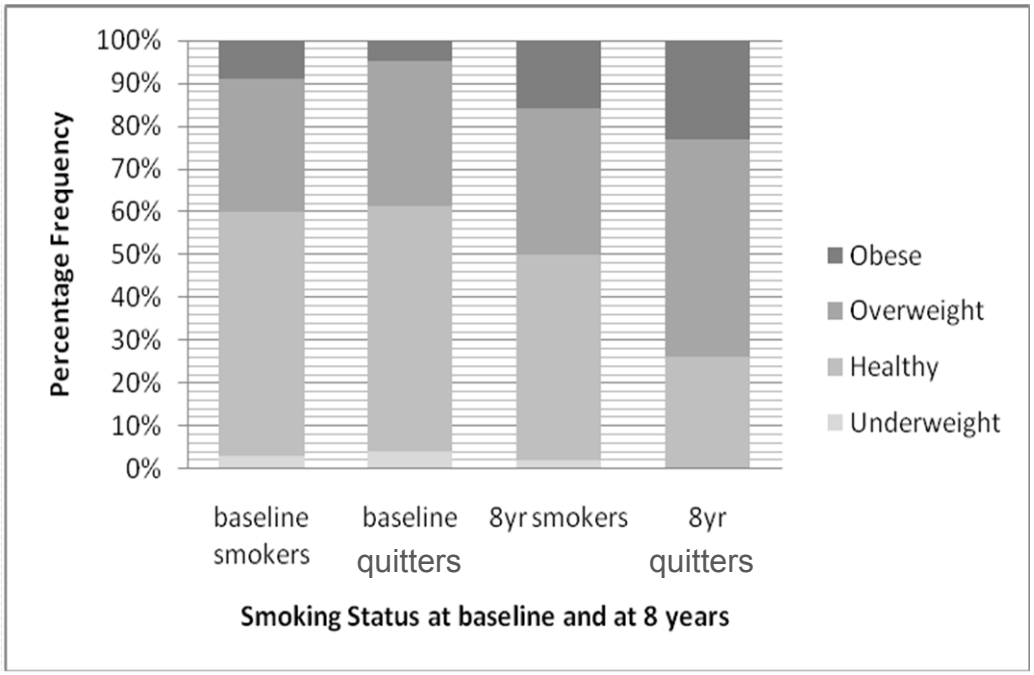


Figure 2. Percentage of smokers and quitters in BMI categories at baseline and at eight years

2.4.4. Weight Change and Baseline BMI

There was evidence that the association between BMI and weight change was modified by smoking status, with a p value for the interaction term being 0.002 both with and without adjustment for potential confounders. Accordingly, separate regression models in quitters and continuous smokers were examined.

Smoking Status	Unadjusted regression coefficient	95%CI Lower	Upper	P value	R^2	Adjusted* regression coefficient	95%CI Lower	Upper	P value	R^2
Constant[#]	2.245	1.692	2.797		0.133					0.182
Quitters	6.576	4.992	8.161	<0.001		6.810	5.232	8.389	<0.001	
Relapsed	1.047	-1.694	3.788	0.454		1.064	-1.655	3.783	0.442	
Late quitters	6.108	4.722	7.494	<0.001		6.324	4.943	7.705	<0.001	

*Adjusted for confounding variables of baseline height, BMI, Horn-Russell Score, daily number of cigarettes, weekly units of alcohol, age in years, socioeconomic status and ethnic origin, gender and treatment group. [#]In the unadjusted model, the constant can be interpreted as the weight gain in smokers (the reference group), but has no useful meaning in the adjusted model.

Table 11. Regression analysis for weight change over eight years according to four groups of smoking status, smokers were used as the reference category

2.4.5. Association between BMI and weight change in quitters

Regression modelling showed a significant linear association between BMI and weight gain in quitters. Adding a quadratic term improved the fit (p for R^2 change = 0.015), but the cubic term did not improve this further. The quadratic model accounted for 11% of the variability in weight change (Table 12) and the coefficients changed only slightly on adjustment for potential confounders (Table 12). This model estimated mean weight change over eight years in quitters of +9.8kg, +7.8kg, +10.2kg, +19.4kg where BMI was 18, 23, 29 and 36 respectively (Table 13, Figure 3).

2.4.6. Association between BMI and weight change in smokers

There was a significant, negative, linear association between BMI and weight change in smokers ($p<0.001$) and the fit was not improved by adding higher order terms (Table 14). The negative association remained largely unchanged when adjusted for confounders ($p=0.002$), (Table 14). This model estimated mean weight change smokers of +3.9kg, +2.6kg, 1.0kg and -0.8kg where BMI was 18, 23, 29 and 36 respectively (Table 13, Figure 3).

2.4.7. Sensitivity Analysis

Late quitters were added to the quitters who had been abstinent for the entire eight years while relapsers were added to the smokers who had smoked for the entire eight years. The regression models on these combined groups gave similar

models and estimates to those derived from the smokers and quitters only (Table 13).

Excluding participants with higher baseline BMIs, extreme weight gain, and excluding outliers judged by visual inspection of a plot did not really change the findings (Table 13).

2.4.8. Estimating weight change in individuals

Although the estimates for mean weight change differed according to BMI, there was overlap in the estimates for individuals. Calculating 95% prediction intervals in quitters using the quadratic model gave values of -3 and 22kg for a BMI of 18, -4 and 20kg for a BMI of 23 and -2 and 22kg for a BMI of 29 and 5 and 33kg for a BMI of 36.

Calculating 95% prediction intervals in smokers using the linear model gave values of -9kg and 17kg for a BMI of 18, -10kg and 16kg for a BMI of 23, -12kg and 14kg for a BMI of 29 and -14kg and 12kg for a BMI of 33.

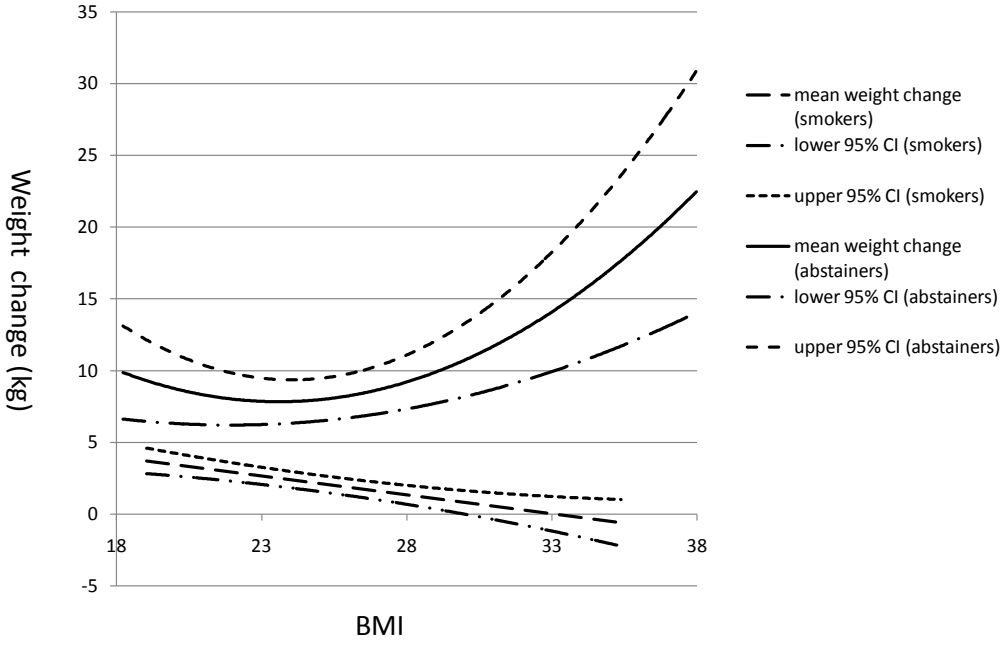


Figure 3. Predicted mean and confidence intervals for weight change according to BMI in smokers and quitters

BMI terms	Unadjusted regression coefficient	95%CI Lower	Upper	P value	R^2	Adjusted* regression coefficient	95%CI Lower	Upper	P value	R^2
Constant	8.972	7.619	10.339							
BMI-linear#	0.382	0.008	0.757	0.045	0.047					
Constant	7.947	6.360	9.514							
BMI-linear#	0.177	-0.225	0.578			0.217	-0.175	0.609		
BMI-quadratic#	0.071	0.014	0.128	0.015	0.114	0.062	0.006	0.118	0.030	0.172

*Adjusted for confounding variables of baseline height, BMI, Horn Russell Score, daily number of cigarettes, weekly units of alcohol, age in years, socioeconomic status and ethnic origin. # Re-centred around the whole sample mean.

Table 12. Regression model for the effect of BMI on weight gain in quitters

Baseline BMI	Mean weight (95% CI) gain estimated from regression models containing:						
	Smokers	Smokers Combined with relapsers	Quitters	Quitters excluding BMI>30kg/m^2	Quitters excluding BMI >30kg/m^2 and weight gain >20kg	Quitters combined with late quitters	Quitters combined with late quitters excluding (BMI>40kg/m^2)
18	3.9 (2.9, 4.9)	4.0 (3.0, 5.1)	9.8 (6.1,13.5)	10.9 (6.4, 15.7)	10.3 (6.3, 14.4)	10.6 (7.9, 13.5)	11.9 (8.6, 14.7)
23	2.6 (2.0, 3.1)	2.7 (2.2, 3.3)	7.8 (6.4,9.3)	7.4 (5.6, 9.1)	7.2 (5.7, 8.9)	8.6 (7.5, 9.7)	8.4 (7.3, 9.6)
29	1.0 (0.2, 1.8)	1.1 (0.3, 1.8)	10.2 (7.9, 12.5)	12.2 (5.7, 14.7)	10.2 (7.5, 16.8)	7.6 (6.2, 9.1)	7.6 (6.3, 8.8)
36	-0.8 (-2.4, 0.8)	-0.8 (-2.4, 0,7)	19.4 (12.7,26.0)			8.3 (7.2, 9.3)	11.2 (8.5, 13.9)
40	-2.6 (-5.1, -0.3)	-2.8 (-5.2, -0.3)				9.6 (7.8, 11.2)	

*outliers are BMI>30kg/m^2, weight gain >20kg and BMI>40kg/m^2

Table 13. Estimated mean weight gain according to BMI for ‘smokers’, ‘quitters’ and ‘quitters without potential outliers*’, ‘smokers combined with relapsers’, and ‘quitters combined with late quitters’

Smoking Status	Unadjusted regression coefficient	95%CI Lower	Upper	P value	R^2	Adjusted* regression coefficient	95%CI Lower	Upper	P value	R^2
Constant	2.206	1.673	2.738		0.155					0.243
BMI#	-0.265	-0.401	-0.128	<0.001		-0.222	-0.358	-0.087	0.002	
Age in years#						-0.131	-0.186	-0.076	<0.001	

*Adjusted for confounding variables of baseline height, BMI, Horn Russell Score, daily number of cigarettes, weekly units of alcohol, age in years, socioeconomic status and ethnic origin. # Re-centred around the whole sample mean

Table 14. Regression model for the effect of BMI on weight gain in smokers

2.4.9. Baseline alcohol consumption as an effect modifier of weight change according to smoking status

In the model including smokers and quitters, baseline alcohol consumption was not associated with weight change. However, there was a significant interaction between smoking status and alcohol consumption before (p=0.019) and after (p=0.010) adjustment for confounding variables.

2.4.10. Association between alcohol consumption and weight change in smokers

Separate linear regression modelling in smokers found no association between alcohol consumption and weight gain (regression coefficient: 0.005, 95% CI-0.037, 0.046; p=0.827). There was no evidence that this effect differed by gender, (p for interaction term 0.728) or baseline BMI (p for interaction term 0.911). Cook's distance did not exceed one (min <0.001, max 0.03).

2.4.11. Association between alcohol consumption and weight change in quitters

There was a significant, negative linear relationship between weight change and alcohol consumption in quitters (p = .015, r^2 = .070). For every additional unit of alcohol consumed per week at time of quitting, mean weight change over eight years was −0.174 kg (95% CI: −0.315 to −0.034) p=0.015 (unadjusted) (Figure 4) (adjusted: −0.180 kg (95% CI: −0.318 to −0.043) p = 0.011). Fit did not improve with higher order terms and effect did not differ by gender (p for interaction was 0.91). Cook's distance did not exceed one (min <0.001, max 0.087).

2.4.12. Variability of weight change in quitters according to baseline alcohol consumption and BMI

We have previously demonstrated that 11% of the variability in weight gain in quitters (Table 12) was accounted for by a J-shaped curve with baseline BMI (Figure 3). There was no evidence that the association between alcohol and weight gain was modified by baseline BMI; p for interaction was 0.290. The effects of BMI and alcohol consumption were therefore independent, together they account for 17% of the variability of weight gain in quitters (Table 15). The regression lines for mean population weight gain according to BMI at different levels of alcohol consumption are plotted (Figure 5).

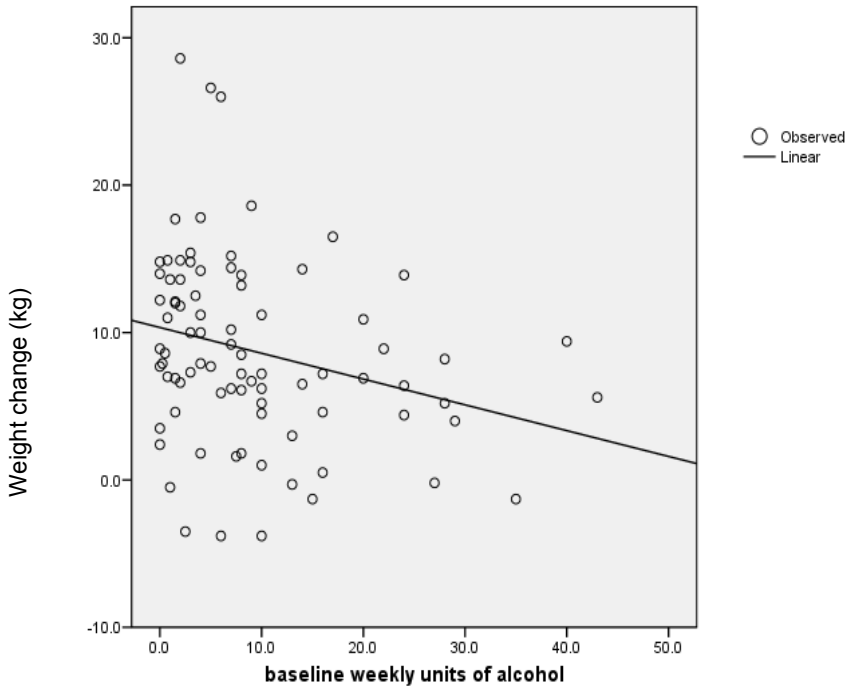


Figure 4. Weight change over 8 years in quitters (n=84) according to baseline alcohol consumption in quitters

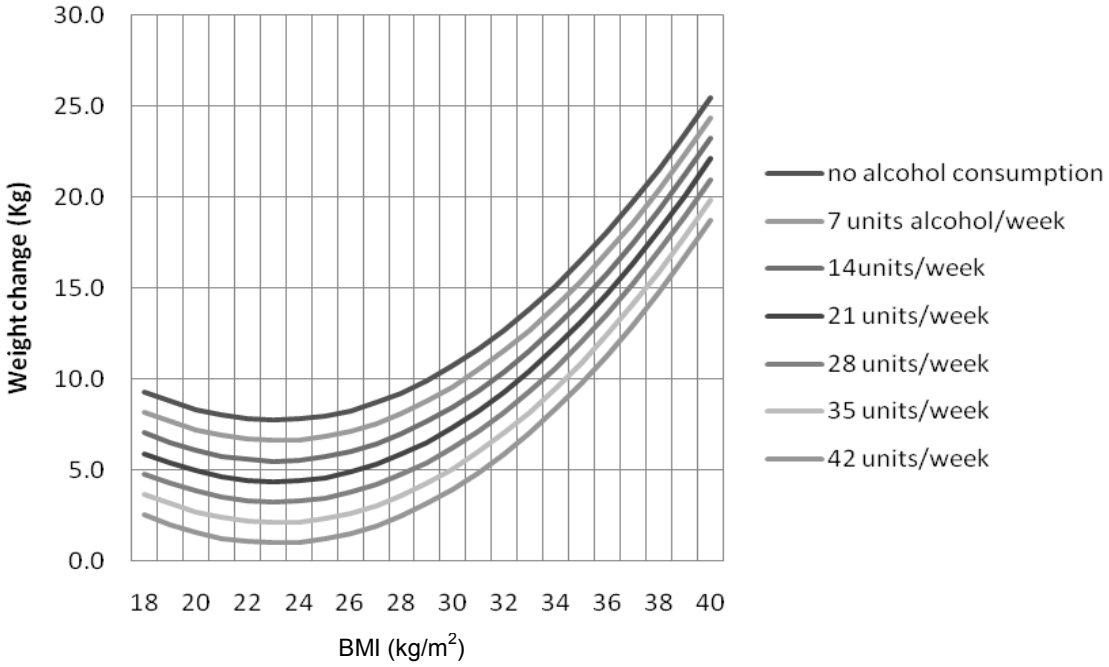


Figure 5. Weight change according to BMI and baseline alcohol consumption in quitters

Variable	Regression coefficient*	Lower 95%CI	Upper 95%CI	p value	r^2
Constant	7.886	6.360	9.412	<0.001	0.172
BMI#	0.217	-0.175	0.609	0.274	
BMI^{2} #	0.062	0.006	0.118	0.030	
Alcohol units/week#	-0.161	-0.296	-0.026	0.020	

*Stepwise adjustment, using p=0.2 cut-off for confounding variables of baseline height, BMI, Horne Russell Score, daily number of cigarettes, weekly units of alcohol at baseline, age in years, socio-economic status and ethnic origin. # Re-centred around the total sample mean.

Table 15. Regression Analysis of weight change according to baseline BMI and alcohol consumption in quitters

2.4.13. Weight change over eight years with patch or placebo use during quitting

On active patch treatment, there were 49 people who remained abstinent for eight years and they gained a mean (standard deviation) of 8.84kg (5.82) while the 36 smokers using placebo patches, who remained abstinent for eight years gained 8.73 (7.11)kg. The mean difference (95% confidence interval) was 0.11kg (-2.68, 2.90).

2.4.14. Associations of weight change over eight years with age, gender, smoking rate and socioeconomic status at baseline

Age, gender, cigarettes per day, Horne Russell score, socioeconomic status and treatment group were not significantly associated with weight change over eight years in our group of continuous quitters (Table 16), although the point estimates required further discussion to examine their clinical importance. The coefficients provide a mean point estimate of these associations (Table 16).

2.4.14.1. *Age*

For age, the coefficient represented a 20g increase over eight years for every additional year of age at baseline. This means a 25 year age difference in baseline age would be required before an associated 0.5kg difference in weight at eight years was seen.

2.4.14.2. *Gender*

The coefficient for gender showed women gained approximately 1.8kg more than men at the end of eight years of abstinence. In unadjusted analysis this was a difference of 1.69kg (-1.09, 4.48).

2.4.14.3. *Smoking rate*

For every additional cigarette smoked daily at baseline, there was an associated mean weight increase of 50g eight years later. So 20 cigarettes (1 pack) extra a day would need to be smoked to see an associated increase of 1kg eight years later. An increase in the level of addiction to smoking, as measured by an increase of 1 in the Horne Russell score, increased weight by 0.2kg after 8 years of abstinence. The mean (SD) HR score in our sample was 14(4) and scores ranged between 4 and 23. Therefore, those who were more addicted, for example scoring 7 points higher on the HR score, had an associated weight gain of 1.4kg more after 8 years of abstinence than those who were less addicted.

2.4.14.4. *Socioeconomic status*

The coefficients for socioeconomic status (SES) categories were large, but the 95% confidence intervals were very wide and outside of the range of weight change within our sample. To get an idea of the overall effect of SES rather than individual effects of smaller categories we examined whether the model without adjustment for SES was improved significantly by adding in all the SES categories. The improvement in fit was not significant (p=0.18).

	Unstandardized Coefficients	95% Confidence Interval for B		
	B	Lower Bound	Upper Bound	Sig.
(Constant)	12.13	2.39	21.88	0.015
SES II (managerial/technical)*	-3.88	-13.77	6.01	0.437
SES III (skilled, non-manual)*	-3.72	-13.97	6.52	0.471
SES III (skilled, manual)*	-3.36	-13.17	6.45	0.496
SES IV (partially skilled)*	-3.79	-13.90	6.33	0.457
SES V (unskilled)*	-4.26	-15.77	7.26	0.463
Age#	-0.02	-0.16	0.12	0.788
Cigarettes smoked per day#	0.05	-0.25	0.35	0.728
(Cigarettes smoker per day#)^2	0.00	-0.02	0.01	0.945
Horn Russell score#	0.21	-0.23	0.66	0.340
(Horn Russell score#)^2	0.01	-0.07	0.08	0.884
Weekly baseline alcohol consumption#	-0.17	-0.35	0.00	0.051
Treatment group*	-1.33	-4.42	1.75	0.391
Gender*	1.83	-2.56	6.22	0.409
BMI#	0.49	0.07	0.91	0.023

*reference category for SES was I (professional), for treatment group was placebo, for gender was male #values were re-centered around the mean

Table 16. Coefficients with 95% confidence intervals for potential explanatory variables of weight gain in continuous quitters over eight years

2.5. Discussion

2.5.1. Findings

2.5.1.1. *Weight change according to smoking status*

In a cohort of people trying to stop smoking, those who failed and continued smoking for eight years gained about 2kg. Those who abstained from smoking for eight years gained nearly 9kg. People who stopped smoking for a whole year but then resumed smoking had a weight gain that was similar to and not significantly different from smokers. Some quitters gained much more weight than average with only a quarter of long-term quitters being a healthy weight after eight years.

2.5.1.2. *Association with baseline BMI*

Quitters who were underweight or overweight on cessation were more likely to gain more weight than those in the healthy BMI range. These findings were robust to sensitivity analyses.

2.5.1.3. *Association with baseline alcohol intake*

For every unit of alcohol quitters consumed at baseline they weighed 0.17kg less eight years later than those who did not drink. This equates to people drinking alcohol at the maximum UK recommended weekly intake for women (14 units or 112g ethanol/week) weighing a mean 2.4kg less than those who did not drink. This association was not significantly different in females and males. The effect was independent of baseline BMI.

2.5.1.4. *Associations of weight change over eight years with patch or placebo use during quitting; age, gender, smoking rate and socioeconomic status at baseline*

We found no evidence of a statistically significant association between weight gain over eight years of abstinence and placebo or patch treatment at baseline, age at quitting, baseline smoking rate, gender or socioeconomic status.

2.5.2. Strengths and limitations of this study

2.5.2.1. *Characterisation of smokers and quitters*

In a cohort of smokers followed for eight years, many smokers will try to quit and many quitters relapse. All quitters were biochemically verified as abstinent four times over the eight year follow up. Likewise although some smokers tried to quit, they were smoking at each follow up point. The strength of this study therefore lies in its accurate characterisation of both these groups, which leads to more precise estimates of weight change. There is evidence that post cessation weight gain is under-estimated when smoking status is measured by point prevalence or by self-report because self-reported point prevalence will classify intermittent smokers and recent quitters as abstinent (Klesges et al., 1989, Klesges et al., 1997).

2.5.2.2. *BMI investigation robust to sensitivity analysis*

The cohorts of late quitters and relapsers are less well characterised as the time of individuals quitting and relapsing is variable, these events could occur at any time after year one and before year eight. However, these groups showed similar estimates of weight change and weight change in relation to baseline BMI, indicating that for most their relapsed or quit state was sufficiently well established for weight change to reflect that of long term quitters and smokers. In support of this, other studies have shown that the greatest weight change associated with smoking status occurs rapidly (O'Hara et al., 1998).

2.5.2.3. *Reporting bias*

This study is limited by use of self-reported weight and BMI data at eight year follow-up. However, sensitivity analysis showed no differences in mean baseline weight, BMI or weight change when measured and self-reported data was compared. The validity of self-reported weight data has also been demonstrated in other epidemiological studies (Spencer et al., 2002), suggesting that reporting bias is not a likely explanation of our results.

To explain the J-shaped association of baseline BMI with post cessation weight change in quitters by reporting bias the pattern of misreporting weight would have to vary in a particular way. Either it would have to vary by baseline BMI such that people with a low or a high BMI eight years previously would over estimate their

current weight or people with an ideal BMI eight years ago would underestimate their current weight. This seems unlikely.

Similarly, alcohol consumption may have been underreported. However, underreporting of both measures could not account for the association we observed. For underreporting to explain the association, those who underreported weight would have had to over-report alcohol consumption and/or vice versa and this seems counterintuitive.

Alcohol was measured by careful questioning at baseline only. There is evidence that a single measure of alcohol consumption is a reasonable estimate of average alcohol consumption over several years. The Nurses' Health Study shows a high correlation between alcohol intake at a single point in time and alcohol intake over the following 6 years (r=0.75) (Giovannucci et al., 1991). Also there is evidence from a large cohort that alcohol consumption does not change as a consequence of quitting smoking (Murray et al., 1996).

2.5.2.4. *Response bias*

Only 52% of the living participants enrolled in the original trial responded at eight year follow up, with success at quitting in the trial being the factor most strongly associated with response. However, non response is an unlikely explanation of our findings and it is reassuring that baseline weight and BMI did not differ

between responders and non responders. The study participants enrolled in a smoking cessation study and responded to a questionnaire on smoking status at follow up, with only a single question on weight. It is unlikely therefore that whether individuals gained weight or their pattern of weight change in relation to BMI was associated with failure to respond. For non-response to explain the association between BMI and weight change, weight change in non responders would have to have been the reverse of what we observed in responders. That is among non-responding quitters weight gain would have resulted in an inverted-J shaped relation with baseline BMI, with those of a healthy BMI gaining the most weight. There is no plausible reason for such an association.

Similarly, if non response were to account for the association of weight change with baseline alcohol intake non-responders would have gained more weight the more alcohol they consumed at baseline. While this remains a possibility, as this was primarily a smoking cessation study, there is no reason to believe that a participant's perception of weight gain or alcohol consumption influenced their decision to complete the questionnaire.

2.5.2.5. *The role of confounding*

It is possible that confounding explains the association of weight change with baseline alcohol intake. As this was a smoking cessation trial analyses on weight change were not planned; consequently behaviours such as diet and physical activity were not assessed. It is possible that those who drank more alcohol at baseline also had better dietary behaviour and did more physical activity than

those who drank less. There is cross sectional evidence which shows a positive correlation between moderate alcohol intake and habitual physical activity ($r=0.41$ $p<0.01$) (Westerterp et al., 2004), but prospective studies have reported higher alcohol consumption is associated with lower weight gain after adjustment for physical activity and diet (Wannamethee & Shaper, 2003, Wannamethee et al., 2004, Wang et al., 2010). To explore this in an ex-smoking population we carried out regression analysis on data from the Health Survey for England (HSE).

The HSE generates a cross sectional dataset from annual surveys on the health and lifestyle of a large number of people in England. For maximum compatibility with our own data set of quitters we carried out our analysis on a subset of white ex-smokers. The distribution of socioeconomic class was similar between both sets of data. We used the 1998 HSE dataset as this was the nearest year to our cohort which contained comprehensive data on alcohol intake, physical activity and dietary patterns in over 4000 ex-smokers. We excluded those classified as problem drinkers.

We found in unadjusted analysis that an extra unit of alcohol drunk per week is associated with an average increase in 2.6 minutes of activity each week, including an extra 0.03 days a month doing 20 minutes or more, moderate to vigorous physical activity. So someone consuming 14 units of alcohol a week compared to no alcohol may be doing an extra 36 minutes of activity each week, including an extra 0.4 days a month doing 20mins of moderate or physical activity. If we consider a 68kg person walking briskly for one hour would burn

approximately 320kcal, an extra 36 minutes of similar intensity exercise each week would burn an extra 192 kcal or theoretically an extra 27kcal each day. A daily deficit of 550kcal is required for a 0.5kg weight loss over one week. So an extra 27kcal expended daily could account for a theoretical weight change of 0.02kg each week. Based on this reasoning over 8 years one might expect an 8.3kg difference in weight to be seen, but this is not born out in epidemiological studies. Current available evidence suggests that even the recommendation of 30 minutes physical activity a day for cardiovascular fitness, is insufficient to prevent weight gain and 45 to 60 minutes moderate intensity activity each day is considered necessary (Saris et al., 2003, Wareham et al., 2005). Given this, the extra 36 minutes of activity a week associated with moderate alcohol consumption is unlikely to account for the impact of alcohol on weight.

We analysed nine indicators of a healthy diet from food frequency questions. There was a statistically significant association with all of these, although the sizes of these associations were too small to be meaningful and the directions of these associations were inconsistent. Some indicators showed alcohol consumption was associated with a less healthy diet, namely more frequent salt use, red meat and fried food consumption, a greater amount of total fat and less frequent fruit and vegetable consumption. Other indicators found alcohol consumption was associated with a more healthy diet, namely more fibre and less frequent consumption of chocolate/crisps/biscuits and cakes. The largest association was seen for cake consumption, which was equivalent to one additional unit of alcohol resulting in an odds ratio of 0.987 for eating less cake.

Therefore although we did not measure physical activity and diet in our cohort, these findings suggest that they are unlikely to be confounding the association we found. However further studies which measure and adjust for these within the same study population are needed before we can be certain.

Our measure of alcohol consumption gave an estimate of total quantity of alcohol consumed on a weekly basis but no detail on the pattern of drinking. As mentioned in the introduction consideration of drinking pattern may have helped to explain our findings further.

2.5.2.6. *Lack of a never-smoker category*

Our cohort did not contain never-smokers so we have been unable to compare weight change in smokers and quitters to never smokers. However data from other cohorts allows some comparison which helps us to consider the impact this weight gain has on the population's weight as a whole. The OXCHECK cohort (Tang et al., 1997) and the Caerphilly male cohort (Munafo et al, 2009) show weight gain in quitters during the first five years after stopping is greater than in never smokers. Cross sectional analysis of these cohorts show never smokers and ex-smokers have a similar BMI in the longer term. However cross sectional studies show the BMI of ex-smokers exceeds that of never smokers, particularly in

men, suggesting that post-cessation weight gain has public health importance (Klesges et al., 1989, Akbartbartoori et al., 2005, section 1.2.2).

2.5.2.7. *Lack of ethnic diversity*

Our cohort included predominately white European people living in Oxfordshire, UK. There is evidence that weight gain varies by ethnic group. For example, African Americans have greater weight after stopping smoking than European Americans (Williamson et al., 1991, Klesges et al., 1998). It is therefore possible that other ethnic groups might have a different pattern of weight gain in relation to baseline BMI or alcohol intake than we observed in this cohort.

2.5.3. Comparison with other literature

2.5.3.1. *Weight change according to smoking status*

We know of only two other prospective studies that have reported on weight gain over the long-term in biochemically confirmed quitters. The Lung Health Study found quitters gained 8.2kg over five years whereas smokers gained 1.6kg, a difference of 6.6kg (O'Hara et al., 1998), almost identical to that we reported here. A smaller study of 45 quitters showed a mean weight gain of 8.9kg over 4 years but did not report weight change for continuing smokers (Daughton et al., 1999).

2.5.3.2. *Association with baseline BMI*

No other studies have looked for a curvilinear relationship of weight gain according to BMI, although some studies have hinted that such a relationship might exist. Froom et al. reported weight gain was lowest in those with a BMI between 25.8-27.7kg/m^2 and higher in those with a BMI above or below these values (Froom et al, 1999). Caan et al. found that lighter and heavier women gained more weight than those of intermediate weight, but this pattern was not seen after adjusting for confounders (Caan et al., 1996). Other studies have reported no association with baseline BMI (Rabkin, 1984, Rodin et al, 1987) some have found a negative linear association (Flegal et al., 1995, Bosse et al., 1980, Nides et al., 1994) and some a positive linear association (Dale et al., 1998, Kawachi et al., 1996). This may be explained because these studies modelled a linear relationship between BMI and weight gain. A linear model would tend to show no association or a weak positive linear association if the true association was U- or J-shaped. Re-evaluating data from the Lung Health Study and the Caerphilly cohort using polynomial modelling would be useful to confirm or refute our results.

2.5.3.3. *Association with baseline alcohol intake*

In a cohort study of smokers and quitters, spanning two to four years, quitting smoking was associated with an increase in BMI, higher alcohol consumption, measured at one point in time, attenuated this rise in BMI. When investigated there was no evidence of effect modification by smoking status. However smoking status was self reported and quitting date was variable (any time after study entry),

so a smaller weight gain may have diluted the results. That study may also have lacked power to detect an effect modification because there were only 65 quitters and alcohol consumption was a binary variable (Froom et al., 1999).

A two year cohort found a small but significant inverse effect of alcohol consumption at the time of quitting and subsequent weight gain in female smokers and quitters. This effect was seen after adjustment for physical activity (Kawachi et al. 1996). There was no investigation of interaction by smoking status. Abstinence was measured by point prevalence which may have underestimated weight gain and accounted for the small effect size seen.

Our findings are similar to the results from the Lung Health Study (Nides et al., 1994) which followed biochemically validated continuous quitters for 5 years. The data showed that for each standard US drink per week consumed at baseline, the regression coefficient was -0.098 (p=0.02) in men and -0.234 (p=0.02) in women. (Although the Lung Health Study team reported these coefficients separately for each gender, there is no statistically significant difference between them according to our calculations). Equating these to UK units gave regression coefficients of -0.083 and -0.132 for men and women respectively. These values fit within the 95% confidence intervals our mixed sample but suggest a slightly lower effect than we found. The Lung Health Study also measured self reported alcohol consumption at baseline only and did not measure or adjust for physical activity or diet.

2.5.3.4. *Weight change over eight years with patch or placebo use during quitting*

Our data showed no evidence that active NRT has a long-term effect on reducing weight gain but are too imprecise to exclude this possibility. However, the data from one year follow up in a Cochrane review (Parsons et al, 2009) also showed no sign of efficacy for nicotine patch to prevent weight gain, with a mean difference of -0.15kg (-1.04, 0.74). The possible effect of NRT seen at one year (-0.44kg (-1.02, 0.14) was generated by three trials of nicotine nasal spray where spray use was allowed for up to one year and 21% of abstinent smokers continued to use it. These trials had a combined effect of -1.55kg (-3.09, -0.00) compared to placebo. Therefore it seems unlikely that patch use at the time of quitting has a long term effect on attenuating post cessation weight gain.

2.5.3.5. *Association with age*

As described in the introduction to this chapter the association between younger age and greater post cessation weight gain has previously been shown in three out of seven studies, with four showing no association. Our study adds another which shows no significant association and again our mean point estimate, of a 25 year difference associated with 1kg difference in weight gain after eight years, was minor compared to other studies. One previous study showed a mean difference in baseline age of one year between those who lost weight and those who gained excessive amounts over 15 years (Swan et al., 1995). Another found the chance of a 5kg further weight gain, in more than one year of abstinence, almost doubled

in those under 55 years compared to those over 55 years old (Williamson et al., 1991). However, our mean estimate again had wide confidence intervals which included larger estimates so we cannot be certain of no association.

2.5.3.6. *Association with gender*

We also found no significant association with gender; however, the coefficient was large enough to be of clinical importance, with an unadjusted estimate of mean weight gain of 1.69kg more in men, after eight years cessation, than women. As described in the introduction to this chapter three out of seven studies have shown a greater weight gain in women. Two studies have shown no association and two studies have shown a greater weight gain in men. Our study continues to leave us with inconsistent results.

2.5.3.7. *Association with smoking rate*

Of all the explanatory variables we included in our regression analysis on weight change in continuous quitters, we expected lower smoking rate to be associated with less weight gain, as this has been the most consistent finding in the literature so far (section 1.2.3). However, we did not find evidence of this in our quitters despite a wide range of smoking rates from 15 to 60 cigarettes per day. Instead, we found a non statistically significant mean difference that showed an extra packet of cigarettes smoked daily was associated with 1kg difference at eight years. However, the confidence intervals were wide and extended to include the

possibility of a larger estimate, so we cannot be certain that no association exists. The magnitude of weight change in those who were more addicted to smoking was a little larger, with an increase in Horne Russell score of seven being associated with an increase of 1.5kg, eight years after quitting. These differences although important from a public health perspective are smaller than previous estimates. Previous estimates have found the increased chance of a further 5kg increase, in more than one year of abstinence, is associated with smoking 10 cigarettes per day more at baseline (Williamson et al., 1991). As discussed in chapter one, three of 14 studies also found no association, and we have now added a fourth, although our study was too small for us to be certain.

2.5.3.8. *Association with socioeconomic status*

We also found no association with socioeconomic status; this is in contrast to two studies so far which have found greater weight gain in those with a lower socioeconomic status. However, the number of individuals split between the categories was small with the majority being between socioeconomic class two to four so there was little scope to allow for differences to be examined accurately.

2.5.4. Implications for clinical practice

Patients in a smoking cessation clinic want to know how much weight they might gain on cessation. The mean and 95% confidence intervals give information about average or population effects, but do not give individuals a range in which their weight is likely to lie. These are better defined by prediction intervals. Our

models showed that someone with a BMI of 22kg/m^2 who quits smoking and maintains abstinence can expect to lose up to 2kg or gain up to 20kg. Therefore the 95% prediction intervals were wide, however, at higher BMIs, the prediction intervals were more useful with a 95% chance that someone with a BMI of 36 would gain between 5kg and 33kg.

Adding alcohol consumption at baseline into the equation enabled us to explain a further 6% of the variability in weight change in quitters, but again the confidence intervals were wide and estimates imprecise. Therefore predicting weight change on these baseline characteristics is currently too imprecise to be used in clinical practice and further analysis in larger datasets is required.

Moderate drinking, with the potential to prevent a weight gain of 2.4 kg over eight years (0.3 kg/year), in a population of ex-smokers could have a significant public health impact. An increase of 0.7 kg/year has been shown to increase the risk of developing diabetes by 86% in those with impaired fasting glycaemia (Gautier et al., 2010). Those who quit smoking are at increased risk of developing diabetes for about five years after cessation, which is unexplained by weight gain alone (Hur et al., 2007, Wannamethee et al., 2001, Yeh et al., 2010). There is also consistent systematic review evidence that shows moderate alcohol consumption is associated with the lowest risk of developing diabetes (Baliunas et al., 2009, Koppes et al., 2005). However, evidence is currently insufficient to recommend quitters increase alcohol intake to moderate levels as a means to prevent weight

gain. Such recommendations would also need to be carefully balanced against the harmful effects of increasing alcohol intake.

2.5.5. Implications for research

If the association between BMI and weight gain on cessation is causal, we would need to delineate behavioural or physiological mechanisms. Nicotine suppresses appetite and increases metabolic rate (Hofstetter et al., 1986). Underweight smokers might gain more weight than ideal weight smokers because they are particularly susceptible to these effects and, when they are removed by stopping smoking, greater weight gain results. Those who are already obese while smoking may have a cluster of unhealthy behaviours if, for example, they also eat a high fat diet, this may be accentuated without nicotine to restrain their appetite. This may result from an increased appetite for sweet and fatty food (Caan et al., 1996). Alternatively those who are obese while smoking might be those who are genetically predisposed to obesity, perhaps through poor expression of appetite regulatory hormones (Cummings & Schwatz, 2003, Wynne et al, 2005) and, once the appetite suppressing effect of nicotine is removed, weight increases more than in healthy weight counterparts.

If the association between alcohol intake and post cessation weight gain was causal it is plausible that MESO induction in quitters may play a role in increasing metabolic rate. We did not measure changes in metabolic rate, energy intake or

physical activity, and studies which do so are required to understand the mechanisms which might account for the associations we found.

2.6. **Conclusions**

Smokers who quit smoking gain 7kg more than if they had continued smoking, while those who quit for a substantial period and then resume smoking seem to resume their 'smoking weight'. This study is the first to look for and find a J-shaped relation between baseline BMI and weight gain in quitters. If confirmed, this has important implications for the treatment of tobacco addiction. Knowing that underweight and obesity predicts greater weight gain on cessation helps clinicians plan interventions with their patients and guides epidemiological and physiological investigations into causes of weight gain on smoking cessation.

A complex relationship exists between alcohol consumption and weight gain. We have found a dose response relationship in quitting smokers, which is consistent across studies. It is plausible that MESO induction may play a role in this. Therefore, advice to reduce alcohol consumption in this population may promote rather that prevent weight gain. Studies are needed to investigate the mechanisms of alcohol metabolism in quitting smokers and weigh the adverse health consequences of increasing alcohol against the benefit of smaller weight gain. Increasing alcohol should not currently be advised for preventing weight gain during smoking cessation.

We found no evidence of an association between weight gain over eight years of abstinence and treatment group, age at quitting, baseline smoking rate, gender or socioeconomic status. However, our estimates were imprecise so we cannot be certain and larger prospective studies in biochemically validated continuous quitters are required.

3. TRIAL PROTOCOL: DIETARY MANAGEMENT IN SMOKERS TRIAL (DeMiST)

Chapters three to six report on DeMiST. A CONSORT checklist for the reporting of this trial is included in Appendix 5.

Chapter three meets objective three of this thesis, to discuss the design of the Dietary Management in Smokers Trial (DeMiST), a randomised controlled trial to investigate the feasibility of dietary interventions to prevent weight gain within NHS stop smoking clinics and examine the effects of these dietary interventions on urges to smoke.

This protocol was published in the journal Trials (Lycett et al., 2010, Appendix 6). The original present tense of the publication has been changed to past tense to fit better with the thesis and some details on statistical analysis have been added.

3.1. **Introduction**

As discussed in section 1.5.4 a Cochrane review (Parsons et al, 2009) showed some evidence that both an individiually tailored dietary plan and a very low calorie diet (VLCD) reduced weight gain and the VLCD increased abstinence.

The effect of the VLCD on improving abstinence was unexpected. One hypothesis is that the VLCD induced ketosis, which actually suppressed hunger (Johnstone et al., 2008) and therefore reduced urges to smoke. This hypothesis is supported by data supplied by Danielsson (personal communication), which showed a statistically significant reduction of urges to smoke and a smaller increase in appetite during the weeks on the VLCD diet than those in the control intervention. There was a 50% reduction in urges to smoke after one week on the VLCD diet compared to a 27% reduction after one week in the control group ($P<0.0001$). There was a 4-fold increase in hunger in the control group after one week compared to only a 50% increase in hunger in the VLCD group ($p<0.0003$).

We compared three dietary interventions. A VLCD, and an individual dietary and activity plan (IDAP) which included a modest energy restriction, using a low fat diet that meets the energy requirements of an individual's BMR. The third was a control condition where general healthy eating advice was provided, but with an emphasis of avoiding hunger, this is typical of the current advice given in NHS stop smoking services.

Feasibility was the trial's primary outcome and we assessed this by measuring recruitment and attrition rates. We also assessed acceptability through seeking the views of the participants and clinicians who took part.

We developed and tested a tool to help non dietary experts assess and advise on diet, this tool also aimed to measure dietary change as a process by which weight change may have occurred.

The other main objective of DeMiST was to test the hypothesis that hunger increases urges to smoke and ketosis reduces urges to smoke. We thought we could include this within the feasibility trial as a small sample provided adequate power to test this association. We developed and tested a tool to measure hunger and food craving for this purpose.

3.1.1. To maximise the difference in hunger between trial arms

The VLCD trial (Danielsson et al., 1998) reviewed in the Parson's et al Cochrane review used a VLCD intermittently. This may have underestimated the potential effect of the VLCD on nicotine withdrawal symptoms. Moving into and out of a ketotic state may influence mood and hunger, both symptoms of nicotine withdrawal.

We expected hunger to be greatest in the IDAP group where a moderate energy restriction creates a negative energy balance. Appetite then increases in response to the usual physiological and neurological mechanisms that work to restore energy homeostasis (Wynne et al., 2005). In the control condition, we expected hunger to be alleviated by eating freely.

We began the VLCD one week before quit day to ensure participants were in ketosis before they quit (verified by the presence of urine ketones) and continued, uninterrupted, for a further four weeks when nicotine withdrawal would be at its peak. The IDAP also began one week before quit day to establish an energy deficit and increase the likelihood of hunger in this intervention before the quit date. The control group were advised to eat as usual. Therefore, at the time of quitting we expected to see the maximal differences in hunger scores between the three groups.

3.1.2. To measure hunger and food craving

To measure a change in appetite, when food is restricted we cannot rely on a measurement of food intake. Rather we need a measure to capture motivation to eat. As discussed in section 1.3.3 motivation to eat which is affected by nicotine can broadly be described as two main responses. A homeostatic response to food deprivation and a hedonic response to food reward (Saper et al., 2002, Blundell, 2006).

The first response we called ‘genuine hunger’, derived predominantly from a physiological need for food, commonly perceived as an abdominal sensation and described as emptiness in the stomach. When hungry, a wide variety of foods will satisfy.

The second motivation we termed ‘food craving’, this is most commonly described in the scientific literature as ‘an intense desire to eat a specific food’ (Pelchat et al., 2004). Food craving can occur irrespective of hunger, although hunger and food cravings have been shown to be interdependent (Gibson & Desmond, 1999).

The precise mechanism of food craving has been much debated. Some studies have demonstrated that like tobacco addiction (Balfour, 2004), dopamine is released in the nucleus accumbens in response to eating the desired food (Martel & Fantino, 1996, Pelchat et al., 2004). Others have suggested endogenous opioid peptides (Mercer & Holder, 1997) or a central serotonin deficit (Wurtman & Wurtmen, 1986) trigger food cravings. However the serotonergic hypothesis has been questioned in later studies (Christensen, 1997). Food craving has also been hypothesied as a learned response (Gibson and Desmond, 1999) and a response to food related cues (Christensen, 2007).

Measurement of hunger and food craving has also been debated. The subjective nature of these terms makes them hard to standardize although several scales have been developed which have shown good internal consistency. The Food Craving Inventory (FCI) measures craving for specific foods (White et al., 2002). The Trait and State Food-Cravings Questionnaires, and modifications of these, measure cravings in general, in terms of preoccupation with food, anticipation of positive effect and loss of control (Cepeda-Benito, 2000, Nijis etal, 2007). The Questionnaire on

Craving for Sweet or Rich Foods (QCSRF) measured both and this was designed to specifically measure food cravings during smoking cessation (Toll et al., 2008).

However no scales have sought to capture both hunger and craving or distinguish between the two outside of laboratory conditions. There is a need to do so, as their nature is different so the strategies needed to control them will be different. None of the scales developed so far are brief enough or designed to capture cravings on a daily basis.

3.1.3. DeMiST dietary assessment

As described in section 1.3.3 an increase in food and nutrient intake, energy from fat and sugar, in particular has been suggested to account for 69% of weight gained following smoking cessation (Stamford et al., 1986). Change in energy expenditure is thought to account for less than 40% (Filozof et al., 2004). The goal of dietary interventions to prevent weight gain in smoking cessation aim to restrict energy intake both prevent this increase in consumption and balance intake with lowered energy expenditure.

To measure this process to check adherence and see whether dietary change explained change in weight we needed a measure for dietary intake and dietary change that could be easily used and assessed in a clinical setting.

The accepted gold standard measure for nutrient intake is the seven day weighed intake diary although validation studies with doubly labelled water have shown that underreporting is common (Livingstone et al., 1990). Data collection and analysis from a weighed intake diary is burdensome and the slightly less burdensome seven day food diary is now most widely used. Portion sizes are estimated using household measures or natural unit sizes (e.g. slices of bread). Individuals can choose to weigh food, but the main purpose of using this method is to avoid the burden of weighing. A comparison of methods in the UK arm of the European Prospective Investigation into Cancer (EPIC) showed that the seven day estimated record, agreed most closely to 16 days of weighed intake (Bingham et al., 1997) and this is now considered the gold standard field measure.

However, frequent recording of food intake even using the estimated seven day food diary is extremely burdensome for trial participants and extremely laborious to analyse. Even when it is done well, its accuracy is still only an estimate and it is prone to misreporting. Food frequency questionnaires (FFQ) and 24 hour dietary recalls are the next best dietary assessment methods correlated to biomarkers (Bingham et al., 1997). However, FFQ are designed to measure average consumption patterns over a long period so are unsuitable for detecting change over short periods in a clinical trial. Twenty-four hour recalls are most accurate by using a multiple pass method. This is a five step method, first a participant lists food and drinks consumed, second frequently forgotten foods are probed, third time and eating occasion are probed, fourth, descriptions and quantity of foods are probed and fifth is a final probe of anything else that can be recalled (Conway et al., 2003, Conway et

al., 2004). However this technique is time consuming requires considerable training and several assessments to take into account day-to-day variability. Diet histories are most commonly used in clinical practice, these take into account habitual intake and 24 hour recall but require lengthy training of clinicians. They provide the basis on which dietary advice is given. We searched the literature for a brief, simple and reliable tool, which could help clinicians not trained in detailed dietary assessment and therapeutic diets, to assess, advise and monitor dietary change. We did not find a tool suitable for this purpose so we designed our own and tested its validity against the gold standard field measure.

3.1.4. Meeting the needs of trial participants

As the aim of DeMiST was to inform a study large and long enough to assess long term effects on dietary change, weight, cardiovascular risk, lung health and smoking abstinence, the design extended beyond the initial quitting stage into a second treatment stage where both the VLCD and the control group received individual dietary and activity planning.

The reason for this in the VLCD group was to provide participants with conventional support to establish long term healthy habits. The greatest criticism of VLCDs in current clinical practice is that they may not establish long term healthy eating habits, although a review by NICE reported that a 5% reduction in body weight is maintained over two years in those following a VLCD plan (NICE, 2006).

The reason for this in the control group was two-fold. Firstly, we wanted to compare the long term effects from IDAP, which restricts energy intake at the time of quitting, with the 'control' group which restricted it after they quit. There is preliminary evidence to suggest that the latter may be more successful than the former, although this has not been tested with an adequately powered trial (Spring, 2004).

Secondly, because the control was unblinded we hoped that by providing IDAP after quitting this group would not feel 'short changed' and abandon their quit attempt prematurely. We investigated this quantitatively investigating the association between belief in trial arm and attrition.

We also asked participants to tell us of their experience in each of the DeMiST trial arms, we did this qualitatively using semi-structured interviews. We chose this method above others for several reasons. Firstly we considered whether a satisfaction survey or an acceptability scale would suffice, this has traditionally been used to measure acceptability of interventions. However, the argument to use more insightful methods is strong (Finn and Sladczek, 2001), these offer the opportunity to discover more than might be predicted and included in preconceived surveys. In other words qualitative research it allows us to develop inductive rather than deductive reasoning. It allows us to embrace subjectivity of the participant and the interviewer (Swift and Tischler, 2010). What this meant in our research is that we were able to take a relativist ontological position, expecting different participants to experience the same trial arm differently. We considered that there may not be one

real experience of trial arm, but rather many which are perceived differently; with perceptions and opinions having been shaped by an individual's life experiences. We were also able to take a reflexive epistemological approach and considering how our own background and interest may have steered the conversation in one particular direction or another.

3.2. Methods

3.2.1. Participants

Overweight (BMI>25Kg/m^2) smokers listed on the databases of participating general practices were invited to take part by a letter from their General Practitioner (GP) (Appendix 7). All participants were from practices in Birmingham East and North Primary Care Trust (PCT) and Worcestershire PCT, in the UK (see Appendix 8, Appendix 9, Appendix 10 for practice recruitment documentation).

Interested participants telephoned the trial office at The University of Birmingham for further information; they provided verbal consent to initial telephone screening for eligibility (Appendix 11, Appendix 12, Appendix 13). If considered eligible they were given an appointment with a trial nurse for full screening where they were invited to give informed consent for participation (Appendix 14, Appendix 15). The trial office sent out participant information sheets (Appendix 16) so that they were received at least 24 hours before their first appointment. The clinics were run at local GP practices. Daytime appointments were offered from 8.30am until 7pm.

3.2.1.1. *Inclusion criteria*

Participants had to:

- Be aged over 18 years
- Smoke cigarettes daily, and have an exhaled CO of at least 10ppm at least 15 minutes after last smoking
- Have a BMI of at least 25kg/m^2
- Be willing to be randomised to any of the three arms and willing and able to comply with the intervention and all study procedures.

We recruited only those with a BMI greater than or equal to 25 for the following reasons: 1) the rate of weight loss on a VLCD is approximately 2kg/week so anyone entering the trial would need to be able to lose 10kg. For example, a woman 1.64m tall weighing 68kg with a BMI of 25.2 could potentially lose 10kg and reach a healthy BMI of 21.6kg/m^2. VLCDs have been shown to be as safe in those with a BMI > 25kg/m^2 as in those with a BMI>30kg/m^2 (RTSC, 2007). 2) Research shows that those who are overweight or obese are likely to gain more weight than healthy weight smokers and so they are an appropriate target for weight gain prevention (Chapter two, Lycett et al., 2011a). 3) The smoking population has a lower mean BMI than the non-smoking population (Klesges et al., 1989) so we could potentially struggle to recruit only those with a BMI >30kg/m^2.

3.2.1.2. *Exclusion criteria*

Individuals could not take part if they:

- Had any of the absolute or relative contraindications to VLCD use. These include situations in which rapid weight loss would be unsafe: pregnancy, breastfeeding, myocardial infarction/unstable angina/acute coronary syndrome in the past 6 months, cerebrovascular accident /transient ischaemic attack /stroke in the past 3 months, major surgery in the last 3 months, severe cardiac arrhythmias, severe hepatic impairment, severe renal impairment (i.e. GFR ≤ 29mls/min), active carcinoma, untreated gallstones, past history of anorexia nervosa or bulimia nervosa, type 1 diabetes, those aged over 70 years with a BMI<30kg/m^2. A large energy deficit alters metabolic rate and so anyone with unstable thyroid function was also excluded. Sudden weight loss may cause fainting or precipitate gout in those who are susceptible so those with regular blackouts or fainting, and untreated gout were also excluded. The VLCD formula is made from milk so is unsuitable for anyone with a milk allergy or intolerance.
- Had uncontrolled hypertension and type two diabetes treated with medication. Although these are not contraindications to the VLCD they are excluded as adjusting the medications in these conditions would require specialist advice beyond the scope of the research nurses in this trial (diet controlled type two diabetics were included).
- Were on oral anticoagulants, digoxin, phenytoin and lithium due to likelihood of increased drug absorption if on a VLCD. Specialist advice beyond the

scope of our research nurses is needed to reduce and monitor these medications.

- Were on diuretics for diuresis were excluded as a VLCD can potentiate diuresis and increase the risk of hypokalaemia. Those on low dose diuretics for treatment of hypertension were not excluded as the risk of hypokalaemic complications on these are low (Franse et al., 2000, Peters et al.,1989). The effects of combining a VLCD with low dose thiazides has not been well studied and may be unpredictable therefore serum potassium was to be monitored weekly and the VLCD discontinued if levels fell below 3.1mmol/l. (Appendix 17 contains the full list of excluded medications and clinical protocol of this developed for study nurses).
- Had previous severe adverse reaction to nicotine patches (which precluded further use).
- Had active phaeocromocytoma as this combined with use of NRT may increase the risk of hypertension and tachycardia.
- Were concurrently using smoking cessation medication i.e. (NRT), vareniciline or bupropion or medication (e.g. nortriptyline) that is known to help smokers quit.
- Were taking weight loss medication e.g. orlistat, sibutramine.
- Were suspected of abuse of alcohol or other drugs as this might confound our measure of cravings.
- Were using smokeless tobacco
- Were concurrently participating in other therapeutic clinical trials.

3.2.1.3. *Removal of participants from therapy*

Participants would discontinue therapy if:

- A contraindication to treatment became apparent.
- An adverse event occurred making it inadvisable to continue treatment.
- Serum potassium fell below 3.1mmol/l in those taking thiazides, the VLCD would be discontinued.
- The person ceased to continue to quit smoking and wished also to abandon the weight management programme. If a person failed to stop smoking they could continue with the dietary treatment intervention, likewise if a person abandoned the dietary treatment they could continue with their quit attempt. Keeping participants like this in the trial would help us to explore the reasons why a treatment was abandoned. We will find out whether abandonment of one treatment ultimately leads to abandonment of both and how these participants have decided to tackle their smoking or weight.

3.2.2. **Dietary Interventions**

Week 0 was quit week, negatively numbered weeks were the weeks before quit week and positively numbered weeks were the weeks after quit week. Week -3 was baseline, three weeks before quit week. Participants were seen and briefed at baseline and a quit day was set for three weeks time. Participants were randomised into the dietary interventions, VLCD, IDAP and Control (SBS), one week prior to quitting (week -1). Each intervention contained two treatment stages. Stage 1 lasted

from week -1 to week +4 and treatment stage 2 lasted from week +4 to week +12 (Figure 6).

3.2.2.1. *Treatment Stage 1 – VLCD*

The VLCD formula we used was called Lipotrim. This was provided for the study at cost price from the manufacturers, Howard Foundation Research Ltd. It was purchased by participating Primary Care Trusts (PCTs) and provided free to participants (Appendix 18). Participants were instructed to take 2-3 shakes each day and drink a minimum of 4 pints of water, but not in excess of 4 litres. Black tea and black coffee could be drunk but no other food or drink could be consumed, as any additional carbohydrate or citric acid may suppress ketone production (Appendix 19).

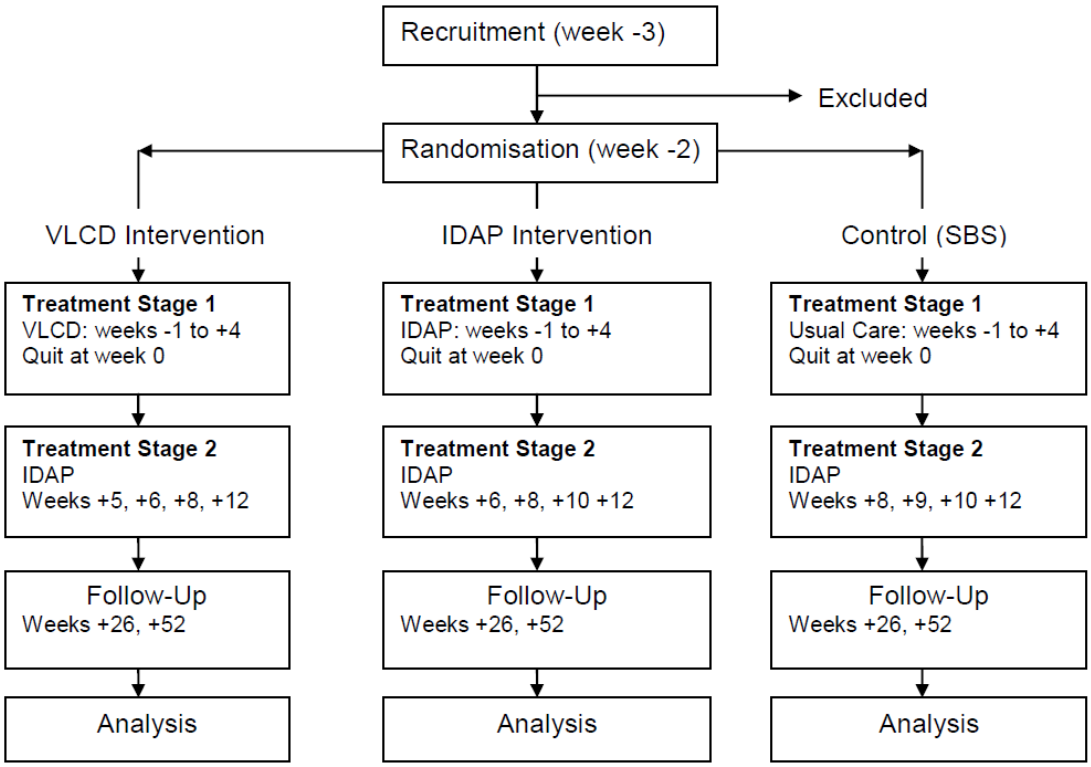


Figure 6. Treatment stages for DeMiST

The female formula was 425kcal/day and the male formula was 559kcal/day, it contained all essential nutrients and complied with the EU codex standard for VLCDs (RTSC, 2002). This diet began one week before quitting, by which time the dieter would be in ketosis. The diet continued during the first four weeks after quitting when nicotine withdrawal symptoms would be at their worst. The rationale for this is that dieters should be comfortably in ketosis when they quit and experience acute nicotine withdrawal. It takes approximately 3 to 4 days to get into ketosis on a VLCD, during which time the side effects of a VLCD are most apparent. After these first four days individuals usually gain a feeling of wellbeing that accompanies ketosis and so

we wanted to coincide this period of ketosis exactly with the time of quitting to maximise any attenuating effects it may have on urges to smoke.

Every effort was made to get the participants to adhere to the VLCD by using behavioural change techniques as defined by Abraham and Michie in 2008 (Appendix 20). These included an explanation of the role of ketones and the necessity for strict adherence in order to remain in a ketotic state. (Providing instruction and providing information on consequences of action are behavioural change techniques 2 and 8.) Ketosis is usually achieved by the third or fourth day on the diet and so participants were advised that they would feel better after this time. Encouragement (technique 6) and prompting of self-encouragement (technique 22) was used e.g. suggestions for self talk: 'today was difficult but if I keep going I will feel better in 2 days', 'if I can stick this out, I can lose weight and stop smoking in time for my birthday'. Support to identify and overcome barriers to adherence (technique 5) was also given.

3.2.2.2. *Treatment Stage 1 – Individual Dietary and Activity Planning (IDAP)*

This contains dietary, activity and behavioural elements. Assessment of current behaviours and food choices was made by using the Health Choice Index (HCI) (the development and validity testing of the HCI is discussed in chapter seven). This is a multiple choice questionnaire designed to get participants to score their food choices, weekly food frequency, eating behaviours and activity. From this, both the participant

and the healthcare professional were able to identify areas for improvement and agreed goals for progress. Typically three goals were decided, one focusing on food choice e.g. I will buy skimmed milk instead of full fat milk; one on eating behaviour e.g. 'I will prepare a packed lunch the night before to take to work so that I don't miss lunch'. And one activity focused goal e.g. 'I will park the car a block away from work and take a brisk walk at lunchtime so that I fit in three ten minute exercise breaks during my working day. Prompting specific goal setting is technique 10 in the behavioural change taxonomy. These goals were reviewed regularly and adjusted as necessary (behaviour change technique 11). Helping the participant to identify and overcome barriers to achieving their goals, discussing time management to incorporate these changes into their daily lives, helping them to plan relapse prevention strategies and general encouragement all formed part of this intervention (behavioural techniques 5, 26, 23 and 6 respectively).

As well as identification of specific goals instructions were given (technique 8) for following a moderate calorie restricted diet plan tailored to the individual's energy requirements. This provided a structure to help consolidate the goals identified and ensure that the participants had the right tools to achieve a sufficient energy deficit for weight control.

The energy prescription used in previous studies to prevent weight gain on smoking cessation has varied. Pirie et al. advised generally to reduce energy intake by 150 to 300kcal/day (which was considered to equate to metabolic slowing upon nicotine

withdrawal, the level of which depended on number of cigarettes smoked) (Pirie et al., 1992). Perkins et al. used a 500kcal deficit tailored to individual energy requirements (Perkins et al., 2001). Hall used a 500kcal deficit tailored to individual requirements should weight increase by 1kg (Hall, 1992). Spring used a 150kcal deficit based on individual food diaries (Spring et al., 2004). Danielsson used a 1600kcal diet compared with a very low calorie diet (419kcal/day) (Danielsson et al., 1999).

We decided to advise an approximate energy deficit of 600kcal, based on individual requirements. This is recommended by NICE for weight loss of 0.5kg/week (NICE, 2006). This is sufficient to counter the mean rate of post-cessation weight gain and promote modest weight loss which is desirable for our population with a BMI>25kg/m^2. Dietetic consensus considers a usual maximum energy prescription of 1800kcal. Anecdotally advising above this appears to be ineffective at achieving weight loss, this may be due to people misunderstanding the volumes of food recommended for larger portion sizes.

To calculate energy prescription in individuals we have assumed all participants will have a physical activity level (PAL) of 1.4, which is consistent with a sedentary occupation and leisure activities. The PAL is the factor by which BMR is multiplied to give an estimate of total energy expenditure. For simplicity in clinical practice we wrote dietary plans that equate to energy intakes of 1200kcal, 1500kcal or 1800kcal. An individual is allocated the closest energy prescription to their BMR (as calculated

by the Tanita body composition analyser) (Appendix 21). Calculating total energy requirement from a PAL of 1.4 and BMRs of 1200kcal, 1500kcal and 1800kcal, shows energy requirement is an increase of 500kcal-700kcal above BMR. This means we can approximately achieve the 600kcal deficit by using BMR alone for the prescription of energy. The energy level advised was translated into the appropriate number of portions from each of the food groups: complex carbohydrates, fruit and vegetables, meat, fish and alternatives, dairy foods, sugar and fatty foods. The proportion of food coming from these food groups make up a healthy diet with 15-30% of energy from fat, 10-15% of energy from protein, 55-75% of energy from carbohydrate and 0-5% energy from alcohol. Therefore, the diet is low in fat and sugary foods which studies have shown significantly increase in the diets of smokers when they quit (Perkins et al., 1990, Rodin, 1987, French et al., 1996, Hall et al., 1989). The dietary plan was a 'pick and choose' format, where individuals choose from a list of items within different food groups at each meal. The food portions were defined in American cup sizes and participants were given measuring cups to measure out their portions (Appendix 22 for example).

3.2.2.3. *Treatment Stage 1* – Control (Step by Step (SBS))

The control group received healthy eating advice when participants mentioned weight concern. This is standard in smoking cessation interventions. Advice was given not to 'diet' but instead to avoid hunger by eating healthy, low fat foods. This is because it is thought that hunger may lead to urges to smoke, and may make relapse more likely. Tips for avoiding hunger include:

- Regular meals, including breakfast (which is often missed in smokers (Nishiyama et al., 2009)
- Handy, healthy snacks e.g. fruit or chopped vegetables (carrot, celery sticks)
- Drink plenty of water, particularly before meals, this helps fill the stomach and satisfy 'oral cravings'.

There is evidence that glucose tablets satiate urges to smoke within minutes, so these can be used (McRobbie & Hajek, 2004). Avoidance of total alcohol for the immediate post-cessation period was advised. This was to avoid lapsing due to disinhibition and the 'cue' which alcohol provides, rather than to control weight. Participants were advised to increase daily activity, e.g. including a 30 minute walk in their day. Advice in the control group was given as general instruction and general encouragement (behavioural techniques 6 and 8) but individual goal setting and energy prescription was not included.

3.2.3.1. *Treatment Stage 2 - VLCD*

This spaned from week +4 to +12 and included four visits (Figure 6). The same number of visits has been included in each of the intervention arms so that number of consultations with a nurse was not a confounder.

The VLCD was discontinued at week +4, participants were weaned back onto food. This weaning took one week. During this week the Lipotrim formula was reduced and replaced by low fat meals with increasing amounts of carbohydrate until healthy

proportions were achieved (Appendix 23). Gradual reintroduction of carbohydrate is necessary to avoid rapid replenishing and storage of muscle glycogen, which could result in a rapid increase of body water weight (up to 5kg over the week). At week +5 lifestyle goals were set and energy prescription was given as described in treatment stage one of IDAP. Behavioural support continued at reduced frequency to week +12. The reason for this second stage of treatment is to cultivate the development of long term healthy habits as explained in the introduction to this chapter (section 3.1.4).

3.2.3.2. *Treatment Stage 2 – Individually Tailored Diet and Activity Plan (IDAP)*

This behavioural support continued to week +12 and visits became less frequent.

3.2.3.3. *Treatment Stage 2 – Control (Step by Step (SBS))*

Participants in the control arm, received IDAP from week +8 to week +12. This allowed them time to become established quitters before they embarked on weight control.

3.2.3. Smoking Cessation Interventions for all Participants

All participants had identical treatment to stop smoking. This was the treatment which is available on the NHS. It is withdrawal orientated such that behavioural strategies (examples in Appendix 24) and nicotine replacement are given to relieve withdrawal

symptoms. This has been shown to be an effective model for stopping smoking (Hajek, 2006). Individuals are seen over seven consecutive weeks, weeks -3 and -2 prepare them for quitting, they quit at week 0, weeks +1, +2, +3 and +4 support them during the first four weeks after quitting when withdrawal symptoms are at their strongest. The sessions incorporate a variety of behavioural change techniques:

- pre-quit sessions prompt intent formation (technique 4) by setting a quit date,
- they prompt barrier identification (technique 5)
- and relapse prevention (technique 23) when participants identify times or places when it will be particular hard for them to resist smoking, they discuss a strategy to help them to deal with these circumstances; for example, changing routine so the usual smoking cues are removed.

Quit week and the weeks that follow provide instruction (technique 8) in the use of nicotine replacement, review of and further planning of strategies (technique 11) to deal with withdrawal symptoms and general encouragement (technique 6). Self-talk (technique 22) is encouraged such that participants are asked to see and describe themselves as a 'non-smoker' and to frequently bring to mind the benefits of quitting that they are looking forward to.

3.2.4. Nicotine replacement therapy (NRT)

Nicorette 25mg transdermal 16 hour patches were provided for 8 weeks followed by a 15mg patch and a 10mg patch each for 2 weeks. Patches were supplied free of charge by McNeil Products Ltd. Other forms of NRT, such as gum or nasal spray or a combination of NRT was not used to avoid the possibility that the amount of NRT

taken would differ by arm. This could confound effects of hunger or ketosis on urges to smoke that we are trying to discover. We used a nicotine patch as it delivers a consistent amount of nicotine to avoid this confounding. As no other NRT products could be used in combination to help with acute cravings we used the 16 hour, 25mg patch which has been shown to yield better abstinence than other available patches (Tonnesen et al., 1999).

3.2.5. Training and supervision

Treatment was provided by trained practice nurses. Practice nurses were trained by NHS stop smoking services (2 days), a research nurse, a general practitioner (GP) (0.5 days), and a registered dietitian (1.5 days). Nurses were given the clinical protocol to read before training sessions (Appendix 25). Training included explanation of dietetic and behavioural interventions and practicing the interventions on each other. The clinical protocol was clarified where needed and questions answered. The aim of the training was to equip the nurses so that, once they had completed it, they felt confident to deliver the interventions according to the clinical protocol.

After the training, 'hands on' supervision was available for the first few clinics. Immediate telephone access to the dietitian and GP were available for all clinical queries throughout the rest of the trial.

Medical history and any medication used or altered during the trial was monitored. Any significant changes in clinical condition of individual participants, as measured on a weekly basis, was discussed with the supervising GP and action taken, e.g. clinically significant fall in blood pressure in participants on the VLCD taking anti-hypertensives would require adjustment of anti-hypertensive medication (Appendix 26). The participant's own GP was kept informed.

3.2.6. Fidelity checking and monitoring

Fidelity to the clinical protocol and record keeping was assessed and monitored against the clinical protocol by the principal investigator every few months; consultations were audiotaped for this purpose. Any deviations were recorded, discussed and corrected either immediately or at following clinics. The trial was potentially subject to audit by the appropriate regulatory authorities and therefore participants were asked to consent to allow their records to be viewed.

3.3. Objectives

3.3.1. Primary objectives

To investigate the feasibility of running this three-armed dietary intervention study as part of the NHS stop smoking services using primary care nurses. This included the feasibility of measuring and monitoring of physiological and biochemical risk factors for cardiovascular disease, diabetes and chronic obstructive pulmonary disease (COPD). It explored the acceptability of the interventions to participants.

3.3.2. Secondary objectives

To investigate whether smoking cessation advice and a nicotine patch in combination with: a very low calorie diet (VLCD), or individually tailored dietary planning (IDAP), or usual support affected urges to smoke, through hunger or ketosis in overweight smokers trying to quit.

3.3.3. Tertiary objectives

To investigate the extent to which changes in smoking status, diet and activity achieved during the treatment stages were maintained at the end of treatment and at six and 12 months in each of the intervention arms. To investigate associations between hunger, abstinence, early and late weight gain.

3.4. Outcome Measures

3.4.1. Acceptability

Participant acceptability was measured qualitatively by semi-structured interviewing and quantitatively by response and attrition rates as described below:

- Semi-structured telephone interviews were conducted after the participant had completed treatment or dropped out of the programme. Participants who were happy to do so gave their consent to this at the start of the trial. To help them remember their thoughts and feelings ‘of the moment’ they were given the

questions they would be asked at the start of the trial, with space to jot down notes, during the trial. We aimed to interview participants until theoretical saturation of responses was reached. We aimed to purposively sample interviewees to encompass the full range of attrition characteristics, for example, those who completed the trial, and those who dropped out of quitting, dieting or both in each of the three trial arms. Interviews were audio recorded and transcribed verbatim. Participants were asked what they found helpful and unhelpful and their reasons for dropping out.

- Rates of response to participant invitation letters and posters.
- Rates of recruitment at telephone screening, at first consultation.
- Rates of drop out before randomisation.
- Rates of drop out after randomisation in each treatment arm.
- Rates of attendance at each session.
- Rates of participant adherence to treatment.
- Quality of life measure, a scale on which the participant can score general life satisfaction and well being at baseline, weeks +4, and +12.

3.4.2. Feasibility

Feasibility of running the trial within the primary care practice was measured qualitatively as described below:

- A focus group of participating nurses to investigate experiences of delivering intervention, e.g. how easy was it to carry out the interventions, was training

sufficient, was consultation time adequate, what difficulties were encountered taking the trial measurements.

- Principal investigator's reflections on their experiences of primary care involvement e.g. ease of GP practice recruitment, willingness for PCTs to participant, obstacles encountered.

3.4.3. Measurement of urges to smoke and hunger,

Degree of smoking addiction was measured at baseline using the Fagerstrom Score (Fagerstrom & Schneider, 1999). Urge to smoke was measured by the Mood & Physical Symptoms Combined Scale (MPSS-C) (West & Hajek, 2004). Hunger and food craving was measured by the Hunger and food Craving (HCS) score (discussed further in chapter five). MPSS-C and HCS were recorded daily in a diary over the first four weeks of quitting and weekly thereafter. The primary outcomes of interest were over the first 24 hours and the first week of quitting; this is where the largest effects are likely to be seen as withdrawal symptoms are at their peak during this time. Comparisons between measures were made for all those who continued in their quit attempt until they decided to abandon quitting, and adjusted for those who lapsed, were point prevalent abstinent at 24 hours, 7 days or continuously abstinent at 4 weeks. Although it is standard practice in smoking trials to primarily analyse those who are abstinent, our interest was in the effects on cravings and we cannot assume that those who did not achieve abstinence did not experience cravings as they tried to do so. Piasecki showed that cravings were heightened in both smokers who were

attempting to quit and lapsed, as well as in smokers who succeeded in quitting. He found that more cigarettes, smoked on more occasions did reduce cravings (presumably as these have served to treat nicotine withdrawal acutely) but also that a few cigarettes increased cravings (100 vs 56 cigarettes $p<0.001$) (Piasecki, 2003). Perhaps this reflects a greater struggle to cope with cravings before a cigarette is finally smoked out of desperation.

3.4.4. Ketosis

The presence or absence of ketones was measured using ketostik test strips dipped into urine samples. This was done weekly during the first six weeks of dietary intervention, to check those in the VLCD were in ketosis throughout the five weeks and come out of ketosis during the re-feeding week. It was also measured during this time in IDAP and control arms to verify the absence of ketosis in these groups or identify any participants which might be self-imposing excessive dietary restriction, (unless undiagnosed diabetes presented itself).

3.4.5. Measurement of smoking status

Twenty-four hour point prevalence abstinence was measured by participants achieving 24 consecutive hours of abstinence that was verified by exhaled CO<10ppm. Seven day point prevalence abstinence was defined as those reporting not smoking over the last seven days, and this was verified by exhaled CO < 10ppm. Participants achieving one, six and 12 month abstinence were to be defined using the Russell Standard which states that no more than five cigarettes have been

smoked since week +2, this was verified by CO<10ppm at each consultation (West et al., 2005). Participants who have not achieved abstinence but were still attempting to quit were termed ‘lapsed’. Smokers who abandoned their quit attempt, such that it was no longer their intention to quit, were considered ‘relapsed’.

3.4.6. Measurement of Disease Risk Factors

These were measured as described below. The schedule of measurements is contained in Table 17 .

- Weekly weight, waist to hip ratio, body composition and blood pressure.
- FEV1 and FVC post 200mg salbutamol as is recommended by the American Thoracic Society 2005 standards for measuring lung function (Miller et al., 2005) at baseline, three, six and 12 months.
- Fasting blood glucose, Total cholesterol (TC), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, TC/HDL ratio, triglycerides, haemoglobin, white blood cell count, platelet count, mean cell volume and c-reactive protein (CRP).

Full details of how these measurements were taken are referred to in the trial clinical protocol (Appendix 25) as standard operating procedures (SOPs) and work instructions (WIs) (e.g. Appendix 26). The nurses were trained in these procedures so that they are carried out consistently at each trial site. The nurses were assessed in practice against these SOPs and WIs, every couple of months, by the principal investigator.

3.4.7. Measurement of diet and activity

Food choices, eating behaviour and activity were measured at baseline, end of treatment, 6 and 12 months using the HCI. Validity between this simple, quick measure of diet quality as an assessment of nutrient intake was investigated by statistical analysis against an estimated seven day food intake diary which was also completed at baseline (discussed further in chapter five). Participants were encouraged to weigh their food when completing the seven day food diary, but portion sizes could also be estimated using household measures or natural food units. As discussed in the introduction to this chapter (section 3.1.3) despite underreporting weighed diaries are considered the most accurate way to record dietary intake and only an estimated food diary comes close to this level of accuracy (Bingham et al., 1995, Bingham et al., 1997). Diaries which reported less than 1.2 x BMR energy intake or were incomplete were discounted. Where necessary the Goldberg cut-off was used to evaluate the mean population bias in reported energy intake (Black, 2000). The seven day diaries also estimated physical activity levels using the method which determined dietary references values for energy in the UK (DRV, 1991).

Those on a VLCD who did not produce ketones or achieve the expected 2kg weekly weight loss were considered non adherent. We expected any weight gain in the IDAP group to be a result of poor adherence, although weight maintenance was acceptable in this group.

3.4.8. Confidence in trial arm

Due to the unblinded nature of the trial, participants were asked prior to randomisation to rate their confidence of each treatment arm being successful. From this we were able to determine whether expectation of success in treatment allocation was associated with attrition rates. We planned to measure this again at weeks +4 and +12 to see if this changed over time.

3.5. Sample Size

Acceptability and feasibility was measured qualitatively through interviews and by recording of recruitment and attendance rates. These outcomes were descriptive and not analysed using statistical tests and so a power calculation for them was inappropriate.

Instead, we based our sample size on the secondary objective to identify whether dietary interventions affect cravings for cigarettes. In the trial by Danielsson (Danielsson et al., 1999) the difference in cravings for cigarettes at week +2 was mean 1.6 in the control and mean 1.1 in the VLCD group with a standard deviation of 0.7.

Treatment week	-2	-1	0	1	2	3	4	5-7	8 - 10		12	26	52
Baseline Questionnaire (with Fagerstrom Score)		√											
Seven day food diary	√												
Weight		√	√	√	√	√	√	√	√	√	√	√	√
Waist/Hip ratio		√	√	√	√	√	√	√	√	√	√	√	√
Blood Pressure		√	√	√	√	√	√	√	√	√	√	√	√
Smoking Status		√	√	√	√	√	√	√	√	√	√	√	√
Urinary ketones		√	√	√	√	√	√						
Fasting Blood test	√										√	√	√
Lung function	√										√	√	√
Russell Standard									√		√	√	√
QOL measure		√					√				√		
Confidence in trial arm	√						√				√		
Body composition		√	√	√	√	√	√	√	√	√	√	√	√
Daily Diaries (MPSS & HCS)		√	√	√	√	√	√						
Weekly Diaries (MPSS & HCS)								√	√	√	√	√	√
HCI		√									√	√	√

Table 17. Schedule of measurements during DEMIST

The control in the Danielsson trial was a standard (not individualised) 1600kcal diet, a moderate energy restriction, likely to lead to increased hunger. We were looking to detect a difference of the same magnitude between our hungry (IDAP) and not hungry (control) or hunger suppressed (VLCD) groups. Using Epicalc with 80% power and a type one error rate of 5% we needed 30 participants in each group and 90 in total to detect a significant difference between them. For sufficient power to detect a difference in an abstinent subgroup, assuming a 60% abstinent rate in the first few weeks, we aimed to recruit 42 in each group.

Such a trial would be large enough to differentiate between dietary changes that reflect a poor to a healthy diet using a dietary index, this is based on the figures by Freisling et al. in 2009 who validated a food frequency index using values of <32 and >39 for a poor and very good diet respectively. With a standard deviation of 5.7, 10 people were needed in each arm of our trial to detect a similar difference.

Running a larger trial to identify long term effects on abstinence and weight was premature at this stage, although we carried out all the measurements that would be needed in such a trial to assess feasibility.

3.6. **Randomisation**

Randomisation was computer generated by an independent statistician within the Primary Care Clinical Research and Trials Unit (PCCRTU) using random permuted blocks of length 6, stratified by practice. The numbers were entered into the trial database by an independent computer programmer within the trials unit. The database concealed randomisation until after participants were screened and entered into the trial. At week -3 the nurses clicked on the randomisation tab in the database and this revealed the arm to which the participant was allocated. The database was set up so that the randomisation 'tab' would not work until all data from week -2 was complete. Therefore, it was impossible for anyone to see treatment allocation beforehand. This greatly minimised any risk of the trial randomisation being undermined.

3.7. **Analysis and statistical methods**

Semi-structured interview and focus group transcripts were coded according to content. Common themes regarding acceptability and feasibility were identified.

Quantitative measures of acceptability were presented as descriptive statistics.

Outcomes (including smoking abstinence, weight, dietary change) between the three arms of the study were compared using statistical tests on adequately powered measures. Descriptive statistics (mean, SD and 95% CI) were presented

on underpowered measures. Analysis of completer data allowed us to determine efficacy of interventions if they were taken as planned. Intention to treat analysis allowed us to determine pragmatic effects of these interventions if they are used in clinical practice.

Multilevel modelling based on the Piasecki model of cigarette withdrawal (Piasecki et al., 2003) was used to investigate the effects of the dietary interventions on urges to smoke during the first four weeks of quitting. We investigated whether these effects were mediated by hunger and food craving score (HCS) and ketosis. We adjusted for confounding variables e.g. active treatment for depression. Analysis was carried out on all those who continued to try to quit regardless of lapses to smoking and this was adjusted for in the model as described above.

Significance was set at the 5% level, 95% confidence intervals and exact p values were given where appropriate.

Analysis of data from treatment stage 1 was undertaken once every participant has completed this stage. Analysis from treatment stage 2 and follow-up at 6 months and one year was planned to be undertaken once participants had gone through each of these stages.

Trajectory of change in outcomes, e.g. weight change over time, was investigated using multi-level modelling and the effects of trial arm and smoking status were tested.

3.7.1. Data Validation

Data cleaning took place by a series of logical checks on the electronic data. (For example, a person cannot be recorded as prolonged abstinent smoker at six months if they were not in such a state at 8 weeks). Discrepant records were checked with the source documents and the database amended as necessary.

3.8. Trial schedule

One Doctoral researcher was principal investigator and supervising dietitian. Part-time support was provided by practice research nurses and research administrators.

Recruiting was planned to continue over a period of one year until sufficient participants were treated in each trial arm. Follow up took place as described and it was estimated that the trial would be complete two years from the start.

3.9. Definition of end of trial

The end of the trial was defined as the final 12 month follow-up where the last measurement was taken from the last participant and the last participant undergoing the trial was debriefed.

3.10. Value of results

The results from this study were to provide new information about dieting during smoking cessation. Their aim was to inform the design of a multi-component intervention that tackles both smoking cessation and its related weight gain in a way which can be rolled out into the NHS.

3.11. Assessment of safety

Potential participants' safety was ensured by screening for eligibility using a structured form completed by the trial nurses. This recorded evidence of eligibility and that the person did not have any exclusion criteria. In addition, the nurses took a general medical and drug history to assess for other complicating diseases. Any queries remaining as a result of this process were resolved by discussion between the trial nurse, chief investigator and the relevant physicians providing routine medical care, usually the participant's GP. Such concerns are unusual but not rare. Typically, they arise from a participant's hazy knowledge or understanding of their past medical history and are usually readily resolved. No blood or further medical testing was necessary to ensure safety.

3.11.1. **VLCDs**

Very low calorie diets are a recognised treatment for obesity. They form part of the NICE (2006) guidelines for the management of adult obesity and are advised for up to three months of continuous use in people with a BMI>30. We used it for 5 weeks only in people with a BMI>25. Weekly monitoring of weight meant that if BMI fell below a healthy level treatment was be discontinued. VLCDs have been used safely for many years including in people with a BMI between 25 and 30 (RTSG, 2002). Since 1987 they have been subject to the regulations of the Committee on Medical Aspects of Food (COMA, 1987). This is an extensively researched evidence based document detailing the formulation of VLCDs to ensure safety. The product used in this study complied with these standards. Thus, there was every reason to expect that treatment in this trial was safe.

Participants were warned about the side-effects of VLCDs and could contact the trial team to discuss any concerns. To this end, all participants were given a credit-card-sized card with the trial team's contact details, this allowed participants to receive advice on the VLCD or report perceived serious adverse effects and receive advice as required. They were asked to carry this card with them at all times so that it could be used to notify medical personnel of a participant's treatment (and the likely presence of urinary ketones) and trial involvement in case of emergency. Participants recorded the occurrence of side-effects of VLCDs as specified by completing a checklist. The checklist was given to the trial nurse who enquired about recorded adverse events, to determine the severity of any adverse event and ensure that appropriate advice was given for its management (e.g.

drinking appropriate amounts of water to treat symptoms of mild dehydration.) Minor adverse reactions were monitored and managed in this way. For each known side effect listed in the checklist, the trial nurse had a definition of clinical severity. Any side effect that was classified as moderate or severe was reported to and discussed with the principal investigator. A decision on stopping therapy was made with the participant, attending nurse, principal investigator and other relevant parties as appropriate (Appendix 27).

3.11.2. Dietary and Lifestyle Advice

Healthy dietary and lifestyle advice was individually tailored to create a mild energy deficit and gentle increase in activity. Appropriately trained nurses gave this advice. It is usual practice and considered very safe. In the unlikely event of side effects participants could contact the trial team to discuss any concerns. To this end, all participants were given a credit-card-sized card with the trial team's contact details to allow participants to report perceived serious adverse effects and receive advice as required.

3.11.3. NRT Patches

NRT has been investigated in several hundred previous clinical trials and is widely prescribed worldwide and subject to safety monitoring. It was replacing a product, nicotine, which the participants were already consuming and will have consumed for many years in cigarettes. Thus, there is every reason to expect that this treatment in this trial is safe. Participants were warned about the side-effects of

NRT and advised not to stop taking the medication without consulting with the trial team or an NHS professional if the trial team were unavailable. Participants recorded the occurrence of side-effects of medication as specified on the summary of product characteristics (SPC) for all relevant NRT preparations, by completing a checklist. The checklist was given to the trial nurse who enquired about recorded adverse events, to determine the severity of any adverse event and ensure that appropriate advice was given for its management (such as rotating the patch site or use of emollients for skin reactions). Minor adverse reactions were monitored and managed in this way. For each known side effect listed in the SPC, the trial nurse had a definition of clinical severity (Appendix 28). For example, a mild skin site reaction to the patch was defined as burning sensation that did not interfere with normal activities, redness or swelling at the site of application, or mild blistering. Any reaction beyond that was classified as potentially moderate or severe and was reported to and discussed with the principal investigator. A decision on stopping therapy was then made with the participant, attending nurse, principal investigator, and other relevant parties as appropriate. Nicotine has a short half-life (2 hours), meaning that the blood concentration does not build up during the course of treatment so that new side-effects were not expected after the first few weeks. In addition, reactions to it relate to local use, such as skin discomfort from patches and people become accustomed to the side-effects after a short time of using the preparation. The advice given depended upon the severity of the reported reaction and those with moderate reactions were invited to an ad hoc consultation.

The SPCs for the relevant NRT products contain no warnings about serious adverse reactions except rare allergic reactions, such as angioedema, and cardiac arrhythmias, occurring in less than 1/1000 users. Thus we expect no or very few suspected unexpected serious adverse reactions (SUSARs) in this trial.

3.11.4. Salbutamol

Salbutamol has been thoroughly investigated in clinical trials and is widely prescribed worldwide and subject to safety monitoring. Thus, there was every reason to expect that its use in this trial was safe. Common side effects to salbutamol are mild (e.g. headache, tremor) and rare with small doses; severe reaction is very rare. Any reaction tends to be immediate. Participants were warned about the side-effects of salbutamol and asked to give verbal consent to taking it. They took a small dose (200mcg) in the company of a nurse and were given a contact number should they experience any adverse events in the hours that followed. This was administered four times during the year, at baseline, 12 weeks, six months and one year. For each known side effect listed in the SPC, the trial nurse had a definition of clinical severity (Appendix 29). Any reaction beyond that was classified as potentially moderate or severe and was reported to and discussed with the principal investigator. If a person had side-effects potentially related to salbutamol then they were not given salbutamol at the next visit.

3.11.5. Reporting of adverse events

The long history of use in and outside of trials for NRT and salbutamol meant that SUSARs were unlikely. On the reverse of the trial card giving the contact number

for advice on side-effect management, there were instructions for reporting of serious adverse events (SAEs) (Appendix 30). Through direct contact from the participant or contact from their attending physician, we became aware of serious adverse events. When any member of the trial team became aware, they informed the principal investigator within 24 hours. The principal investigator assessed the seriousness, causality, expectedness and severity of the adverse effects. An immediate decision was made on the interim use of medication for that participant. If an event was judged severe, it was reported to the trial sponsor, who report the event to the research ethics committee (REC). Definitions of adverse events (AEs) are contained in Appendix 30.

Participants were asked weekly to report intercurrent illnesses and the response was recorded. If any of these intercurrent illnesses contra-indicated salbutamol, NRT, VLCD or healthy dietary advice, this was immediately reported to the principal investigator and a decision made about continued use.

3.12. Ethics and Research Governance

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of the International Conference on Harmonisation (ICH) - Good Clinical Practice (GCP) and run in accord with EU Clinical Trials Directive and all of the applicable regulatory requirements. The study protocol and other documentation was approved by South Birmingham Research Ethics Committee (Appendix 31), Birmingham and Black Country Comprehensive Local

Research Network and West Midlands South Comprehensive Local Research Network (example in Appendix 32). Protocol amendments were submitted to the REC for approval and the other bodies when necessary (example of approval in Appendix 33). We complied with ICH-GCP Guidelines over the reporting of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reaction SUSARs. In addition, we provided the REC with progress reports as well as a copy of the final study report.

3.13. Data management, protection and confidentiality

The trial was run as part of the portfolio of trials in the Primary Care Clinical Research and Trials Unit (PCCRTU), NIHR accredited trials unit number 33, in Primary Care Clinical Sciences at the University of Birmingham. The data management was run in accord with the standard operating procedures (SOPs), which are fully compliant with the Data Protection Act and ICH GCP. The trial was registered with the Data Protection Act website at the University of Birmingham. Participant identifiable data was shared only within the clinical team on a need-to-know basis to provide clinical care and ensure good and appropriate follow up. Participant identifiable data was shared with their general practitioner and approved auditors from the REC or NHS Research & Development (R&D) as was necessary. Otherwise, confidentiality was maintained and no one outside the trial team had access to either the case report forms (CRFs) (Appendix 34) or the database. The source documents for the trial were CRFs which were stored in a locked cabinet at the participating practice. The trial database was securely held

and maintained by the PCCRTU. On completion of the trial and data checking, the CRFs were transferred to Modern Records, a secure archiving facility at the University of Birmingham, where they are held for 15 years and then destroyed. The database was anonymised and a secure compact disk containing the link between ID number and participant identifiable information was stored in Modern Records.

4. FEASIBILITY AND ACCEPTABILITY OF THE DeMiST TRIAL

4.1. **Introduction**

The primary objective of DeMiST, as described in chapter three, was to investigate the feasibility of running a trial to investigate the most promising dietary interventions identified in a Cochrane review (Parsons et al., 2009) to prevent smoking cessation related weight gain. These were individual dietary and physical activity planning (IDAP) and a very low calorie diet (VLCD) which we compared with a control intervention of usual care; this was Stage 1 of the trial. Stage 2 included delivery of IDAP to both the control arm and the VLCD arm for reasons discussed in section 3.1.4.

The main reason for a feasibility trial was to prepare for a trial large enough to provide evidence of beneficial effects on weight and smoking abstinence in these interventions compared to usual care. No trial has yet compared all three options and no trial has examined the feasibility of these specialist interventions in nurse led clinics, typical of NHS stop smoking services. A commentator on the Danielsson trial of VLCD doubted that the intervention could be delivered in usual clinical settings (Jones K, 1999).

We measured the response and recruitment rates. We assessed the acceptability of each of these interventions to participants and investigated attrition rates and reasons behind these. We explored the feasibility of training nurses to deliver

these interventions in primary care clinics. For clarity we have dealt with each of these aspects of feasibility in three separate sections each with their own methods, results and conclusions. This chapter therefore meets objective four of the thesis: to report on the feasibility of running DeMiST, including discussion of recruitment rates and experiences of the participants (Chapter 4).

4.2. Response and recruitment rates

4.2.1. Methods

As described in chapter three, (section 3.4.1) we measured rates of response to participant invitation letters and posters, we measured rates of recruitment at telephone screening, and at first consultation. This included a count of drop out prior to and post randomisation in each trial arm, which reflected attendance rates at visits.

In an effort to improve our recruitment rates we amended our recruitment strategies in several ways. However, we had to consider the following limitations:

Location

We had to stay within Birmingham East and North (BEN) and Worcestershire Primary Care Trusts (PCTs) to run the trial as they had funded the excess treatment cost of the VLCD formula up front.

Timescale

We only had another six months in which to meet our recruitment target in order to complete the trial in time

Finance

We had only budgeted to run one training course for our research nurses.

4.2.1.1. *Recruitment improvement strategy 1*

Therefore, we first tried to increase recruitment within BEN PCT, as there was one of our trained nurses available to cover this. We needed to target more people from more general practices to boost our recruitment rates quickly. The general practice participating in the trial refused to allow our research nurse to see participants from other practices on their premises for insurance reasons. However, we were able to use a room at the PCT run health centre, and one of our trained nurses had spare capacity to work locally as a bank nurse here. We did not have the facilities to run routine blood tests at the PCT so we amended our protocol and obtained further ethical approval to use skin prick measures instead. We also amended our protocol to allow us to advertise more widely, which we did by placing flyers and adverts in local newspapers (Appendix 35). Flyers inside newspapers were distributed to 9000 homes and an advert in a newspaper went to another 2000 homes.

In addition to widening the geographical area for recruitment we also widened the inclusion criteria. We no longer excluded those who were unsuitable for a VLCD and we opened the trial to all smokers, regardless of BMI, this meant we were effectively running two trials, side by side. DeMiST 1, which used the original exclusion criteria, and randomised participants into three arms and DeMiST 2 which independently randomised participants into either the SBS or the IDAP arm. Although we would not increase recruitment into the VLCD arm by doing this, we

hoped to increase numbers in the other two arms sufficiently to meet the sample size to compare those two arms. Without the strict exclusion criteria, this trial was now suitable for most smokers regardless of their BMI, energy prescription protocols were amended to prevent weight gain without achieving weight loss in those with a BMI <25kg/m^2 (Appendix 36). Broadening the inclusion criteria made it more suitable to advertise the trial to the general public. We anticipated a large response and so fewer screening criteria also improved the ease of initial of telephone screening.

4.2.1.2. *Recruitment improvement strategy 2*

Our final attempt to boost recruitment was to adapt a method previously used in Nottingham. This had demonstrated recruitment into the NHS stop smoking service could be enhanced from 5% to 30% by first offering a telephone consultation with a stop smoking advisor (Murray et al. 2008). We amended our protocol to do this and sent out the first 100 letters containing a questionnaire, stamped addressed envelope and an offer of a consultation (Appendix 37).

4.2.2. **Results**

4.2.2.1. *Original recruitment strategy*

Three family practices in the West Midlands (Bromsgrove, Redditch and Sutton Coldfield) identified 1892 potential participants through electronic searching of their databases using search criteria of ‘current smoker’ and ‘BMI above 25kg/m^2

or BMI unrecorded' as per protocol. After the research nurses and general practitioners (GPs) checked these records for exclusion criteria, 68% were suitable and invited to participate in the trial. Of those unsuitable no specific reason was given by the practice in 44% of cases, although most of these were from one practice which reported significant difficulties searching their database. The other practices reported that 37% of participants were medically unfit to follow the VLCD or on medication that would require adjustment, beyond the scope of our research nurses (Figure 7).

It took nine months to negotiate with the PCTs, obtain NHS permission to run the trial at these sites. It took a further five months to recruit the three general practices and train our research nurses. Over the following six months these three practices yielded 32 respondents, of which 14 were randomised into the trial. Most of the other responders did not enter the trial because they dropped out without giving a reason or they were not willing to be randomised to the VLCD (Figure 7).

4.2.2.2. *Recruitment improvement strategy 1*

We had two responses (Figure 7) and one new recruit from advertising with flyers through the newspaper. The cost of advertising in this was £1000.

Widening our exclusion criteria allowed us to carry out a second more inclusive search of the general practice databases. However, after initial poor recruitment only one of our practices was willing to carry out a second search, we sent out 100

more letters and received one response. Therefore, overall 33 out of 1282 (2.6%) potential participants who received a letter (original recruitment strategy plus improvement strategy one) telephoned the research office. With

the addition of newspaper advertising we were able to bring the total of responders up to 35 (2.7%) (Figure 7).

4.2.2.3. *Recruitment improvement strategy 2*

We received two responses both of whom were unsuitable for recruitment as they had already stopped smoking.

At this point, it was apparent that we could no longer recruit our original target sample size within the timeframe of writing up this PhD, so we closed trial recruitment.

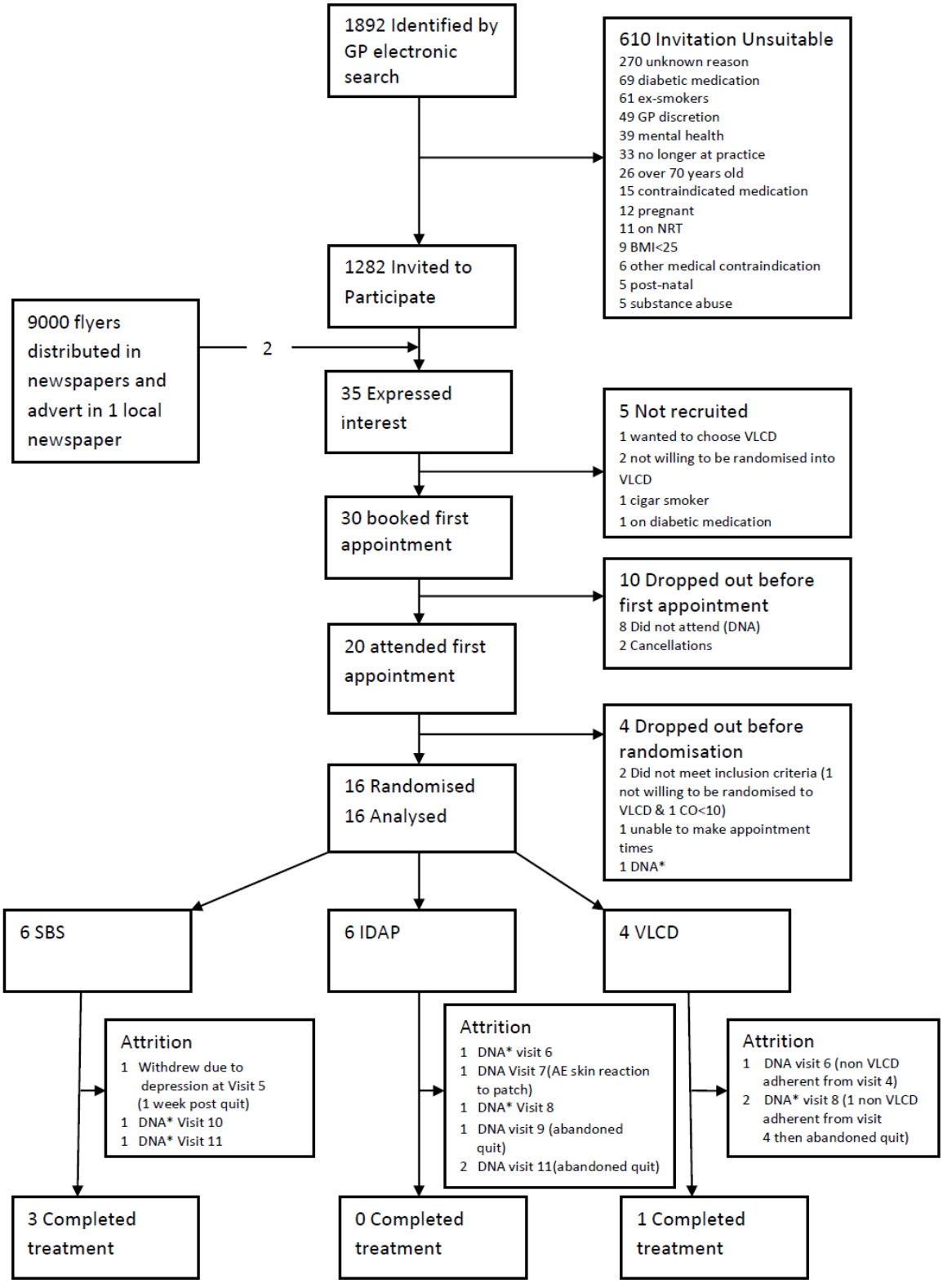


Figure 7. Flowchart of participants through demist from identification of potential participants to numbers who completed trial

4.2.3. Discussion

It took us 15 months to recruit two PCTs, three general practices and randomise 16 people into DeMiST. The response rate from GP letters was 2.6% and the overall recruitment rate from all our efforts was 1.2%. This recruitment rate was less than our estimates which were based on a local weight loss trial which recruited 10% of those invited to take part by GP letter (Jolly et al., 2011).

Based on our recruitment rate to meet our minimum sample size of 90 we would have needed another 15 months, 17 general practices, with two full time nurses to travel and cover these clinics. This was beyond our resources.

We have demonstrated that recruiting into a trial which offers help to control weight together with smoking cessation is very difficult. This was unexpected given the anecdotal evidence that many smokers are concerned about weight gain and ask stop smoking advisors for help control it.

4.2.3.1. *Potential reasons for poor recruitment*

Our results show that at least 37% of those who were identified as smokers with a BMI over 25Kg/m^2 could not be invited to take part because of the exclusions due to using a VLCD in this clinical environment. In addition, 16% of those who wanted to take part, when it came to signing up, were unwilling to be randomised to the VLCD. Therefore, use of a VLCD, a drastic weight loss measure, was one reason

that limited our ability to recruit but it did not account for all of the difficulty we experienced.

The poorest response to recruitment seemed to occur at the point of GP invitation and newspaper advertisement. It seemed that there was very little interest in this particular study and this may have been for the following reasons:

4.2.3.1.1. Poor marketing

We need to consider whether the invitation letter and flyers were insufficiently captivating to generate interest. However, we modeled our invitations on materials that had previously resulted in good recruitment into stop smoking trials. The main difference was the added element of weight control.

4.2.3.1.2. Weight control during smoking cessation

Perhaps weight control during smoking cessation is more of an excuse for not quitting rather than a true obstacle. This may mean that when smokers are offered this help they do not accept it and choose to continue smoking. Indeed evidence from trials and cohort studies suggests that the impact of weight concern on quit attempts is conflicting as we have discussed in chapter one (section 1.4).

Perhaps smokers consider weight control during smoking cessation too insurmountable a task to attempt it. Perhaps the message from the NHS, that

smokers should stop smoking first and not tackle weight at the same time, overrides the desire to do so. However, surveys of smokers do not seem to support this. In addition, other studies in other countries, such as those cited in a Cochrane review (Parsons et al, 2009), have had a good recruitment form advertising for such studies.

4.2.3.1.3. The target population

The problem may therefore lie in the population from which we were trying to recruit. We were 'cold calling' in an area with easy access to stop smoking services, so many of those keen to take such an opportunity may have already done so. The resulting population may have been the 'hardened smokers' who are either complacent about their smoking and weight or, after repeated failures, have given up attempting to change their habits.

4.2.3.2. *Potential solutions to poor recruitment*

We did try to widen our inclusion criteria by running a trial without the VLCD element and this remains an option to improve recruitment, however by the time we did this some of our practices had become so disillusioned with the poor recruitment rates that they pulled out of the trial. However knowing the difficulty of recruiting into a VLCD trial means this may mean it is not feasible to use in a future trial within stop smoking clinics.

Engaging individuals with research is notoriously difficult and ways to improve recruitment be it through marketing strategies or tailoring it to specific 'hard to reach' communities has been the subject of much research. A Cochrane review (Treweek et al, 2010) reviewed studies investigating ways to improve recruitment into randomised controlled trials. It reported that the most effective strategies were telephone reminders to discuss the trial with those who had not responded to the original invitation to participate. This increased the chance of recruitment more than 2 ½ fold (RR 2.66 95% CI 1.37, 5.18). Secondly using an 'opt out' rather than an 'opt in' procedure, for example, notifying participants that they will be called regarding the invitation to take part unless they request otherwise, increased recruitment by 37% (RR 1.37, 95% CI 1.07, 1.84). However an 'opt out' procedure is ethically controversial.

If we used telephone reminders to GP letters in a future trial we could potentially increase the number we randomised into this trial, over the same time period, from 15 to 40 individuals. This would come at the additional cost and labour of making at least 1249 phone calls, but this is likely to be considerable less cost per participant than the rate of recruitment we got from the newspaper flyers.

We still need to bear in mind the added challenge of attempting to engage smokers in changing two health behaviours simultaneously. This may mean that realistically we cannot achieve a better recruitment rate than this. One option is to accept that recruiting for such a trial will yield a smaller return for the time, advertising costs and labour required than other trials. Budgeting for this

adequately in future trials would be one solution but with scarce resources of funding bodies this may not prove possible.

Another option is to recruit from a population who were already planning a quit attempt. For instance, we could attempt to recruit on entry to the stop smoking services, rather than cold calling from the GP population of eligible smokers. A trial in Scotland in stop smoking groups successfully randomised 90% of their smokers entering the service into a nutrition education programme that ran alongside it (Hankey et al., 2010).

In designing DeMiST we had considered running group sessions to maximise recruitment in a short space of time, this was contained in an earlier version of the protocol (Appendix 38) for which we gained ethical approval. However this was labour intensive and required further funding. We applied to the NIHR Research for Patient Benefit stream for this. However, our application was rejected and the feasibility of running groups was questioned (Appendix 39) and so, in consideration of reviewers comments, we substantially amended our protocol and ran the trial as reported in this thesis.

4.2.4. Conclusion

Recruitment from GP invitations and newspaper flyers into a three armed randomised controlled trial of dietary interventions to prevent weight gain during quitting smoking was poor in a population with easy access to NHS stop smoking

services. Recruitment may be improved somewhat by avoiding the use of a VLCD, and offering telephone reminders, but the additional time and resources that would be needed may prove too expensive to be feasible. However recruiting from those already intending to quit and attending the stop smoking services offers a potentially viable alternative.

4.3. Acceptability to participants

4.3.1. Methods

We investigated participant acceptability of trial arm qualitatively by semi-structured interviews. The interviews were conducted by telephone; evidence suggests that well planned telephone interviews can gather the same material as those held face to face (Sturges et al, 2004, Taylor et al, 1998). They are less intrusive, which may be particularly useful to engage with those who dropped out of the programme, and they do not require payment of travel expenses.

Interviews were conducted after the participant had completed treatment or dropped out of the programme. Participants could not be interviewed before this time point in case the interview influenced their views of the trial or the intervention being delivered.

Participants were asked to discuss what they found helpful and unhelpful with regard to the intervention they received. What did they attribute to their success or abandonment of an intervention? To draw this out we asked the following open

ended questions: What did you expect to get from taking part? What did you actually get from taking part? What, if anything disappointed you? How would you have liked things done differently? If you needed to try things again what would you do? How did you get on with quitting? (What worked well? What was hard?) How did you get on with the dietary side of things? (What worked well? What was hard?) How do you feel about your smoking status now? How do you feel about your weight now? If you pulled out of the trial early, why was this? (Appendix 40 contains the interview schedule) To help participants remember their thoughts and feelings 'of the moment' they were given the questions they would be asked, with space to jot down notes, during the trial. Interviews lasted 10 to 20 minutes.

With participant consent, the interviews were audio recorded and transcribed intelligent verbatim (words such as 'um' were not transcribed). Audiofiles were outsourced for transcription to Type Research, a recommended transcription service for qualitative research. The data was analysed thematically, as discussed below, so that comparisons could be made within and across the interviews, and the views participants held towards particular issues, e.g. the intervention they received or preventing weight gain whilst quitting smoking, were highlighted.

4.3.1.1. *Sampling*

We had hoped, as described in the protocol (chapter three, section 3.4.1), to obtain a wide set of experiences within each trial arm. We wanted to include all

aspects of attrition, for example, those who completed the trial, and those who dropped out of quitting, dieting or both. We wanted gain maximum variation in relation to gender, age, socio-economic background, ethnicity, smoking rate and research site. We wanted to sample until theoretical saturation was reached and to do so purposively. However due to the small sample size and the unwillingness of some people to be interviewed, we interviewed all those who were willing, and ended up with a convenience sample.

4.3.1.2. *Analysis*

We carried out a thematic analysis that was informed by the five stage framework approach described by Pope et al in 2000. However, it was not a full framework analysis as we did not want to test an 'a priori' concept or framework. We wanted to deduce solely from the participants themselves the experiences they found helpful and those they did not. As described by Lacey and Luff in 2007 there is no one way to analyse qualitative data but rather a considered approach which best answers the research question must be taken (Lacey & Luff, 2007).

Our analysis contained the following steps:

4.3.1.2.1. Familiarisation

We immersed ourselves in the data by listening to the audio recordings, reading and re-reading transcripts (Pope et al, 2000).

4.3.1.2.2. Coding/Indexing

We reassembled fractured discourse by pulling together scattered responses to questions from wherever they came in the transcripts. For example where an earlier question was expanded on later in the conversation, this was cut and pasted together as an expanded chunk of conversation. Then we coded the content of these responses, our codes were identified predominantly from ‘in vivo’ words, group of words, sentences, or paragraphs from the transcripts (Lacy and Luff , 2007) that described a particular positive or negative experience of the trial. Each new code was highlighted using a different coloured pen (Lacy and Luff , 2007).

We included both literal and interpretative coding and considered reflexively whether interviewer prompting or empathy could have led the response or changed it over time (Swift and Tischler, 2010).

We did not carry out a discourse analysis (coding for signs to latent meanings), this went beyond the scope of the PhD. Instead we noted where content appeared particularly emotive, or aspects were stressed repeatedly and it was intuitively clear that opinion was strong or contradicting of itself.

4.3.1.2.3. Identification of themes

We then grouped our codes into broader themes and sub themes (Lacy and Luff, 2007). We did this in Microsoft Word by cut and pasting quotes and/or their codes into sub themes under the heading of a broader theme. We took care to keep the quote linked to the participant identifier. An example of the worksheet for the development of negative themes and subtheme from quotes/codes is contained in appendix 41.

4.3.1.2.4. Charting themes by trial arm

We then developed a matrix of themes and subthemes according to trial arm to observe the similarities and differences between them. We took note of the presence or absence of any links to trial outcomes. Throughout the process we kept the data of responses linked to the individual who gave them.

4.3.1.2.5. Interpretation

Finally we considered whether the most acceptable and least acceptable aspects could be defined by trial arm or by the characteristics or typologies of participants (Lacy and Luff, 2007).

A selection of codes and themes were peer reviewed for credibility purposes. A colleague reviewed a transcript and comparsion was made between the two sets of codes identified by different researchers from the same transcript. Ongoing discussion with other qualitative researchers regarding the development of

themes, particularly given the context in which codes were identified within transcripts, also took place.

4.3.2. Results

4.3.2.1. Baseline Characteristics

We carried out semi-structured interviews on 13 participants, baseline characteristics are shown in Table 18.

	Mean	(SD)
n	13	
Age (years)	50	(11)
Cigs/day	24	(8)
Fagerstrom score	5.3	(1.7)
Weight (kg)	83.2	(10.8)
BMI (kg/m^2)	30.80	(5.41)
SBS	46%	
IDAP	23%	
VLCD	31%	
Gender (% female)	77%	

Table 18. Baseline characteristics of DeMiST participants engaging in semi-structured interviews

4.3.2.2. Hindering factors

Seven main themes, each with subthemes, emerged which described what participants found unhelpful or hindered their success at weight control or stopping smoking. These are listed in Table 19 and how these were developed can be found in Appendix 41. , some aspects were common to all trial arms and others were specific to individual trial arms. We have expanded key themes in the text below and substantiated these with quotes.

Theme		Trial arm		
	Sub theme	VLCD	IDAP	SBS
Displeased with trial arm allocation	Unreasonable*	X		
	Did not address weight adequately*			X
Diet fell below expectations	Taste*	X		
	Food choice*		X	X (Stage 2 only)
	Thought knew better*		X	X (Stage 2 only)
	Hunger	X	X	
	Portions			X (Stage 2 only)
	Feeling unwell	X		
Perceived lack of support	Not frequent enough*			X
	Negative rather than a positive approach*		X	
	Feeling alone*			X
	Wanting peer support*		X	X
	Wanting more psychological therapy*		X	X
Disappointed with self	Low self-worth*			X
	Inability to stop smoking*	X		X
Socially difficult	For diet	X		X
	For smoking	X		X
Personal circumstances	Inconvenient appointments*	X	X	X
	As a reason for limited success	X	X	X
Difficulty of task	A sense of loss of coping mechanism*	X	X	X
	Tackling both smoking and weight at the same time*	X	X	
	Could only focus on diet	X		
	Could only focus on smoking	X		X
	Stopping smoking	X	X	
	Getting out of the habit/changing routines	X	X	X
	Mood changes*	X		
	Something to do with your hands			X
	A sense of loss of identity*	X	X	X

*some participants who reported these difficulties also dropped out of the trial early

Table 19. Themes and sub-themes of difficult experiences during DeMiST, according to trial arm

4.3.2.2.1. Displeased with trial arm allocation

There was dissatisfaction with trial arm allocation in both the VLCD and SBS arms. The VLCD evoked an emotive response:

> *"I was allocated in to that stupid powder stuff...I think it is totally unreasonable to ask somebody to...eat that stuff"* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

this was linked to the taste of the Lipotrim formula

> *" surely in this day and age somebody can make that food taste better than it tasted..."* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

In the SBS arm participants expressed both mild disappointment

> *"I would have preferred..."* Female, quit, weight gain in Stage 1, weight loss in Stage 2.

and strong objections

> *"I was absolutely gutted..."* Female, SBS, left at week +9 smoking no weight loss.

to being allocated the SBS arm. This was because weight was not being addressed adequately or soon enough, some even felt cheated

> *"that was one of my major reasons…was the weight as well and to be told that oh no, just carry on as you are for a few…more weeks,"* Female, SBS, left at week +9 smoking no weight loss.

> *"I found it a bit of a misnomer really thinking I was going to give up smoking I mean I understand with the trial but I did honestly expect some sort of assistance with the diet side I didn't really expect to be just left to get on with it.... I think I was a little misled on that score."* Female, SBS, temporarily stopped smoking, dropped out of programme before diet given in Stage 2.

One particular participant was so dissatisfied that they could not adhere to the programme:

> *"I didn't really fully go with the trial if you like, because I did start cutting back on some sort of food in that first 8 weeks because I was not prepared to put a stone on."* Female quit smoking, resorted to dieting during SBS Stage 1.

No participants reported any dissatisfaction with being randomised into the IDAP intervention.

Therefore although at the time of consent participants agreed to randomisation, it was clear that while participants were willing to take a chance, they had strong individual preferences, and these were linked to acceptability of the programme.

> *" I know the programme said you haven't got a choice...*I was h*oping and praying that I, on which one I would be allocated to and when, when I got one I was disappointed anyway but when I tried eating it, crikey, you know, it went downhill after that."* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

4.3.2.2.2. Diet fell below expectations

In all the trial arms, there were those for whom the diet fell below expectations, this was caused by difficulty in a number of areas. Firstly, in the VLCD arm the taste and smell of the formula was a problem. For some this led to them abandoning the diet

> *"Absolutely vile it was – I couldn't...I even like I was nearly sick just even smelling it"* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

Whereas others continued despite this, when probed as to whether it improved one response was:

> *"No, every single one of them was revolting!"* Male, VLCD, lost weight, reduced smoking, did not quit, did not complete programme.

Initial hunger and feeling unwell was also a problem in the VLCD arm. The reasons behind continued adherence despite these difficulties are explored in section 4.3.2.4.

In the IDAP arm and Stage 2 of the SBS arm diet fell below expectations of some with respect to food choice,

> *"I mean, I thought... the options that were recommended were clearly restrictive and not very imaginative* [interviewer probed further]*... more or less the same the everyday".* Female in IDAP, stopped smoking for 8 days, lost weight, did not complete programme

Hunger was also a problem in the IDAP arm. Other participants did not like to be told what to do, they thought they knew how to do these things better themselves:

> *"I won't lie, I love pasta and rice* [large portions] *and I don't particularly like measuring cups of vegetables, you know if I want a plate full of vegetables I like a plate full of vegetables. I have to say..."* Female in SBS, quit, weight gain in Stage 1, weight loss in Stage 2.

It is important to note that these themes ran through IDAP and SBS (where IDAP was received in Stage 2), but there was no dissatisfaction with IDAP in Stage 2 of the VLCD arm. It is possible that disgruntlement was due to disappointment in trial arm allocation and not just to the nature of IDAP. In particular, it was interesting to note that one individual who initially was rather angry with both allocation to SBS and the Stage 2 diet on further probing did in fact change her mind:

> *"I probably will* [use the cups], *I'd use them for like, cos I was amazed when I did go on the diet that the nurse gave me after 8 weeks that the portions are really, really small so I'm trying, I am aware of the portion size because of what you've given me. It has been quite positive yeah there's only that little minor negative that, about the whole situation."* Female quit smoking, resorted to dieting during SBS Stage 1.

Whether probing encouraged the participant to reflect on opinion and establishing a rapport dissipated anger such that a reasoned opinion was reached; or whether

the initial reaction is more in keeping with true opinion is hard to tell. Researcher belief in IDAP, coupled with clinical skills, which encourage a reasoned, well informed response to treatment, may have biased this response.

4.3.2.2.3. Perceived lack of support

In the IDAP and SBS arms, but not in the VLCD arm, there was a perceived lack of support for some, which was related to the desire for peer support:

> *"I thought I would have liked to have listened to how other people were getting on with their different things, you know and that you know, I think that would've been good."* Female SBS, temporarily stopped smoking, dropped out of programme before diet given in Stage 2.

Also some participants felt they should have received further psychological support:

> *"Well something about you know* [helps with] *feelings of deprivation, if you have any, feelings of not being who you were, feelings of loss...trying to balance that..."* Female in IDAP, stopped smoking for 8 days, lost weight, did not complete programme.

Some of these needs may have stemmed from underlying issues which went beyond dealing with withdrawal symptoms and this was expressed as another theme about how participants felt about themselves as described below.

4.3.2.2.4. Disappointed with self

For one participant this seemed related to low self-worth:

> *"I just think I am so stupid and then I get annoyed with myself and then you just think 'Oh have a fag'...the way you think about yourself...you're not really that important, so what if you overeat and smoke and pop your clogs, you know."* Female, SBS, temporarily stopped smoking, dropped out of programme before diet given in Stage 2.

In the VLCD and SBS arms participants were disappointed in their own ability to quit smoking:

> *"I just, just so disappointed you know, I don't, no, I can't tell you how much disappointed that I couldn't stop smoking, you know."* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

4.3.2.2.5. Socially difficult

Participants in the VLCD and SBS arms reported on the social difficulties of following the diets and those encountered when stopping smoking:

> *"*[I] *didn't sit at the table...normally* [I] *sit and talk."* Female on VLCD, successfully controlled weight and then quit smoking.
>
> *"Sticking to it* [the diet] *because my neighbour across the road bakes cakes, that was hard."* Female in SBS, left at week +9 still smoking, no weight loss.
>
> *"So my friend at work who smokes I wasn't going outside with her so I wasn't speaking much"* Female on VLCD, successfully lost weight and then quit smoking.

4.3.2.2.6. Difficulty of task

Many participants in the VLCD and SBS arms described the most difficult thing as

> *"the giving up",*

this is one participant's account of his preoccupation with cigarettes as he tried to live without them:

> *"It was just on me mind 24 hours a day and I just could not shake it off, I could not. I couldn't wake up in the morning without thinking about cigarettes, I couldn't go to sleep at night without thinking of cigarettes and it – I mean, I was, I was just cracking up, I actually couldn't, you know, I needed something to block me brain out and, you know..."* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

The difficultly of changing diet and stopping smoking at the same time was also apparent:

> *"there was a difficult period with no food and no cigarettes... it was just almost unbearable."* Female on VLCD, successfully lost weight and then quit smoking.

For some this meant that they concentrated on the weight loss attempt and for others they focused on smoking cessation:

> *"that* [VLCD formula] *started to show effect...I think I put all the effort into that"* Female, VLCD, abandoned quit attempt first and so later gave up on diet too and pulled out of programme.

> *"And to be perfectly honest, because I wasn't smoking I thought, well, you know, that's what I want* [whole tubs of Haagan Das ice cream]*...have it"* Female in SBS, quit, weight gain in Stage 1, weight loss in Stage 2.

Stopping smoking was perceived as being difficult for a number of reasons, these were changing moods, which were most apparent in the VLCD arm, and aggression:

> "*I felt slightly miserable and like let down with myself"* Female VLCD, did not stop smoking or lose weight or complete programme.

> *'my aggression, I was just so aggressive..."* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

One person in the SBS arm mentioned the difficulty of not

> *"having something to do with my hands."* Male SBS, lapsed intermittently, weight maintained during Stage 1, lost weight in Stage 2.

In all trial arms trying to change habits and routines were difficult:

> *"the hardest thing has been the habit, routine of having a cigarette,"* Female in SBS, quit, weight gain in Stage 1, weight loss in Stage 2.

And there was a sense of loss, a loss of identity:

> *"...feelings of not being who you were..."* Female in IDAP, stopped smoking for 8 days, lost weight, did not complete programme.

And a loss of support:

> *"... feels like a crutch...kind of lost without that"* Female on VLCD, successfully controlled weight and then quit smoking.

This loss of support was linked to no longer having a coping mechanism when circumstances were difficult:

> *"it was just pressure of work, pressure of life, you know...the pressure of everything just...the pressure really"* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

Therefore, despite the dietary interventions, it seems that for many the stopping smoking that was the main difficulty. For a few this was compounded by being hungry or trying to control food intake.

4.3.2.2.7. Personal circumstances

In all trial arms there was evidence that personal circumstances made it difficult to keep appointments (see next section) and achieve outcomes:

> *"...from a personal point of view I actually found myself in extremely difficult circumstances just after I started and that was the main reason for failure…"* Female in SBS, quit smoking, no weight gain (resorted to dieting during Stage 1) did not complete programme.

4.3.2.3. Reasons for and links with attrition

Both participants who did not abandon the treatment programme early and those who did reported the problems described above (Table 19). Some attributed their lack of adherence to the insuperability of these problems. When participants were specifically questioned about their reason for drop out two key themes emerged (Table 20).

4.3.2.3.1. Difficulty in keeping appointments

In all trial arms personal circumstances changed which made keeping appointments difficult, both the time and frequency of appointments were no longer convenient. Then once an appointment had been missed participants became embarrassed to go back to see the nurse or they lost motivation.

> *"Ahh, I had so much crap at home and also I wasn't able to get up to the doctor's at half past nine..."* Female in SBS, left at week +9 still smoking, no weight loss.
>
> *"But it was that that stopped me going back it wasn't that it wasn't working, it wasn't that it wasn't very good or that I felt it wasn't worth it; it was purely work and hospital commitments..."* Male, VLCD, lost weight, reduced smoking, did not quit, did not complete programme.
>
> *"I popped into the surgery the other day and* [she] *gave me a wry smile, and I just sort of hid!"* Male, VLCD, lost weight, reduced smoking, did not quit, did not complete programme.

The associated loss of motivation may be a key theme here as the inconvenience of appointment time could have been overcome by changing the appointment schedule, if motivation was high enough to do so.

4.3.2.3.2. A sense of failure

In all trial arms a participant's sense of failure in their own ability to stop smoking, or their inability to both stop smoking and control weight were also reported as reasons for leaving the trial early.

> *"....but I think, as I say, once I knew that I wasn't going to quit the smoking then obviously it went downhill pretty quickly..."* Female, VLCD unable to maintain weight loss or quit smoking .
>
> "*Yeah, I ended up smoking again and I wasn't sticking to the diet"* Female, IDAP temporarily stopped smoking, lost weight after pulled out of trial.

However no one reported abandoning the programme just because they were unable to control their weight.

Theme		Trial arm		
	Sub theme	VLCD	IDAP	SBS
Difficult to keep appointment	Personal circumstances	X		X
	Time was inconvenient			X
	Frequency of visits was inconvenient	X	X	
	Embarrassment	X		
	Lost motivation		X	X
Sense of failure	Quit smoking only	X		X
	Unable to do both	X	X	

Table 20. Themes and subthemes of reason for not completing the trial

Theme		Trial arm		
	Sub theme	VLCD	IDAP	SBS
Pleased with trial arm	Enthusiasm/excitement	X		
	Satisfaction		X	X
Weekly support	Seeing someone /accountability	X		X
	CO monitoring		X	X
	Weight/fat mass/blood pressure monitoring	X		X
	Clear instructions			X
	Discussions, tips to tackle cravings			X
Peer support	Support from partners/friends	X		X
NRT Patches	Controlled cravings			X
Dietary aspects	Portion control using cups		X	
	Cups simple to use		X	X (Stage 2 only)
	Structure			X (Stage 2 only)
	Increase of fruit and vegetables			X (Stage 2 only)
	Variety of food			X (Stage 2 only)
	Lack of hunger	X		X
	Mood stability	X		
	Replacing cigarettes with healthy snack			X
	Able to continue dietary plan after end of trial	X (stage 2)		
Evidence of success*	Rapid, dramatic weight loss	X		
	Moderate weight loss			X (Stage 2 only)
	More money	X		
	Smell of smoke gone			X
	Improved taste and smell	X		X
	Reduction in number of cigarettes smoked	X		
	Eating more healthily	X		
	Feelings of being in control of smoking	X		
	Feelings of being in control of eating	X		
	Sense of achievement on behalf of family			
	Sense of achievement for self			
Feeling good about self*	Encouraged by own success	X		X
	Motivation/determination	X		X
Timing	Lose weight at same time	X	X	
	Lose weight after quit			X
	Preference to lose weight before quit	X	X	X

*strongly overlapping themes

Table 21. Themes and sub-themes of helpful experiences during DeMiST, according to trial arm

4.3.3.4. Helpful factors

Eight themes with sub-themes emerged that participants found helpful in DeMiST (Table 21).

4.3.3.4.1. Pleased with trial arm allocation

In all trial arms there were participants that were happy with their allocated intervention, a quiet satisfaction characterised responses in the IDAP and SBS arms whereas there was notably more enthusiasm and excitement for some of those allocated the VLCD:

> *"I knew that diet was right for me! ...I just knew that that was the only thing that was going to work!"* Female, VLCD, lost weight then quit smoking.

4.3.3.4.2. Weekly support

In all trial arms participants said they found the weekly support helpful. Particularly helpful aspects were accountability (SBS and VLCD) and carbon monoxide (CO) monitoring (IDAP and SBS),

> *"...seeing* [the nurse] *every week knowing that I was gunna have to blow into a thing, knowing that she'd know whether I'd had a fag or not huh, just gave me the incentive to keep going. I mean I did slip a couple of times but I find it a lot easier to get back into stopping smoking knowing that I was being monitored every week."* Female, SBS, quit smoking, gained weight.

Monitoring of CO, weight, fat mass and blood pressure (VLCD and SBS) were also helpful, not only for reasons of accountability but also, for motivation arising from fear and shock at health status:

> *"I was actually told exactly what my weight was, my BMI and all those things you know, and I think that's quite helpful when you… to look at your… to actually find out what, oh I forget what they called it now, but the volume of … basically in your body. It's sort of a bit scary actually when you're told that a certain percentage of your body is…*[fat] *I know it kind of makes you sit up and think."* Female, SBS, initially motivated then could not quit so abandoned diet and programme.

Monitoring was also a source of encouragement:

> *"[I] saw my blood pressure come down, my carbon monoxide level, the weight come off..."* Female on VLCD, lost weight, then quit smoking.

Other helpful aspects of support were the clarity of instructions and the opportunity to discuss how to resist urges to smoke

> *"The discussions were very helpful; she was giving me useful tips on how to get around the cravings and getting over the willpower side of things."* Male, SBS, lapsed intermittently, weight maintained during Stage 1, weight lost in Stage 2.

4.3.3.4.3. Peer support

As well as clinical support, support from others was also an important aspect, if the venture was acceptable to those around the participants then it seemed to be acceptable to them too:

> *"Yeah it was a bit hard during the first few days but because I had sort of told all my work colleagues what I was doing, but it wasn't 'oh where is your food today and why have you got?' they were really, really supportive."* Female, VLCD, initially enthusiastic then couldn't quit, abandoned diet and programme.

4.3.3.4.4. NRT Patches

Several participants in the SBS arm mentioned the usefulness of the NRT patches to help control cigarette cravings.

4.3.3.4.5. Dietary aspects

In all trial arms, there were various aspects attributed to the diets that participants found helpful. In the VLCD arm participants were surprised by their lack of hunger and mood stability

> *"and I've got to be honest, it did really fill you up, I mean I've been on one of these for… but this, it did fill you up and, you know, I was amazed at that"* Female VLCD, lost weight then quit smoking.

> *"the lack of food...it worked far better than the patches. There were many days when I didn't put the patches on at all...*[my mood] *was more controlled, yeah, it was more even."* Male, VLCD, lost weight, reduced smoking, did not complete programme.

In the IDAP arm and Stage 2 of the SBS arms, simple control of portion size using the measuring cups were reported as useful,

> *"...cups were the most helpful. I cut my portion sizes down..."*

as was the structured nature of the diet

> *"Well, she just – what, what she did was give me, erm, a list of what I could have, breakfast, dinner, tea which was far better, saying you can have that off that list, that off that list and that off that list.* [probed: what sort of advice have you had in the past?] *"Make your own really."* Female, SBS, left at week +9 smoking, no weight loss despite being pleased with diet, as abandoned programme due to personal circumstances. Also, initially very disappointed with allocation to SBS.

And advice to eat a greater variety of food

> *"It* [Stage 2 food plan] *did point out that I wasn't eating as varied a diet maybe...Yeah it was very good."* Male, lapsed intermittently, weight maintained during Stage 1, lost in Stage 2.

and increase fruit and vegetables; this was in contrast to others described previously who felt that the variety of the diet was poor.

4.3.3.4.6. Evidence of success

The main aim of the programme was to assist cessation and control weight; however, participants also measured success in several other ways, some of which were a result of stopping smoking e.g. having more money, improved taste and smell, the smell of smoke gone.

> *"when I'm driving behind somebody now that's smoking in their car I can smell it coming into mine, you know and you can smell people in the supermarket and I think oh god did I used to smell like that?"* Female, SBS, quit smoking, gained weight.

Some success was related to feelings of being in control, of both food and smoking; this was linked to a sense of achievement. This seemed important as participants were able to do what they felt was right for themselves, and pleasing to their families.

> *"and having tried before...one thing I will say, it made me very, very grouchy and very irritable. I didn't find comments from my family, this time, so obviously this was...* (Laugh). *My wife has just chipped in with "yeah, you're just grumpy some of the time instead of all of the time"* Male, VLCD, lost weight, reduced smoking, did not complete programme.

> *"I'm not eating as many fatty foods, I mean, I read all my leaflets and stuff like that and, you know, I'm trying well, the whole family's trying to eat more healthily anyway so ..."* Male on VLCD, abandoned VLCD after 3 days, stopped smoking for 5 weeks, did not complete programme.

Initial successes spurred participants to further success, making them more determined to persevere through difficulties. This was particularly noticeable in the VLCD arm where weight loss was rapid and dramatic, and a sense of achievement came at considerable cost. For example

> *"...if I hadn't had lost nine pounds or something like that in the first week I wouldn't have carried on that was the incentive, that's why I knew that diet was right for me. Having gone through all of that torment and then found it would have*

been 2 lbs I would have gone to the chip shop or got a packet of cigarettes..." Female on VLCD, successfully controlled weight and then quit smoking.

"It's instant, you do start to notice within days and that's the good thing, and of course, when you get that buzz and when your clothes start feeling loose so quickly. Obviously it's so very planned and very boring but you get over that first stage, you know, it's like any diet isn't it, once you see the results, but because that's a bit quicker" Female, VLCD, unable to quit smoking and so later gave up on diet too and pulled out of programme.

"giving up the food the week before, you're to question whether you really needed something... it got me used to saying no to myself ....so then when it came to the cutting out the smoking it was well, 'do I really need that?' ... I began to take control of my smoking instead of having them out of habit or of them controlling me; telling me when I wanted them, so it was good, it was very good." Male, VLCD, lost weight, reduced smoking, did not quit, did not complete programme

[So what made you really...persevere though every time they tasted awful?] *"Because I didn't think I would and actually thought it was a very…it was a good opportunity to try and control if not give up smoking. I then saw the benefit of the weight loss*…[I thought] *Hey! This is really cool..."* Male, VLCD, lost weight, reduced smoking, did not quit, did not complete programme.

However early evidence of success or early positive experiences were not always associated with clinical outcomes of long term weight loss maintenance or smoking cessation, as shown by the outcomes labelled beside the participants' quotes.

4.3.3.4.7. Feeling good about oneself

As well as a sense of achievement and doing what is right for oneself and others, becoming self motivated was valued highly:

"I was very motivated, I was absolutely determined I was going to do it. I was, I was very… my mindset was right and I felt that talking to the nurseand getting sort of the health checks and things kind of made me think." Female quit smoking, resorted to dieting during SBS Stage 1.

4.3.3.4.8. Timing

In all trial arms the timing of the dietary intervention in relation to the quit attempt was important. For some in the SBS arm they were pleased to tackle weight after the stopping smoking, others would have preferred to have tackled it at the same time. In the IDAP and VLCD arm some were pleased to tackle weight at the same time, others wanted to have tackled it before, but none in these arms wanted to wait till afterwards.

> *"I think you probably would've been better to get used to being on the diet first. And then like slowly, maybe cutting, maybe I don't know which is the best way to do it maybe cut down on the cigarettes but such a drastic diet and then you feel that there is just nothing, you can't do anything really."* Female on VLCD, successfully controlled weight and then quit smoking.

> *I'd have probably started the diet a month before…got used to it and then stopped. Lose weight first, but you know, quite a bit of weight.* Female, IDAP temporarily stopped smoking, lost weight after pulled out of programme.

4.3.4. Interpretation and Discussion

4.3.4.1. Poor acceptability

4.3.4.1.1. When the trial did not meet participants' perceived needs

Participants described several main themes that they believed hindered their full participation in, and successful outcome from, DeMiST. We saw in DeMiST when participants were allocated to the SBS arm they were disappointed because it did not address their weight from the start. All our participants were overweight, and so some felt the desire for weight loss keenly, some participants particularly wanted rapid and dramatic weight loss. Both disappointment with allocation to control arms (Lindstrom et al., 2010) and unfulfilled high expectations of weight

loss (Foster et al., 1997) have been previously shown to be a source of considerable disappointment.

Disappointment in trial arm allocation was also seen in the VLCD arm by those who found it too unpalatable and too drastic a dietary restriction to continue with. Therefore poor acceptability may be due not only to allocation to control but to whichever arm did not meet participants perceived needs. Systematic review evidence shows that whether participants feel they will personally benefit from a programme is closely linked to their preferences within a clinical trial (King et al., 2005) and their decision to participate (Edwards et al., 1998).

In addition, many studies have shown that many participants do not understand randomisation (Kerr et al., 2004, Moffat et al., 2006) which can cause participants to feel their needs are not met. There can be an expectation that even in trials, clinicians will do what is of most benefit to the individual (Kerr et al., 2004). This is considered a therapeutic misconception, where the goals of research, which are for the benefit of future patients, are confused with the goals of clinical care of the individual. It is proposed that this can result in participants misplacing their trust in research as though it were clinical care and this creates a barrier to the acceptability of research (de Melo-Martin & Ho, 2008). We found evidence to suggest mistrust of this kind as some of our trial participants felt cheated.

Once participants received the dietary intervention in Stage 2 of SBS, some were satisfied, but others continued to feel hard done by. Initial disappointment may have contributed to a negative appraisal of the dietary intervention in Stage 2 of

the SBS arm. People allocated to IDAP initially were generally more positive about it than those who received it later. As discussed in chapter three (section 3.1.4) we included IDAP in a second stage of SBS with the aim of avoiding such disappointment, but for some this was not enough as they were not prepared to wait.

Support, in particular lack of peer support and psychological help, also fell below expectations. Although some of this may have been due to underlying psychological issues. Such issues are known to be prevalent among smoking and obese populations, but whether they are caused by or an effect of smoking and obesity is unclear (Strine et al., 2008).

We explored whether allocation to the trial arm that participants thought would work was associated with time until drop out, but we found no evidence of this (Chapter five). However, our sample was too small to be conclusive.

4.3.4.1.2. When participants are 'expert'

Dietary intervention also fell below the expectations of some participants allocated to the IDAP arm, who received this from the beginning. The participants with these views tended to be seasoned dieters who felt they had received better dietary advice in the past and were experts themselves. This is in line with studies showing tensions between 'expert' or self-reliant patients and their acceptance of medical advice. These individuals consider medical advice highly reflexively, in the light of their own experiences (Fox et al., 2005).

4.3.4.1.3. When problems become in surmountable

Participants found it difficult to stop smoking because of mood changes and the loss of a 'coping mechanism', particularly if personal circumstances were difficult. Many smokers experience these problems on trying to quit (Hughes et al., 1991, Shiffman, 1982). Participants who were unable to quit were disappointed and felt they had failed.

4.3.4.2. Acceptability

4.3.4.2.1. When trial met participants' perceived needs

What some participants found helpful others found a hindrance. Some people were happy at concurrent weight management and dieting, while others preferred to tackle both of these sequentially. Participants also found helpful the same aspects of the same interventions that others perceived as poor. For example, in contrast to the lack of support described by some, others praised nurse support highly and considered it an important source of advice, motivation and reassurance.

Some in the VLCD arm were particularly excited and enthused by this intervention. They found that the rapid effects of weight loss and improved sense of self-control provided a sense of achievement from which they took tremendous encouragement. In the VLCD arm, this achievement came at considerable personal cost, but the evidence of their success motivated them to persevere in

spite of difficulties. This process is very much in line with the theory that behaviour change is prompted by self-efficacy (Bandura, 1977). However, despite early success, excitement and enthusiasm this was not always sustained or associated with retention in the programme or long term successful clinical outcomes. It seemed that, for some, early success was overtaken later by the inability to stop smoking or the demands of other life circumstances.

Emotive responses of excitement and disappointment were not so apparent in the IDAP arm which may have resulted from quiet satisfaction that both smoking and weight were being handled sensibly.

4.3.4.3. How can we improve acceptability?

We can make steps to improve the acceptability of SBS based on these findings. For example, future trial arms involving a sequential weight control element after quitting smoking could reduce the delay in receiving this from eight to four weeks. However, different views were held on what was acceptable within each trial arm.

To be able to randomise individuals so that they accept their allocation whatever it is we need to consider how an individual may view or respond to it, rather than just the inherent properties of that particular intervention. In other words, acceptance may depend on whether properties of each intervention meet participants'

individual needs and expectations, which may have been shaped by their previous experiences of treatment.

Where participants experience the benefit of their needs being met, this may have lead to potentially unacceptable treatments being tolerated despite the cost. This seemed to continue until the cost became too high because the demand of life circumstances took priority. Therefore to provide effective interventions we need to design programmes which are not just well received initially, but stand the test of time when things get difficult. We need to explore further what elements will help participants to persevere and keep them motivated. Given that both stop smoking and weight loss interventions have a high degree of non attendance, a larger sample size would be needed to evaluate attrition, this then becomes a question which needs answering quantitatively.

So how can we address the issues raised by our trial participants to make the clinical trial experience more positive and prevent them abandoning interventions in the future. Perhaps we need to preempt some of these challenges and prepare participants on an individual basis to deal with them. This could be done in the first visit where not only is the understanding of the trial checked and consent taken, but time is taken to explore an individual's response to events during the trial which might sabotage it. For example embarrassment at unachieved goals or missed appointments; disappointment in trial arm allocation, or treatment falling short of expectations. Helping participants to prepare for these events and plan how to deal with them at the outset may alleviate disappointment and reduce

emotional distress which can undermine self control and self regulation (Tice et al., 2001). Discussing participant needs and how far the trial is able to fulfill these would be an important aspect of this. A qualitative study has shown that treatment preferences within a randomised controlled trial are dynamic and exploration of these can help participants accept other treatment options (Mills et al., 2011). Both lowering expectations and investing extra effort in obtaining an outcome are two key strategies used to avoid disappointment (Van Dijk et al., 2003). We could build on these principals to improve acceptability of randomisation and the interventions offered in clinical trials.

Additionally, are there ways in which we could design a trial that will allow us to better tailor interventions to individual needs? A number of trial designs have considered this. Pragmatic trials randomise participants to either usual care or a package of care in which participants are given the intervention which best suits their needs (Thorpe et al, 2009). However, these may still contain dissatisfied participants in the usual care group. Trials with a Zelen design randomise participants to usual care or intervention prior to consent. They are only told about the intervention if they are randomised to it; this is when they are asked if they will consent. Analysis is carried out as intention to treat (Zelen, 1979). This means that those in usual care may not know there is an alternative treatment to which they could have been randomised and as such, there is less chance that they will object to usual care. However, post randomisation consent trials have raised ethical concerns. Preference trials ask participants if they have a treatment preference and randomise those with no preference to either intervention or control; those which have a preference are allowed to chose the intervention

which they feel will best suit their needs (Brewin & Bradley, 1989). This is a design that theoretically would fit best with the findings from our participant interviews. However a systematic review of patient level data compared attrition of those who did not received their preference to those who did showed there was no significant difference (Odds ratio 1.35, (95% confidence interval 0.78 to 2.33) P=0.29 (n=1583)). A number of trials included in the review contained behavioural interventions, so there is little reason to suggest findings from our type of interventions would be any different.

4.3.4.4. Methodological strengths and limitations

4.3.4.4.1. Strengths

We used semi-structured interviews to understand participants' views on the acceptability of the DeMiST treatment programmes. This revealed a response to experiences which we could not have predicted. If we had carried out a survey, with a set agenda, we may have missed some of these. For example, considering the clinical priority for this population was smoking cessation, we may have asked participants if they would have preferred to tackle weight when they stopped smoking or afterwards. We may not have discovered that some wanted to lose significant weight before quitting.

Immersion in the interview data provided a depth of insight which we could not have gained otherwise. This has led to new ideas for how we can work to make clinical trials more acceptable to participants, for example, by pre recruitment

counselling which explores participants needs and expectations as described in the previous section.

We took a reflexive approach to our analysis, we reflected on the effect of our own bias where this seemed to occur as in the example of exploring the influence of clinical skills which may have led to one participant changing their opinion (section 4.3.2.2,2). This meant we could identify instances that may not have yielded a true perspective of the experience at the time. For the same reason we also tried to avoid leading questions or suggestive lines of enquiry during the interview.

4.3.3.4.2. Limitations

There were several limitations to our interviews and qualitative analysis which we have discussed in turn below.

4.3.3.4.2.1. Sample size

As described above we did not have enough people to 'purposely sample' all those we wanted to or reach theoretical saturation of responses in each of the trial arms. This means at best our data can only describe some of the experiences of our trial participants, which have led to suggestive interpretations, but we cannot infer that these are typical of all those who will enter such a trial. Therefore we cannot be certain of our conclusions. Acceptability to interventions may for example differ according to gender or social group and our sample was too small to explore the responses within these different groups.

4.3.3.4.2.2. Data collection and interview skills

With hindsight from analysing the data, we could have probed responses further to gain a greater understanding of the balance of driving forces which made participants decide to drop out or remain in the programme. We could have explored further what may have helped them to stay in. Where we did probe, we were cautious to avoid making assumptions about the meaning behind a response, by asking respondents to explain what they meant and to confirm our understanding of their response. However, there seemed to be a fine line between probing sufficiently and not leading a response, this is a qualitative interview skill, which is likely to improve with experience. The interviewer was relatively inexperienced in qualitative research and this may have accounted for the limited understanding we gained on some issues.

4.3.3.4.2.3. Organising data

Much of the organising of data for analysis, for example, the tagging of who said what within which theme was carried out manually. This became difficult to keep track of, particularly as new themes and links rapidly emerged. Therefore, despite a relatively low volume of data, if we had had the resources it may have been a worthwhile investment to use a qualitative analysis software package such as NVivo.

4.3.3.4.2.4. Method of analysis

We have previously justified our choice of thematic analysis, but we are aware that opinions on how best to analyse qualitative data will vary. With hindsight, we appreciate there were issues for which we could have collected further data, and these may have warranted an analysis based on grounded theory methods. For example, as mentioned above, the balance of driving forces leading to attrition could have been further explored. In addition, the reasons why participants prioritised weight loss over quitting and vice versa would have been an interesting exploration. However, these are wider questions requiring further studies to answer them fully. Such studies are important as they may lead to the development of theories regarding attrition in clinical trials such as this one and why individuals chose to change one health behaviour over another.

4.3.3.4.2.5. Validation of findings

We did not return our analysis of an individual's response to them for confirmation of meaning. Doing so might have added credibility to our findings. However, it may also have allowed a participant to reflect and change their responses from a reactive to a more reasoned one. This would have lost some emotion that was an important component in understanding reactions to the interventions.

Also considering the time constraints and the resources available we were unable to peer review the analysis of all transcripts, so as we have previously described only a selection were discussed and interpretation agreed upon.

4.3.4. Conclusion

Individual responses to the DeMiST interventions did not seem to depend on the trial arm to which they were allocated, but rather on whether the trial arm met their individual needs. As we were unable to purposely sample or reach theoretical saturation our analysis can only offer preliminary findings and suggestive conclusions. Further studies are required with adequate sampling and further 'probing without leading' interview techniques to answer fully how acceptable these dietary interventions are to quitting smokers and what leads to attrition. A grounded theory approach may be helpful to explore the theory of attrition more fully. Our effort to reduce disappointment in the control arm by offering IDAP intervention after the initial treatment stage (Stage 1) was not successful. It may be worth exploring whether more in-depth counselling prior to randomisation might reduce disappointment with random allocation to a non-preferred trial arm, and help participants remain in the trial arm when difficult circumstances arise.

4.4. Feasibility of trial delivery

4.4.1. Methods

4.4.1.1. Fidelity checking

We visited sites to assess how well the behavioural interventions were being delivered and assess adherence to other aspects of the protocol. These were formative visits in that we used them to identify where nurses needed further training. The visits were audio recorded with the participant's permission and an assessment form was completed during the visit. The form audited, against the

clinical protocol, how many of the required behavioural change techniques were used and how many of the required procedures were carried out during the consultations (Appendix 42).

We also entered the trial database on an ad hoc basis to assess the quality of data management and identify any problems which needed addressing.

4.4.1.2. Nurses debriefing

Our protocol (chapter three, section 3.4.2) stated that we would carry out a focus group with our nurses at the end of the trial. However, with poor recruitment and the changes in protocol we decided to hold a debriefing session, six months into the trial, instead. Debriefing sessions are becoming increasingly recognised for their value in the evaluation and education of medicine practice (Rudolph et al., 2008, Raemer et al., 2011). A debriefing session rather than a focus group provided the opportunity for reflective learning of both the research nurses and investigator, which we considered was a more appropriate way to evaluate and resolve issues with trial delivery that were apparent at the time.

The debriefing session lasted two hours, and the discussion was semi-structured to ensure all aspects were covered (Appendix 43). The session was audio recorded so an accurate record was kept. We reported on the factual content of the debriefing, i.e. what went well and what did not go well with running the trial,

the discussion of potential solutions and action points to be carried out. We did not intend to analyse this discussion as qualitative data. The objective here was to understand descriptively what worked and what did not, rather than explore nurses opinion.

4.4.2. Results

4.4.2.1. Fidelity checking

Eight trial consultations were assessed, in five of these there was no deviation from either the clinical or the research protocol. In the other three, the following issues needed addressing. With each the nurse was prompted and helped at the time to avoid deviation from the protocol. The issues were noted for inclusion of additional training in these areas:

- A reminder that participants must have bare feet on the Tanita scales, tights should not be worn.
- There was difficulty in measuring waist and hip circumference particularly for individuals who had a large amount of adipose tissue which hid the exact location of the inferior margin of the last rib and the crest of the ilium.
- Avoiding hunger in the SBS arm needed greater emphasis.
- Dietary goal setting needed to be more participant-centred and less prescriptive.

Thirteen consultation entries were reviewed in the trial database. One of these had no data recorded and a problem with the save function was identified. Data

was re-entered from the case report form (CRF). There were two other queries. One was missing the date of stopping a medication. This was checked with the participant and completed on the database. The other was a missing CO reading, which was missed when data was transferred from the CRF to the database and was subsequently filled in.

4.4.2.2. Nurses debriefing

Several aspects of the preparation and practical working out of the trial were discussed (Table 22 and Table 23). For each of these there were positive aspects, difficulties, and suggestions of improvements which could be made. Some of these suggestions were implemented with immediate effect for the remainder of the trial; others were unsuitable for incorporation at the time, but noteworthy for consideration in the management of future trials in this field.

Issues	Positive aspects	Difficulties	Suggested Solutions	Action taken
Training and support	Initial supervision by research nurse	Complicated study, especially with three arms Dietary interventions were most difficult to grasp Delay between some of the training and use of skills e.g. spirometry meant their confidence waned for some procedures. Interpreting body composition and providing feedback on diaries and clinical measures in response to participants questions How to deal with those who include their own dieting strategies, how much flexibility is allowed within the protocol?	Expanded training sessions Back ground session with incentive i.e. those on bank being paid hourly rate to read and become thoroughly familiar with protocol, to practise filling in diaries to gain a participants perspective. More opportunity for role play, to run through first two or three sessions and practice the following Explaining the trial and gaining consent Giving the dietary advice Consolidating training on new clinical procedures	To consider in nurse training session for future trial in this field
Logistics and data management	Database entry encouraged a double check that everything had been completed	The volume of VLCD formula created storage difficulties Some equipment was very heavy if it needed transporting to different clinic rooms e.g. Tanita scales Accessing the Citrix database was sometimes a problem depending on clinic room Data entry was time consuming	Starting pack of equipment and products Central storage space possibly at the university stock could be ordered and/or collected Extra time to set up and wrap up each clinic and enter data	Consider for future trials
Recruitment	Worked well where practice had an expert who could search GP database	Difficulties with some appointments booked centrally while others booked by the nurse Problems with identifying and excluding potential participants from GP databases	Nurses preferred to be responsible for booking all participants, Step by step guide with list of read codes (although not all practices use the national read codes ranking Identify and agree who will carry out searches at a planning meeting involving everyone who will be dealing with the trial	Changes made to appointment booking process Other suggestions to be considered in the future

Table 22. Nurses report of training and support, logistics, data management and recruitment. Improvements made during DeMiST

Issues	Positive aspects	Difficulties	Suggested Solutions	Action taken
Clinical aspects	Some appointments were an appropriate good length of time Gaps in clinics between participants were useful for overrunning appointments	Some appointments needed more time: the initial appointment and appointment to provide dietary advice especially if giving quit advice at the same time. Keeping participants focused when keen to talk about food Apprehensive with regard to some clinical measures e.g. spirometer (but actual procedure was easier than expected) Consistent measures of waist and hip circumference were difficult due to clothing, overhanging fat and embarrassment. Logistics of carrying out fasting blood tests were difficult in some surgeries Some practices acted on blood test results which went through their system e.g. participant in control arm was advised by practice nurse to follow a low fat diet	Training on managing consultation time, how to redirect clinical conversations but maintain rapport Pre-clinic practice session on spirometry The necessity of all the measures were queried, is waist to hip necessary when we have a measure of body fat? Further planning and discussion regarding blood tests needed with some surgeries and what to do if trial participants need treatment Alternative skin prick testing may be suitable for some measures	Appointment times amended financial implications of this considered for future trials Clinical measurements to be added to further training and considered further for future trials
Protocol	Everything needed was within the clinical protocol Summary sheet was particularly helpful	Difficult to see when forms have to be completed or given out. Reasons behind protocol changes not always clear Some abbreviations were not clear Some diaries contained typographical errors	Packs made up for different visits, for each trial arm Checklist for each consultation	These suggestions were implemented Improved system of proof reading required
Interventions	Healthy choice Index was useful guide for nurses Portion guide easy to explain	Ketotic effect of VLCD hard to explain Resetting goals was quite difficult as participants felt they had achieved them when it was obvious they had not IDAP 8 weeks after quitting smoking seemed too long a wait in the SBS arm*. Participants seemed keen to quit sooner than fourth visit So many visits seemed too long a commitment to some.	Consider four week gap before given dietary help	Simplified explanation of VLCD given Number and timing of visits to be considered in the future Further training on goal setting needed in the future
Dealing with failure to attend		Hard to get hold of participants for follow up phonecalls, suspected embarrassed to discuss*	Should an independent person do these phonecalls?	For consideration in future trials

*These perceptions were born out in interviews with participants

Table 23. Nurses report of the clinical aspects, protocol, delivery of interventions and dealing with failure to attend. Improvements made during DeMiST

4.4.3. Discussion

Despite lack of confidence expressed in the nurses debriefing, fidelity checks within clinics showed that they delivered the intervention competently and collected data appropriately as described in the protocol. We have demonstrated that we were able to train nurses to provide specialist dietary interventions within NHS stop smoking clinics.

The nurses debriefing session and fidelity checks provided us with suggestions to increase nurses' confidence in delivering the interventions and to streamline the practicalities of doing so. The nurses appreciated the debriefing session and such opportunities are important for their job satisfaction and morale which positively influences their job performance (Kennedy et al., 1990) so they should not be underestimated.

There were several technical difficulties encountered with the Citrix onsite trial database. These were resolved but this emphasised the value of completing a paper copy in clinic, so that trial data is not lost.

4.4.4. Conclusion

We found that it was feasible to train nurses to provide each of the DeMiST interventions according to a randomised controlled trial protocol within primary care stop smoking clinics typical of the NHS.

5. DEMIST: PROCESS MEASURES

5.1. **Introduction**

Chapter five is concerned with the measures of underlying processes, which may have led to changes in outcomes in DeMiST. To capture the processes of change we designed a number of questionnaires, some of which needed to be tested to examine their reliability and validity. This chapter meets objective five: to report on the development and validity of a dietary assessment tool for use within DeMiST consultations, and objective six of the thesis: to report on the development of a questionnaire to measure both hunger and food craving during quitting smoking.

However as we were unable to recruit our sample size to test the reliability and validity of these questionnaires with any degree of certainty we have analysed the data using the same methods, as we would have done if we had been able to recruit full numbers. The reasons for this were two-fold. Firstly, they allowed me to show that I can carry out such analyses for the purposes of the PhD and secondly allowed us to identify large effects that may provide preliminary evidence on which further research may be developed.

The healthy choice index (HCI) (chapter three, section 3.4.7), was developed as a simple tool to identify and be used to promote change in eating pattern and physical activity; to explore how much this influenced change in body composition. We tested

the validity of HCI as a nutritional assessment tool against the gold standard field measure of the estimated seven day food diary.

The hunger and food craving score (HCS) (chapter three, section 3.4.3), was developed to measure hunger and food craving to explore whether changes in these mediated changes in cigarette cravings (this mediation analysis is covered in chapter six). We tested the reliability of this questionnaire using factor analysis.

We also asked participants which trial arm they thought would be most successful (chapter three, section 3.4.8). We did this to explore whether there was greater attrition in those who were allocated a treatment which they did not think would work. This helped us to understand the influence that the unblinded nature of the study had on retaining trial participants.

This chapter provides further background, it describes the methods, results and discusses the findings concerning each of these process measures in turn.

5.1.1. The healthy choice index (HCI)

5.1.1.1. *Introduction*

As described in chapter three (section 3.1.3), a gap exists for a dietary assessment tool that is brief, reliable, and can be used in routine clinical practice as a prompt for

behaviour change. We developed the Healthy Choice Index (HCI) to do this (Appendix 44). This multiple-choice questionnaire required participants to score their usual eating patterns, level of physical activity and usual choices of key foods known to contribute a large proportion of the intake of a particular nutrient in a typical British diet. For example, we know from national surveys that the major contributors of fat in the population's diet are dairy produce, fatty meats and cereal products (FSA and DOH, 2009). Therefore, our questions relating to fat asked about the type of these foods eaten, the portion size and the frequency of consumption. Depending on the participant's answer, they were scored one to three, one being the score for the least healthy and three for the healthiest answer. From this the clinician, led by the participant, set guided goals to increase healthy choices and decrease unhealthy choices. This was part of the IDAP intervention where these dietary goals were consolidated with individual energy prescriptions (chapter three, section 3.2.2.2).

There were 25 questions designed to capture some of the assessment, and prompt discussion of key behaviour change needed for weight loss, that would typically be contained in a dietitian's initial consultation. This was a simple approach to enable non-dietitians to provide similar advice without the need for lengthy training and detailed dietary history taking. Questions covered:

- eating pattern and response to hunger (questions 1 and 2),
- portion size (questions 4, 7 and 12)
- fat (questions 9, 10 , 11, 12, 13, 14, 15, 16 and 20)
- carbohydrate (questions 3, 4, 6, 8, 10, 16, 17 and 18)

- energy (question 2 and questions for fat and carbohydrate)
- non-starch polysaccharide (NSP) (dietary fibre) (questions 5 and 8)
- calcium (question 10)
- sodium (questions 11, 19 and 20)
- alcohol (questions 23 and 24)
- vitamin C (questions 6 and 7)
- time spent being active (question 25)

We measured HCI at baseline and at the end of treatment (week +12). The food diary was completed at baseline only. So, how valid was the HCI as an assessment of nutrient intake? Did it serve as a sufficiently accurate method to determine whether diets were high or low in particular nutrients?

5.1.1.2. *Methods*

We investigated agreement between baseline measures of nutrient intake from the HCI and the widely accepted seven day estimated food diary (Chapter three section 3.4.7, Appendix 45). We analysed the nutrient values from the food diaries using the WISP version 3 dietary analysis package (Tinuviel software, based on the McCance and Widdowson's food tables). This provided data on the DeMiST sample to compare with population and recommended dietary intakes. We estimated the nutrient values from the HCI from representative food items described by each question (using McCance and Widdowson's food tables FSA, 2002). We estimated portion sizes of these foods from standard tables (MAFF, 1994), participants answers to the proportion of the plate a food covered, and the frequency of consuming these foods daily or weekly.

We assessed correlation between the nutrient intakes from the food diary and the HCI using Pearson's regression coefficients. We calculated the limits of agreement between these two assessments using the Bland–Altman technique. Where there was evidence of a relation between the difference and the mean, we log transformed the data to base e for improved accuracy of the limits of agreement (Bland and Altman, 1986).

We applied the limits of agreement for the HCI to the mean, minimum and maximum nutrient values of our sample to see whether the HCI could differentiate between the higher and lower intakes.

Where limits of agreement were acceptable we compared the change in HCI scores and the reported behaviour changes by trial arm and investigated their effect as mediators on change in body fat.

5.1.1.3. *Results*

5.1.1.3.1. Baseline nutrient intakes from food dairy

The food diary data showed a mean energy intake of 2053kcal/day, 2666kcal/day in men (n=3) and 1942kcal/day in women (n=10) (Table 24). This may represent an underreporting of about 8% in men and 13% in women. These are the values by which the actual intakes differ from the expected intakes. Expected intakes are

calculated from using the Schofield et al. (1985) energy prediction equation based on the average weight in the male and female participants (Table 24), and using the mean physical activity level of 1.5 (2896kcal/d and 2228kcal/day respectively).

5.1.1.3.2. HCI Scores

Scores could potentially range from 25 to 75. Mean HCI score was 52. Minimum and maximum HCI scores in the DeMiST sample were 40 and 66 respectively. Minimum scores were generated from the least healthy food choices and eating behaviours described, and maximum scores from the most healthy.

5.1.1.3.3. Correlation and agreement between mean nutrient values measured by the food diary and HCI

Correlation was significant between the two measures for total energy, carbohydrate and alcohol, but not fat, fibre, sodium, calcium, vitamin C or protein (Table 25) (Figure 8). The Bland-Altman plots for alcohol (Figure 9), calcium (Figure 10), fat (Figure 11), energy (Figure 12), carbohydrate (Figure 13) and vitamin C (Figure 14) showed a relation between the difference and mean which was partially improved with log transformation of these data. Log transformation of the Bland-Altman plots for fibre, sodium and protein (Figure 15) were not appropriate.

Trial arm	All	SBS	IDAP	VLCD
Nutrient Intake and physical activity level at baseline (7 day diary)				
N	13	5	5	3
Energy (kcal/day)	2053(552)	1891(513)	1937(401)	2517(745)
Men only (kcal/day)	2666(256)	2485	-	2847
Women only (kcal/day)	1942(520)	1743(451)	2353(974)	2353(974)
Total Fat(g/day)	89(24)	84(24)	70(16)	105(32)
Fat (% Energy)	39%	40%	33%	38%
Of which saturated fat (g/day)	34(12)	36(15)	30(10)	38(10)
Saturated fat (% Energy)	15%	17%	14%	14%
Carbohydrate(g/day)	220(58)	218(82)	217(41)	228(57)
Carbohydrate(% Energy)	43%	46%	45%	36%
NSP (g/day)	10(2)	10(2)	10(3)	11(1)
Protein (g/day)	79(22)	70(16)	70(16)	100(34)
Protein (% Energy)	15%	15%	14%	16%
Sodium(mg/day)	2896(976)	2397(583)	2720(807)	4022(1065)
Salt(g/day)	7.4(2.5)	6.1(1.4)	6.9(2.0)	10.2(2.7)
Alcohol (g/day)	17(26)	3(4)	13(15)	45(44)
Alcohol(% Energy)	6%	1%	5%	13%
Calcium (mg/day)	882(238)	847(234)	739(73)	1170(185)
Vitamin C (mg/day)	78(80)	127(107)	59(50)	27(1)
Physical Activity Level (PAL)	1.5(0.3)	1.4(0.2)	1.3(0.2)	1.8(0.3)
HCl	52(7)	54(4)	53(1)	47(3)

Table 24. Baseline nutrient intake and physical activity level for all participants and by trial arm (Mean (SD))

The range of agreement for the nutrient values for raw data and log transformed data showed that the HCI overestimation or underestimation of food diary values was too wide ranging for differentiation between high and low intakes of most of the nutrients measured. The one exception was dietary fat, after log transformation the range of agreement was 32% (4% above to 28% below) the mean food diary value (Table 26). Applying these limits to the minimum, mean and maximum values of our sample showed that the limits of agreement did not overlap and the HCI could detect between high, medium and low intakes in our population (Table 27).

Nutrient	Pearsons correlation coefficient
Energy (kcal)	0.77*
Fat (g)	0.51
Carbohydrate (g)	0.74*
NSP (fibre) (g)	0.26
Sodium (mg)	0.42
Alcohol	0.57*
Calcium (mg)	0.37
Vitamin C (mg)	0.13
Protein (g)	0.26

*p<0.05

Table 25. Correlation coefficients for nutrients measured by food diary and HCI

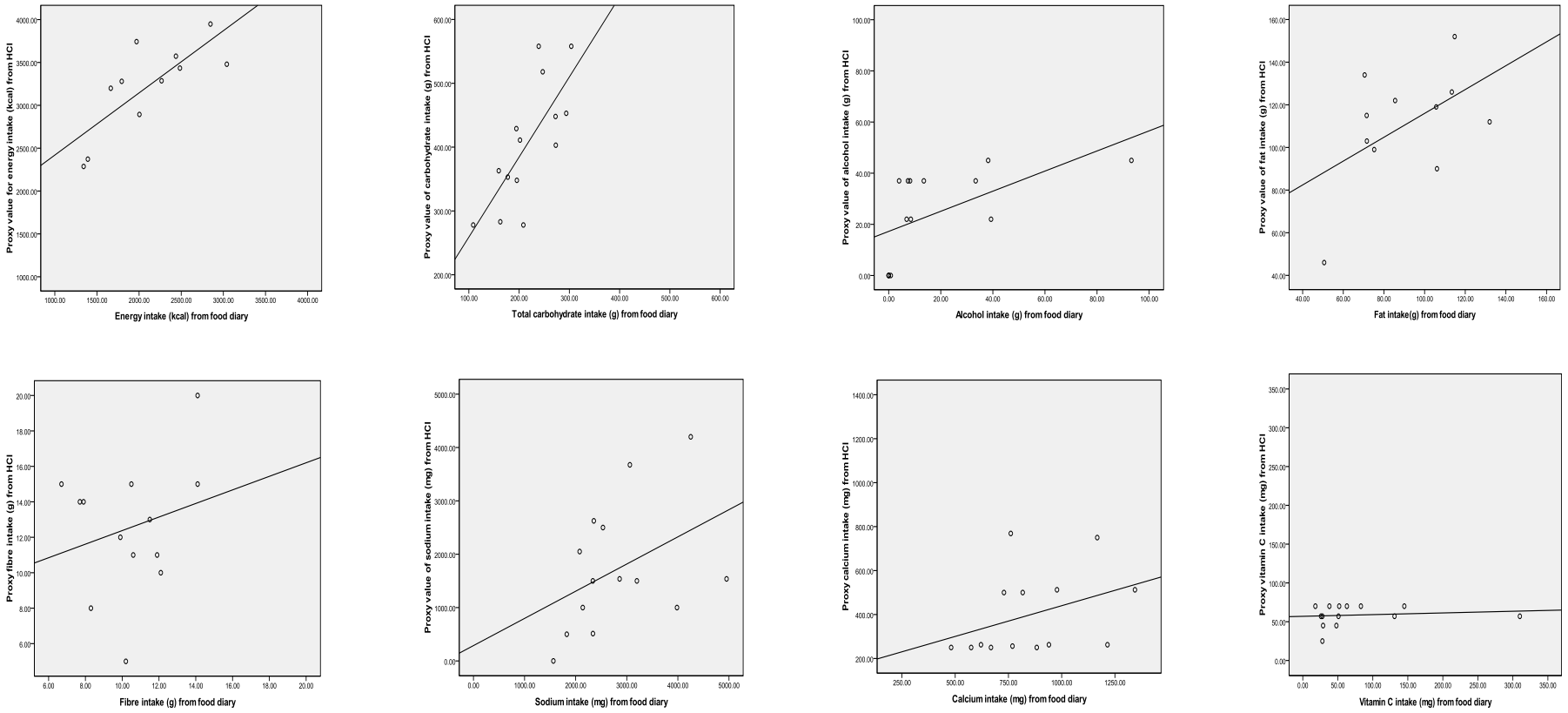
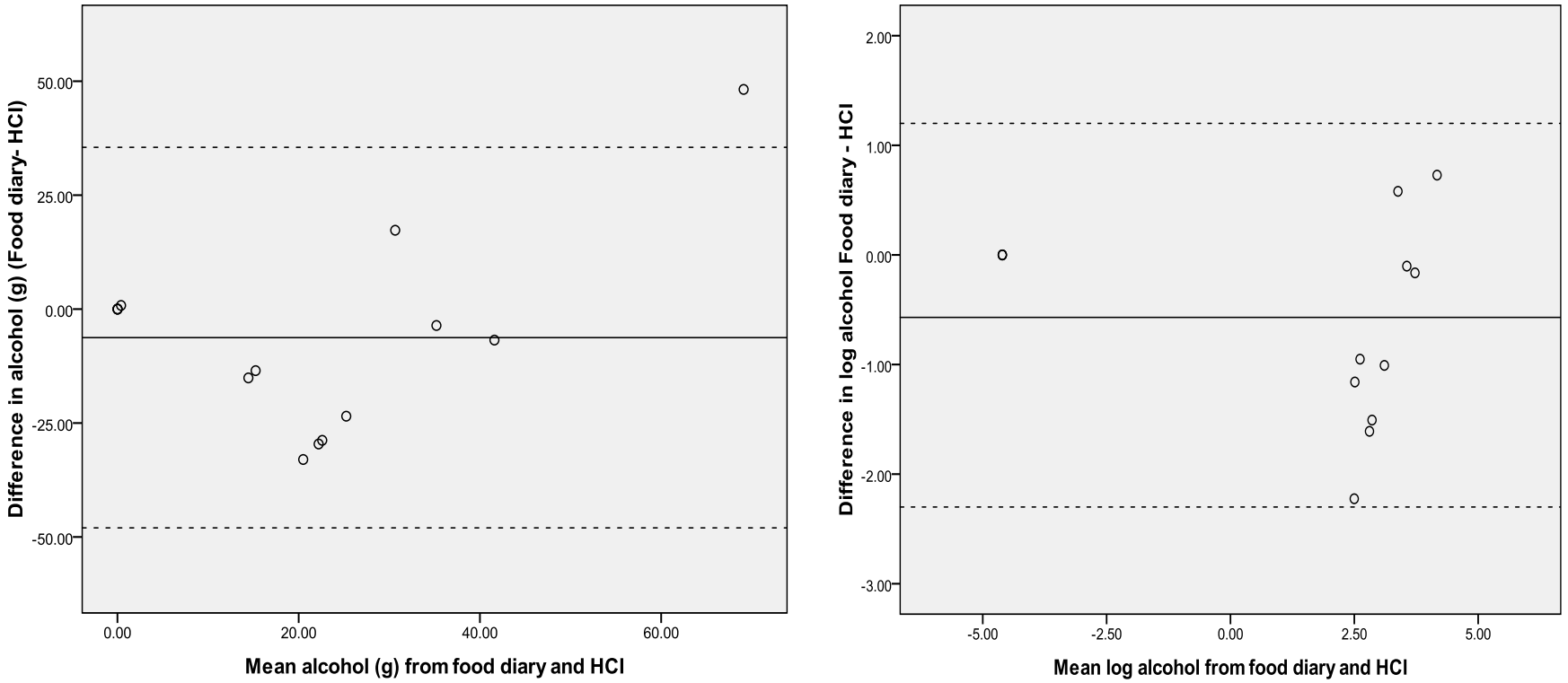
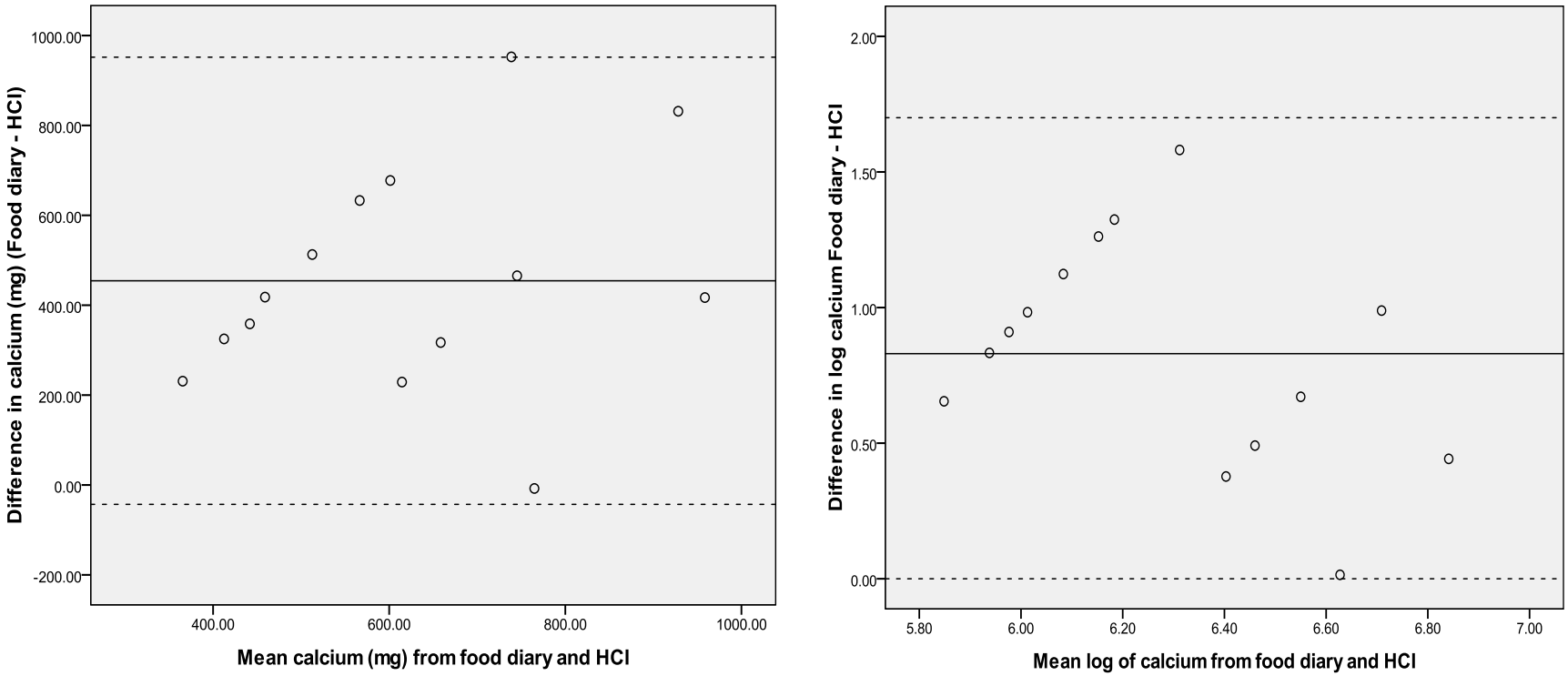


Figure 8. Scatter plots of nutrient intake (energy (kcal), carbohydrate (g), alcohol (g), fat(g), fibre (g), sodium (mg), calcium (mg) and vitamin C (mg)) from food diary compared to HCI with lines of best fit



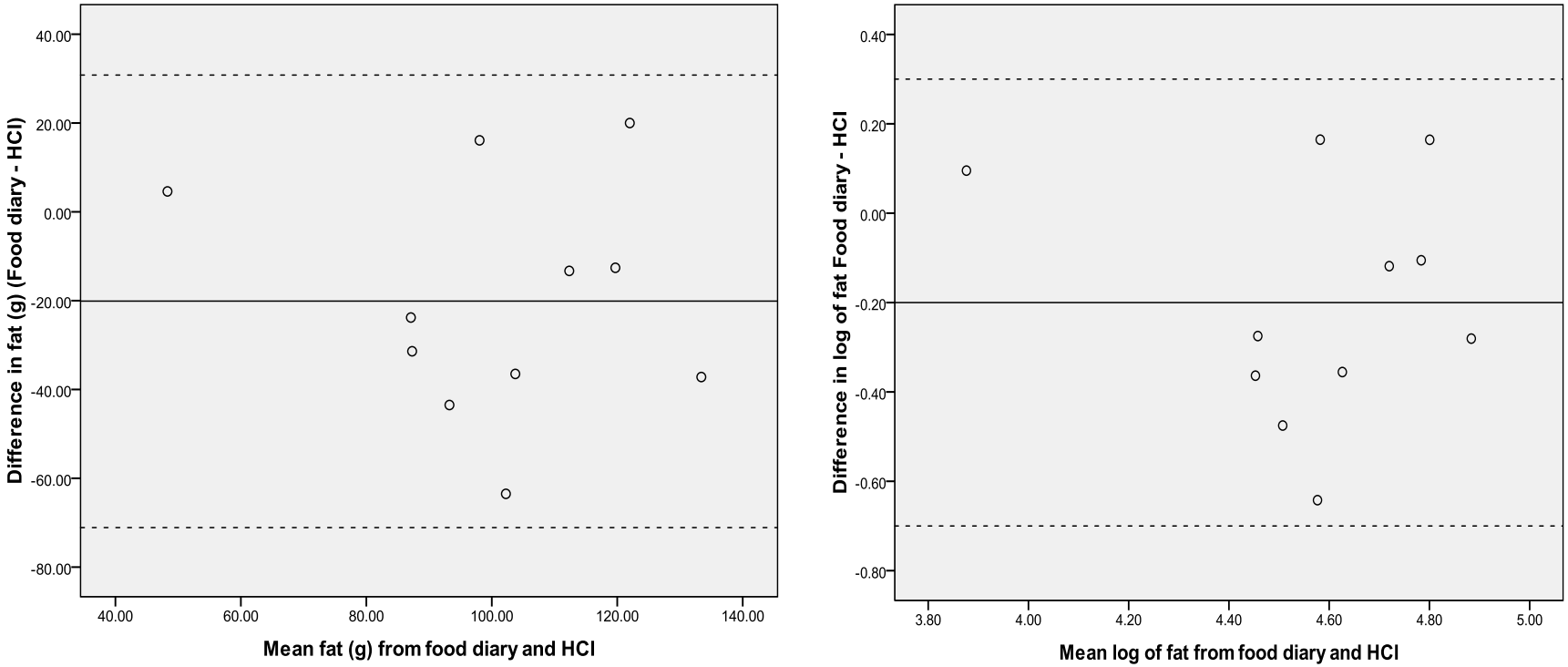
Mean difference (solid line) and upper and lower limits of agreement are plotted (dashed lines)

Figure 9. Bland-Altman plot of mean alcohol intake from food diary and HCl with difference in alcohol between food diary and HCl (graph on the left hand side). Bland-Altman plots of log mean alcohol intake from food diary and HCl with difference of log alcohol intake between food diary and HCl (graph on the right hand side).



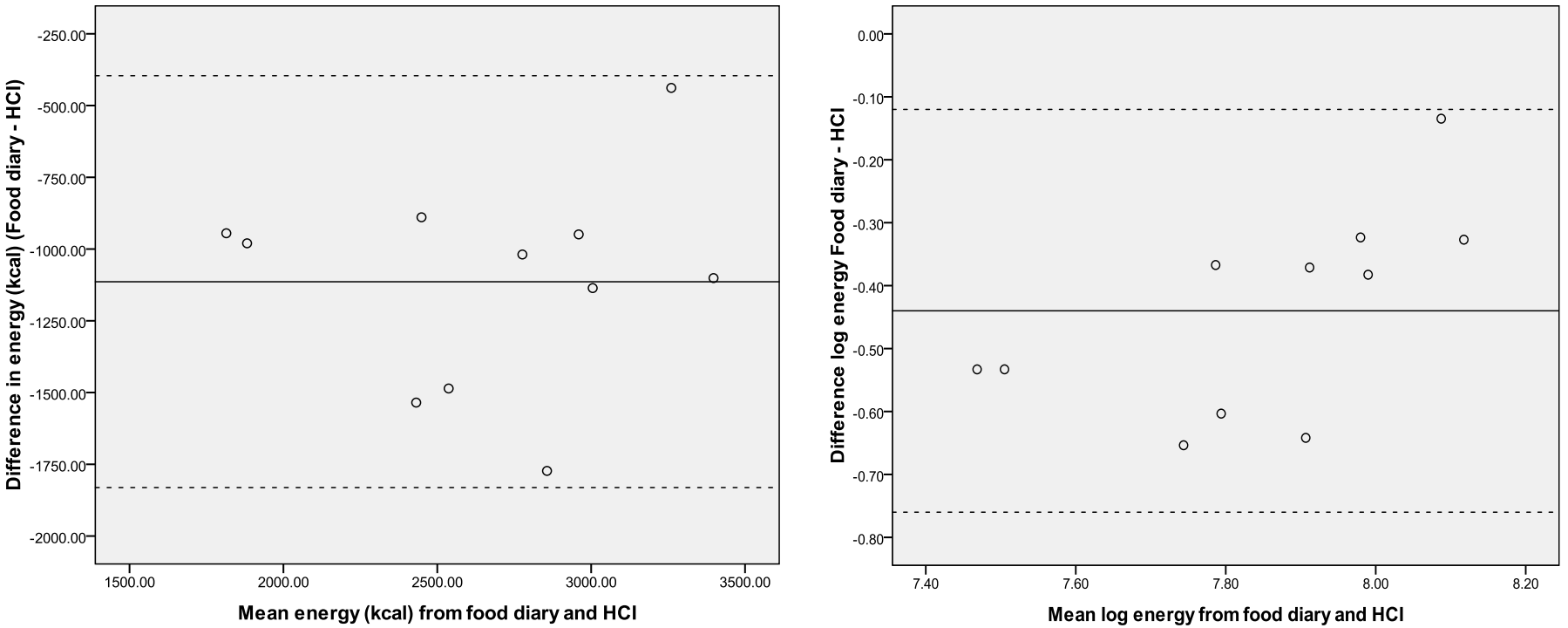
Mean difference (solid line) and upper and lower limits of agreement are plotted (dashed lines)

Figure 10. Bland-Altman plot of mean calcium intake from food diary and HCl with difference in calcium between food diary and HCl (graph on the left hand side). Bland-Altman plot of log mean calcium intake from food diary and HCl with difference of log calcium intake between food diary and HCl (graph on the right hand side).



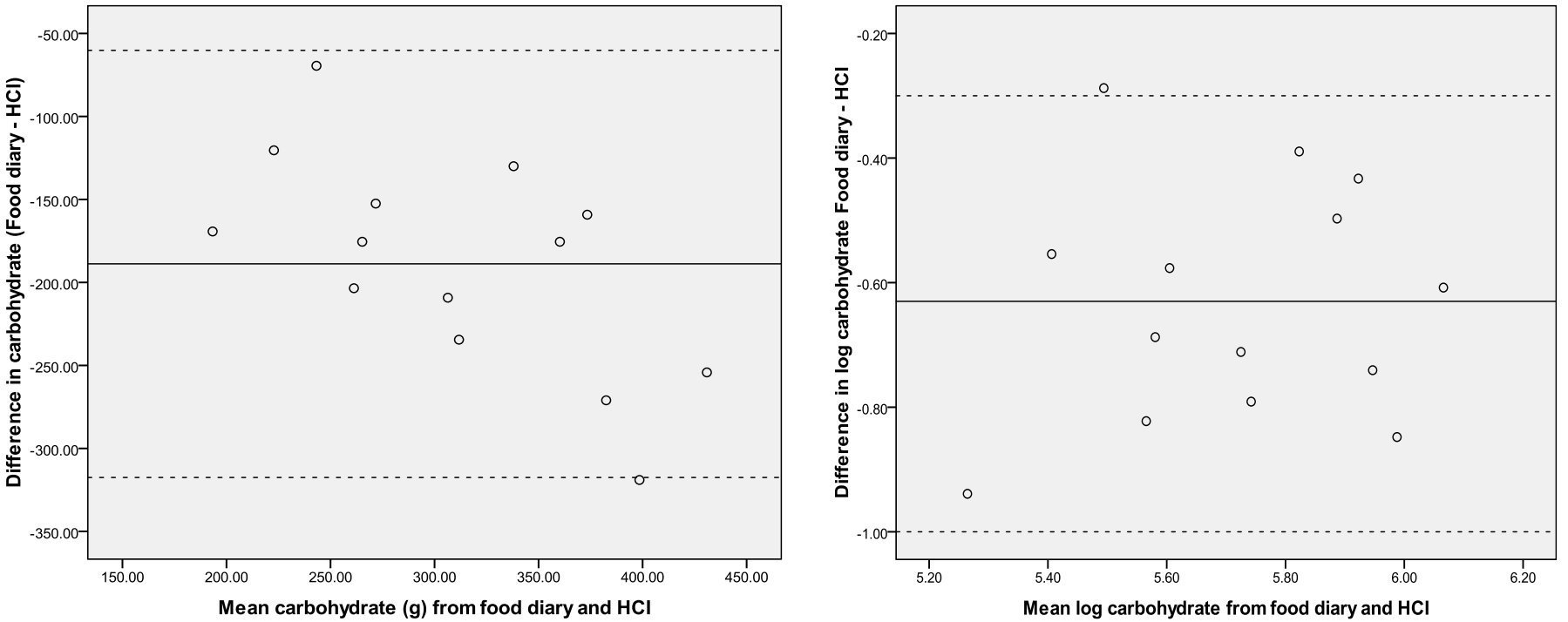
Mean difference (solid line) and upper and lower limits of agreement are plotted (dashed lines)

Figure 11. Bland-Altman plot of mean fat intake from food diary and HCI with difference in fat between food diary and HCI (graph on the left hand side). Bland-Altman plot of log mean fat intake from food diary and HCI with difference of log fat intake between food diary and HCI (graph on the right hand side).



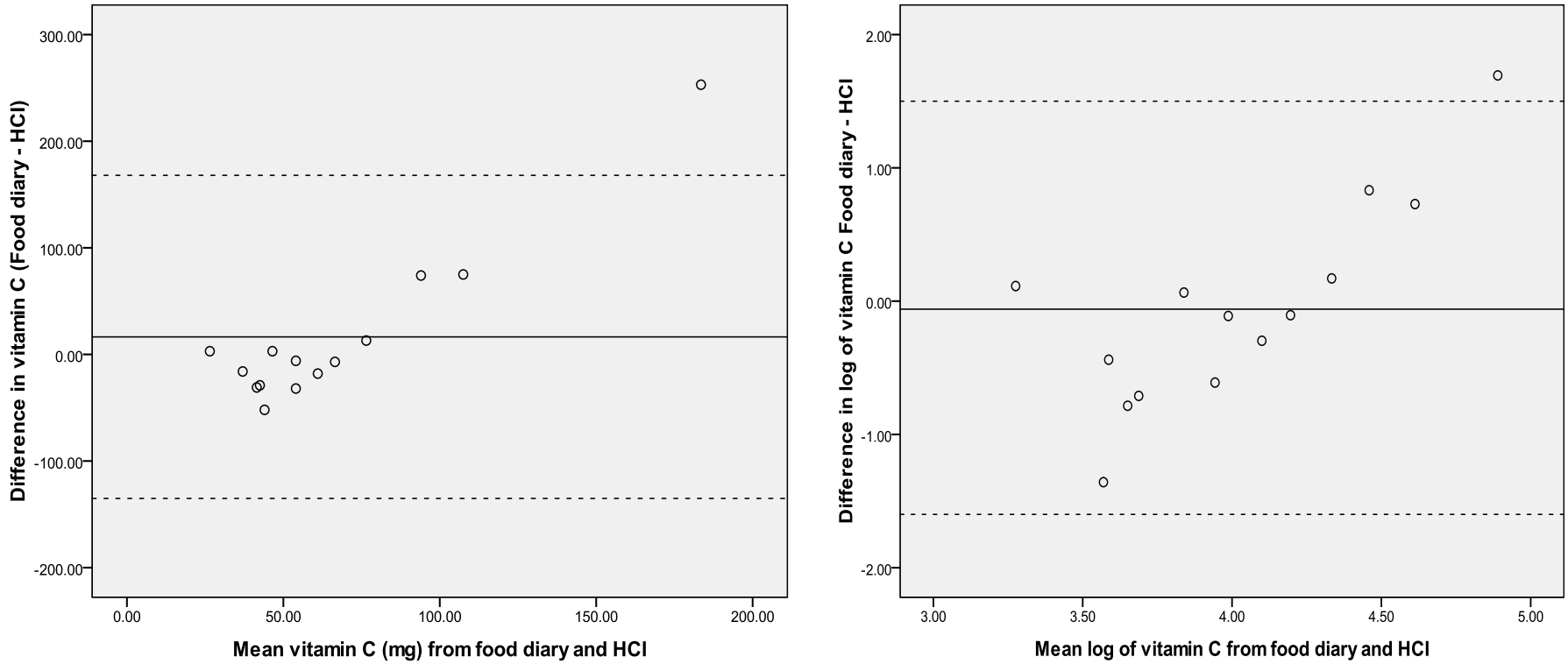
Mean difference (solid line) and upper and lower limits of agreement are plotted (dashed lines)

Figure 12. Bland-Altman plot of mean energy intake from food diary and HCI with difference in energy between food diary and HCI (graph on the left hand side). Bland-Altman plots of log mean energy intake from food diary and HCI with difference of log energy intake between food diary and HCI (graph on the right hand side).



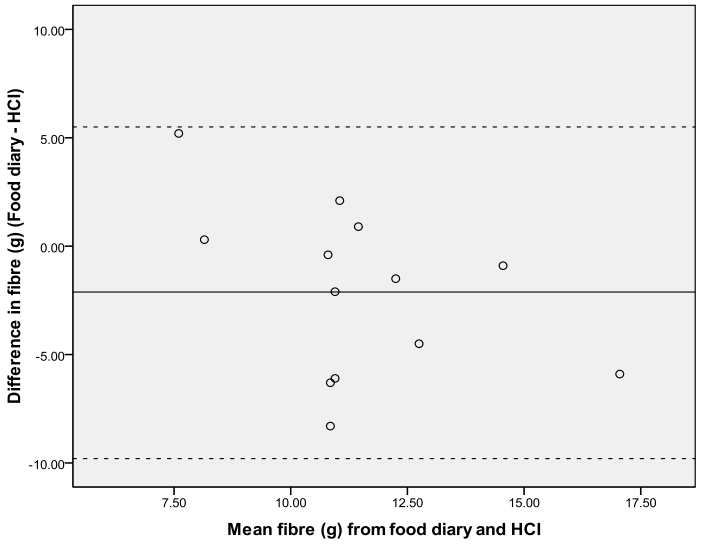
Mean difference (solid line) and upper and lower limits of agreement are plotted (dashed lines)

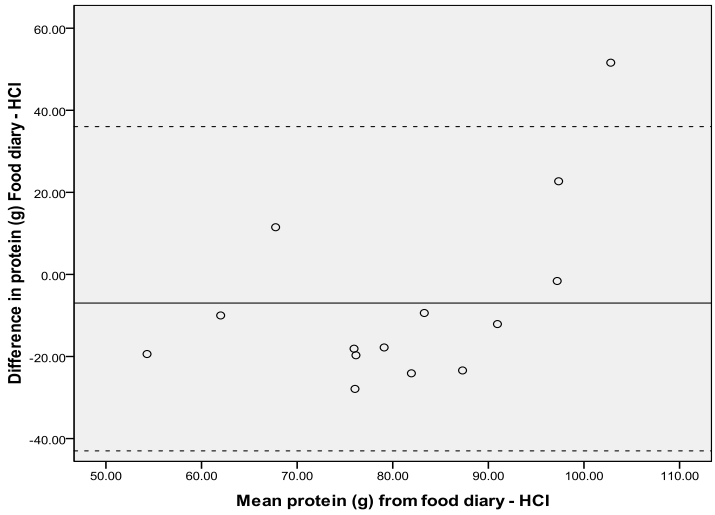
Figure 13. Bland-Altman plot of mean carbohydrate intake from food diary and HCI with difference in carbohydrate between food diary and HCI (graph on the left hand side). Bland-Altman plot of log mean carbohydrate intake from food diary and HCI with difference of log carbohydrate intake between food diary and HCI (graph on the right hand side).



Mean difference (solid line) and upper and lower limits of agreement are plotted (dashed lines)

Figure 14. Bland-Altman plot of mean vitamin C intake from food diary and HCI with difference in vitamin C between food diary and HCI (graph on the left hand side). Bland-Altman plots of log mean vitamin C intake from food diary and HCI with difference of log Vitamin C intake between food diary and HCI (graph on the right hand side).





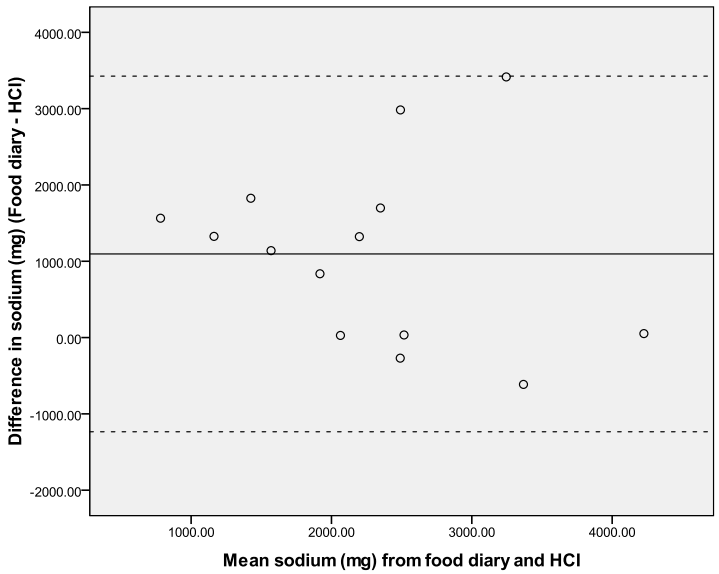


Figure 15. Bland-Altman plot of mean protein and fibre intakes and sodium from food diary and HCl with difference in nutrient between food diary and HCl

Nutrient	Mean difference	SD	LLA	ULA	Range of agreement	Mean difference (log transformed data)	SD (log transformed data)	LLA (log transformed data)	ULA(log transformed data)	Antilog LLA	Antilog ULA	% range HCI over or under estimates nutrients from food diary		Range of agreement (%)
Energy(kcal)	-1114	366	-1831	-396	1435	-0.4428	0.16222	-0.76	-0.12	0.47	0.88	212	113	99
Fat(g)	-20.1	26.0	-71.1	30.9	102.0	-0.1993	0.26511	-0.72	0.32	0.49	1.38	104	72	32
Carbohydrate (g)	-188.8	65.6	-317.5	-60.2	257.3	-0.6347	0.18980	-1.01	-0.26	0.37	0.77	270	130	140
NSP (g)	-2.1	3.9	-9.8	5.5	15.3	-0.1598	0.39384							
Sodium(g)	1096	1189	-1235	3426	4661	1.4039	3.09456							
Alcohol (g)	-6.3	21.3	-48.0	35.5	83.4	-0.5706	0.90124	-2.34	1.20	0.10	3.31	1000	30	970
Protein (g)	-7.0	22.0	-50.1	36.1	86.2	0.8325	0.42315	0.00	1.66	1.00	5.27	100	19	81
Calcium(mg)	454	254	-43	952	995	-0.0583	0.77128	-1.57	1.45	0.21	4.28	476	23	453
Vitamin C (mg)	16	77	-135	168	303	-0.1093	0.25436	-0.61	0.39	0.54	1.48	185	68	117

Table 26. Mean (SD), lower, upper and range of agreement of raw and log transformed data for difference between food diary and HCI measurements. Also shows interpretation of antilogs as a percentage of nutrient values.

Nutrient	Minimum FD values	HCI range		Mean FD values	HCI range		Maximum FD values	HCI range	
		Lower HCI	Upper HCI		Lower HCI	Upper HCI		Lower HCI	Upper HCI
Fat(g)	51	37	53	86	62	89	132	95	137

Table 27. Mean, minimum and maximum values of fat intake from food dairies and the corresponding range identified by the HCI

5.1.1.3.4. Change in fat intake, HCI score and health behaviours

The HCI was completed at baseline and at the end of treatment. By the end of treatment all arms had been given the intervention to develop long term healthy eating patterns through IDAP. So we would expect some improvement in all arms, although perhaps less in the SBS group who had only received IDAP in the last four weeks of the trial.

As an assessment of nutrient intake, the HCI was only reliable for measuring dietary fat within the margins of error described above. Questions that did not relate to dietary fat, or were not sensitive enough to measure other specific nutrients, described healthy food choices and behaviours only.

5.1.1.3.5. Change in fat intake

Fat intake reduced by an amount that was measureable by the HCI in the IDAP and the VLCD arms (39% and 31% reduction in IDAP and VLCD respectively). The difference between the rise in the SBS arm and the reduction in the IDAP and VLCD arms was also measurable by the HCI and of a clinically important amount (63g/day and 57g/day fat respectively)(Table 28).

5.1.1.3.6. Change in HCI score

HCI score increased most in the IDAP arm. An increase of one shows a move from a less healthy to a more healthy choice or behaviour on a scale of one to three. A mean increase of 11 represents a moderate improvement in 11 food choices or lifestyle behaviours, or a more dramatic improvement in five to six of these. This was an increase of 21% from baseline HCI score (Table 28).

5.1.1.3.7. Change in health behaviours

Based on the percentage frequency of each of the answers to the multiple choice questionnaires. The following change in behaviours were reported in our sample as a whole:

- More regular meals, including breakfast (Table 29),
- increased fruit and vegetable intake (Table 30)
- more high fibre food choices (Table 30)
- more high calcium food choices (Table 30)
- greater daily fluid intake (Table 30)
- more low fat food choices (Table 31),
- reduced use of sugar and salt (Table 32),
- reduced alcohol intake (Table 32),
- and increased frequency of activity (Table 32).

Participants began to choose more high fibre food and fewer convenience foods, these changes were similar in all arms (Figure 17, Figure 18).

Participants ate more breakfast (Figure 16), calcium rich foods on a daily basis (Figure 17) and more oily fish on a weekly basis. They ate fewer fatty snacks on a daily basis (Figure 18) and increased their daily fluid intake. These changes were most apparent in the SBS arm (Figure 18).

Choosing to consume fewer fatty meats (Figure 18) and fewer high sugar foods (Figure 19) was reported most in the IDAP arm. Increasing daily fruit and vegetables consumption (Figure 17), adding less oil when cooking (Figure 18) was reported most in both the SBS and IDAP arms. Changing to lower fat choices of dairy food and spreading fats was reported most in the IDAP and VLCD groups (Figure 18). Daily alcohol consumption and reduced mealtime salt use was reported most in the VLCD arm (Figure 19). Weekly activity levels increased most in the SBS and VLCD arm (Figure 19).

	Whole sample	SBS	IDAP	VLCD	SBS-IDAP	SBS-VLCD	IDAP-VLCD
Change in fat intake (g) (mean (SD)	-15 (35)	+16 (16)	-47 (6)	-41	63	57	6
HCI score	4 (8)	1 (6)	11 (1)	-1	10	0	12

* between trial arms p<0.05 (ANOVA) but sample too small for post hoc tests.

Table 28. Change in fat intake and HCI score from baseline to week +12 according to trial arm and between trial arm

	All		SBS		IDAP		VLCD	
	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment
Daily miss breakfast & lunch	7		20					
Sometimes miss breakfast & lunch	64	50	20	33	83	50	100	100
Daily breakfast and 3 meals a day	29	50	60	67	17	50		
Eat even if feel full	21	13	20		17		33	100
Sometimes eat when not hungry	29	50		67	33	50	67	
Eat when hungry & stop when full	50	38	80	33	50	50		
Eat similar foods and meals every day of week	14	13			33	25		
Eat similar foods and meals several times a week	29	38	60	34		25	33	100
Eat different foods and meals every day	57	50	40	67	67	50	67	

Table 29. Percentage frequency of response to multiple-choice questions on eating behaviours in the whole sample and by trial arm at baseline and end of treatment. Inside borders differentiate between questions.

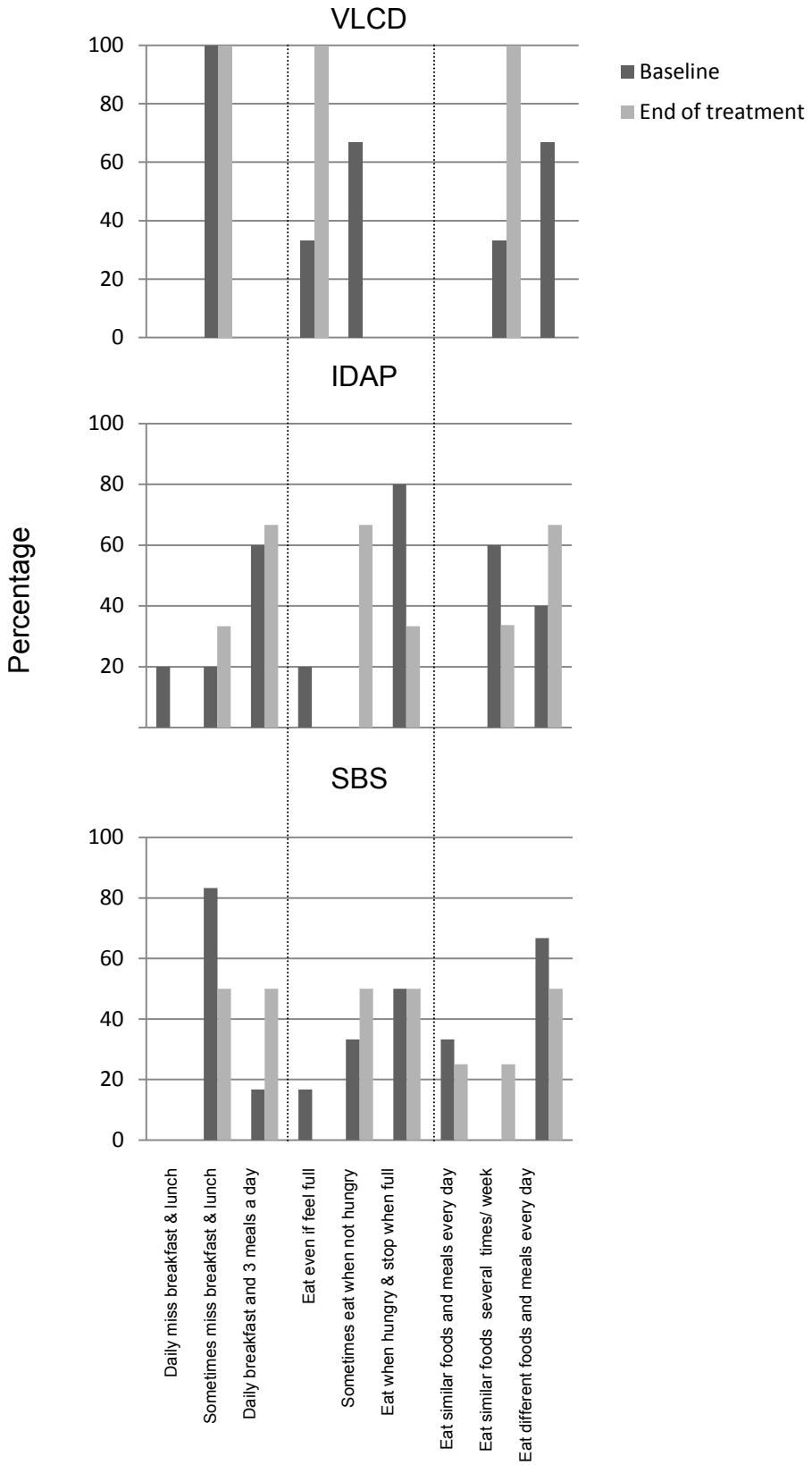


Figure 16. Percentage frequency of response to multiple-choice questions on eating behaviours by trial arm at baseline and end of treatment. Dashed lines differentiate between questions

	All		SBS		IDAP		VLCD	
	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment
Eat white cereal products	36	13	40		17	25	67	
Eat wholemeal cereal products	50	38	40	33	66	25	33	100
Eat seeded cereal products	14	50	20	67	17	50		
Hardly ever eat fruit and vegetables	7	13					33	100
Eat 1 - 4 portions fruit or veg/day	86	50	80	33	100	75	67	
Eat 5 or more portion fruit or veg/day	7	38	20	67		25		
Eat 0-1 dairy portions/day	57	50	80	33	50	50	33	100
Eat 1-2 dairy portion/day	29	25		33	33	25	67	
Eat at least 3 dairy portions/day	14	25	20	33	17	25		
Drink less than 3 glasses fluid a day	7	13	20	20				100
Drink 3-5 glasses fluid a day	29		20	20	33		33	
Drink 6-8 glasses fluid a day	64	88	60	60	67	100	67	

Table 30. Percentage frequency of response to multiple-choice questions on food choice behaviours in the whole sample and by trial arm at baseline and end of treatment. Inside borders differentiate between questions.

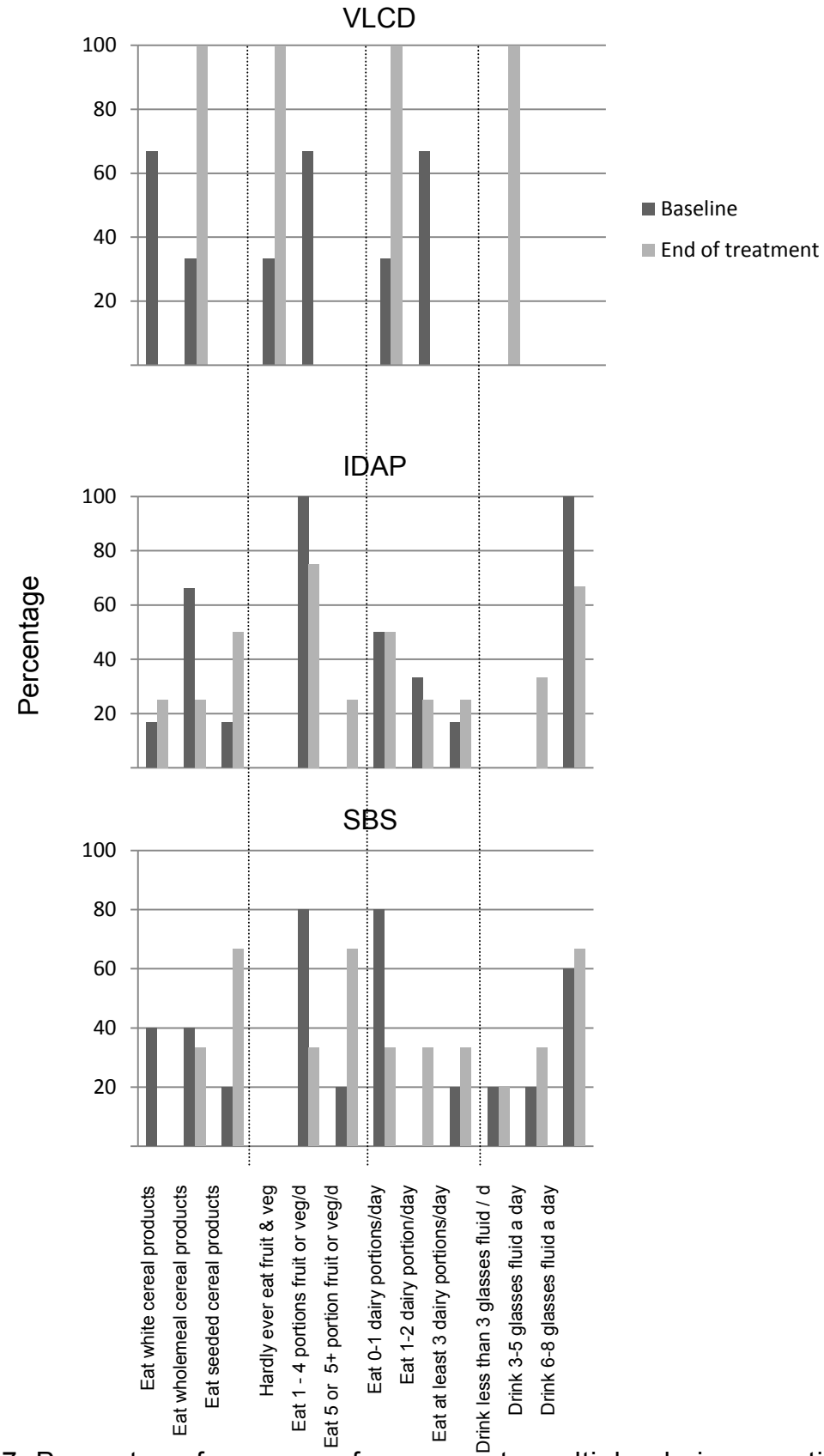


Figure 17. Percentage frequency of response to multiple-choice questions on food choice by trial arm at baseline and end of treatment. Dashed lines differentiate between questions

	All		SBS		IDAP		VLCD	
	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment
Eat full fat dairy products	21				33		33	
Eat reduced fat dairy products	50	63	60	67	33	50	67	100
Eat virtually fat free dairy products	29	38	40	33	33	50		
Eat fried or fatty meats regularly	64	25	40	33	67		100	100
Occasionally eat fried or fatty meats	7	13	20	33				
Eat lean meats only	29	63	40	33	33	100		
Meat portion covers half of plate	7				17			
Meat portion cover 1/3 of plate	50	38	60	67	33		67	100
Meat portion covers 1/4 of plate	43	63	40	33	50	100	33	
Eat fried fish each week	36	13	60		17		33	100
Eat plain white fish each week	21	13			33	25	33	
Eat plain white fish and oily fish each week	29	50	40	100	17	25	33	
Pour oil freely	36	13	20	33	40			
Measure out oil	50	38	60		60	50	67	100
Use oil spray	7	38	20	67		25	33	
Use butter or margarine	50	25	40	67	50		67	
Reduced fat spreads	21	25	20		17	25	33	100
Low fat spreads	29	50	40	33	33	75		
Eat 3 or more fatty snacks a day	7		20					
Eat 2-3 fatty snacks a day								
Eat fatty snacks once a day or less	93	100	80	100	100	100	100	100

Table 31. Percentage frequency of response to multiple-choice questions on sources of dietary fat in the whole sasmple and by trial arm at baseline and end of treatment. Inside borders differentiate between questions.

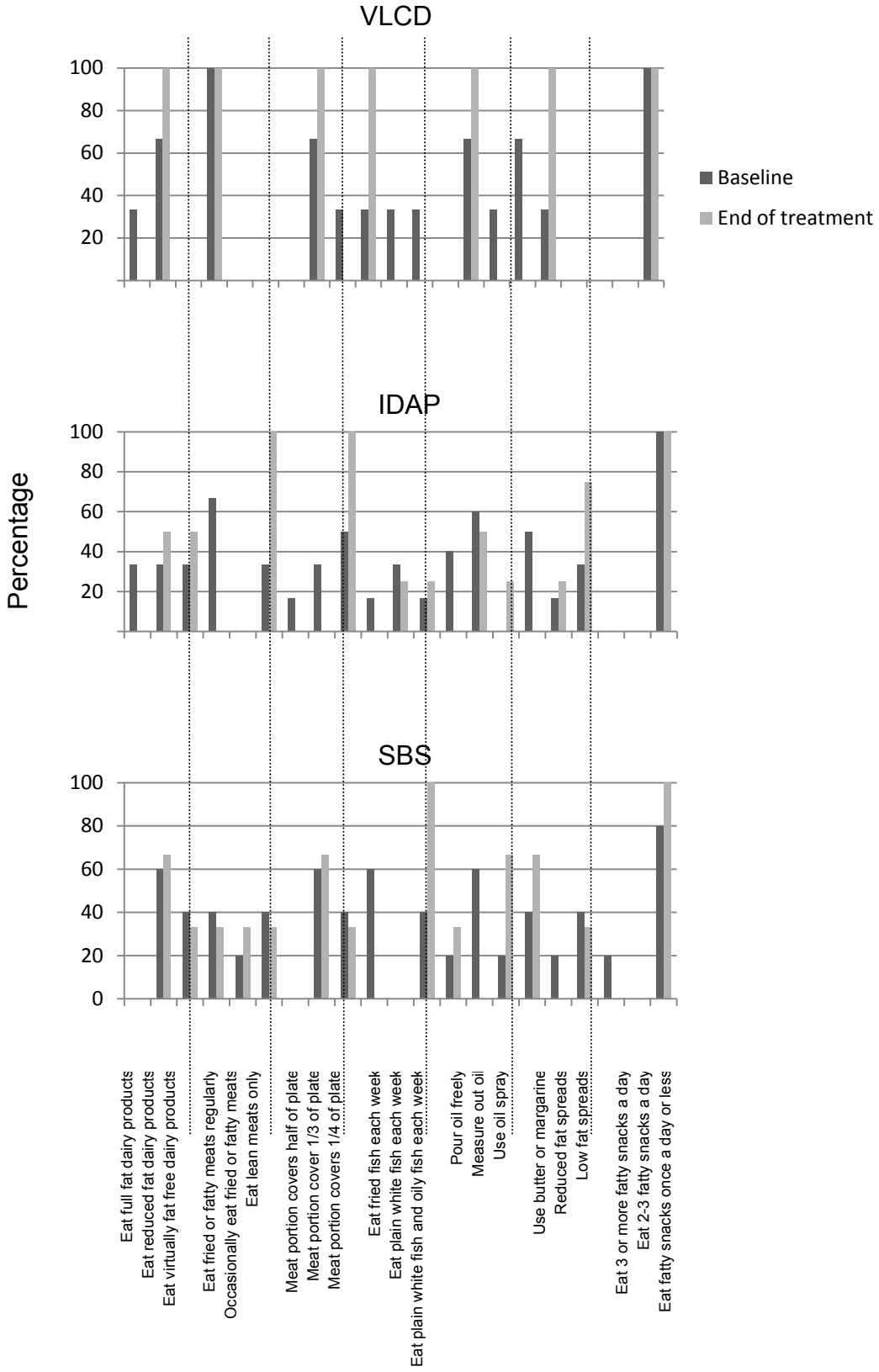


Figure 18. Percentage frequency of response to multiple-choice questions on dietary fat by trial arm at baseline and end of treatment. Dashed lines differentiate between questions.

	All		SBS		IDAP		VLCD	
	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment	Baseline	End of treatment
Always add sugar	29	13	20	33	17		67	
Sometimes add sugar	29		40		33			
Never add sugar	43	88	40	67	50	100	33	100
Eat sweets every day	7				17			
Eat sweets most days	14	13	20	33	17			
Eat sweets less than once a week	79	88	80	67	67	100	100	100
Add salt to cooking and food	36	22	40	33	33		33	
Add salt either to cooking or food	50	36	40	33	50	75	67	
Use herbs and spices instead of salt	14	53	20	33	17	25		100
Use processed foods often	21		20		17		33	
Choose reduced fat salt & sugar varieties								
Rarely use convenience food	79	100	80	100	83	100	67	100
Drink alcohol daily	14	13			17	25	33	
Drink alcohol 1-5 times a week	57	50	40	33	67	50	67	100
Don't drink alcohol	29	38	60	67	17	25		
Drink more than 2-3 units alcohol/day	57	13	20		83	25	67	
Drink less than 2-3 units alcohol/day	14	50	20	33		50	33	100
Don't drink alcohol	29	38	60	67	17	25		
Spend most of spare time sitting down	43	13	60		33	25	33	
Exercise on 2-3 day of the week	29	38	20	67	33	25	33	
Exercise 30 minutes or more each day	29	50	20	33	33	50	33	100

Table 32. Percentage frequency of response to multiple-choice questions on sucrose, salt alcohol and activity for the whole sample by trial arm from baseline to end of treatment. Inside borders differentiate between questions.

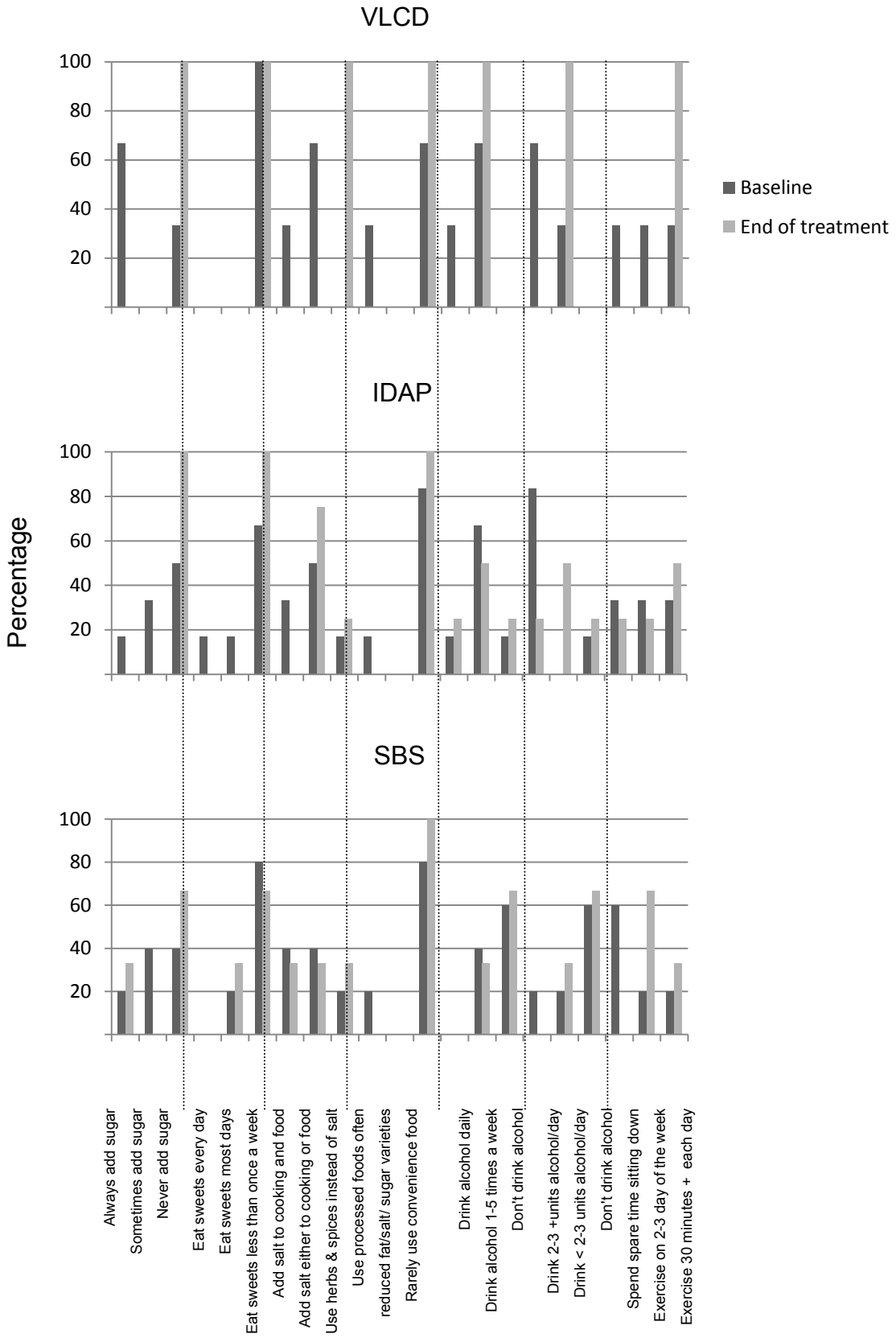


Figure 19. Percentage frequency of response to multiple-choice questions on sucrose, salt alcohol and activity by trial arm from baseline to end of treatment. Dashed lines differentiate between questions

5.1.1.3.8. Change in fat intake and HCI score as mediators of change in body fat

We investigated whether change in dietary fat intake or HCI score mediated the effect of dietary intervention on fat mass. This is reported, together with other multi-level models, in chapter six.

5.1.1.4. *Discussion*

5.1.1.4.1. Baseline nutrient intake

In comparison with the Department of Health dietary reference values (DRV) for nutrients (DOH, 1991), mean intake data showed the participants exceeded recommendations for total fat, saturated fat, alcohol (although only the VLCD group exceeded alcohol recommendations) and salt (again only the VLCD group notably exceeded this). The participants met the recommendations for protein and calcium intake. They met the reference nutrient intake (RNI[2]) for vitamin C, but not quite for vitamin C in smokers; those in the VLCD group only met the estimated average requirement (EAR[3]) for vitamin C. The participants fell short of the requirement for carbohydrate and non-starch polysaccharides (fibre) (Table 33). These aspects of the participants' diets were also poorer than the general population as determined by the national diet and nutrition survey (NDNS) (FSA and DOH, 2010) (Table 33).

[2] The RNI is the level of intake considered to be sufficient to meet the requirements of 97.5% of the population

[3] The EAR is the level of intake considered to be sufficient to meet the requirements of 50% of the population.

Nutrient	Participants	DRV (DOH, 1991)	General Population (FSA and DOH, 2010)
Total fat (% energy)	39	33	33
Saturated fat (% energy)	15	10	12
Total Carbohydrate (% energy)	43	47	45
Alcohol (% energy)	6	5	6
Protein (% energy)	15	15	16.5
Salt (g/day)	7.4	6	6.1
NSP (g/day)	11	18	14
Calcium (mg/day)	882	RNI: 700mg	824
Vitamin C (mg/day)	78	RNI: 40mg (Smokers: 80mg)	94

Table 33. Baseline nutrient intake in comparison to the dietary reference values and current intakes of the general population

This is in line with a meta analysis of cross-sectional studies by Dallongville et al in 1998 that also showed smokers have a higher intake of total and saturated fat and a lower intake of fibre than non smokers (Dallongville et al., 1998). The meta analysis also provided evidence of higher intakes of energy and alcohol, lower intakes of polyunsaturated fat, vitamin E and β-carotene. The authors showed that protein and carbohydrate intakes did not differ between smokers and nonsmokers.

Comparing DeMiST measures of energy intake with estimated energy requirements showed that the underreporting in our sample might have been below that previously observed in overweight populations (Kretsch, 1999, Hill and Davies, 2001). The food diary was very similar to others used in the field and there is no reason to expect its format led to more accurate reporting. However, participants were advised that if they were to take part fully in the trial they had to demonstrate their commitment to it by

completing the food diary accurately. This incentive may have resulted in more careful self reporting. Secondly, there was a potential source of personal bias. I carried out the analyses of the food diaries and I am keenly aware of underreporting, so where there was ambiguity I tended to over rather than underestimate.

5.1.1.4.2. The Healthy Choice Index (HCI)

Despite good correlation between measures of nutrient intake from the food diary and the HCI, investigating the levels of agreement between these two measures showed that the HCI could not provide a valid estimate to determine high or low intakes of energy, carbohydrate, fibre, sodium, alcohol, calcium, vitamin C or protein. The risk in accepting any new clinical measure to replace a gold standard measure through considering only correlation between the measures rather than their limits of agreement has been well documented since the 1980s (Bland & Altman, 1986). However, some studies that do so continue to be published (Paxton et al., 2011).

The HCI was able to estimate fat intake reasonably accurately, giving limits of agreement from 28% below to 4% above the value obtained from food diary data. This was accurate enough to differentiate between high, medium and low intakes of our population. Changes in the frequency of responses to food behaviours, food choice and physical activity were captured by the HCI. The sample was too small to look for statistically significant changes between arms and over time. However, it did show worthwhile improvements in eating behaviours, for example daily breakfast eating and fruit and vegetable consumption increased and participants chose to eat

foods that were high in sugar and fat less frequently. Improvements, that are all necessary, in the diets of smokers (Stefanikova et al., 2009, Margetts and Jackson, 1993).

However, we have assumed that a reported change in HCI score reflected a change in behaviour. But, it is possible that after help and support to change behaviours participants scored what they had learnt they ought to do or what they had agreed they would do, rather than what they actually did.

The HCI was not a good indicator of whether diets were high or low in many nutrients, but it may identify large changes in dietary fat and improvements in food choices and eating behaviours. Future efforts could focus on refining questions to improve sensitivity to detect smaller changes in fat intake and change in the other nutrients discussed. It could then be used in an adequately powered sample to test its validity. Before it can be used as a nutrient assessment tool within clinical trials its repeatability and sensitivity to dietary change associated with a change in clinical outcomes is needed.

5.2. The hunger and food craving score (HCS)

5.2.1. Introduction

As discussed in chapter one, there are no scales which capture both hunger and craving for food or distinguish between these two motivations. In addition, no current food craving scales are brief enough or designed to be administered daily. We

needed such a scale to identify day-to-day change in hunger and food craving, which may differ by dietary intervention, to show whether hunger and/or food craving is associated with urges to smoke.

We mirrored the questions on craving for food on the mood and physical symptoms scale (MPSS) which has been shown to be a reliable measure of cigarette withdrawal (West, 2004). The MPSS is brief and asks two questions to measure cigarette cravings: “How much of the time have you felt the urge to smoke in the last 24 hours?” and “How strong have these urges been?” Answers are chosen from a six point rating.

To capture the amount of time craving food and the strength of food craving we asked analogous questions. Food craving was broken down into desire for sweet food, sweet and fatty food, and savoury and fatty food. These categories were chosen as previous studies have shown an increase in the intake of sweet foods (Rodin, 1987, French et al., 1996), sucrose and fat (Hall et al., 1989) after smokers quit. Women typically crave sweet, and sweet and fatty foods. Men typically crave savoury foods (Pelchat, 1997). The questionnaire also included a question on hunger and a desire for healthy food, which aimed to assess genuine food need or hunger (Figure 20).

We measured hunger and food craving at baseline and daily for the first four weeks after quit day. So how well did the HCI capture different components of food desire and food need? Was it possible to reduce the data for ease of analyses?

Rate how you have felt about food in the last 24 hours

Circle the number in the column that best describes your feeling

	Not at all	Slightly	Somewhat	Very much	Extremely
1. I have felt genuinely hungry and in need of food	0	1	2	3	4
2. I have wanted or craved:					
a. Sweet food e.g. sweets, sugary drinks	0	1	2	3	4
b. Sweet and fatty foods e.g. chocolate, biscuits, cakes	0	1	2	3	4
c. Savoury and fatty food e.g. crisps, chips	0	1	2	3	4
d. Healthy snacks e.g. fruit, raw vegetables	0	1	2	3	4

3. How much of the time have you craved sweet or fatty food in the past 24 hours? *(Circle one number)*

Not at all	A little of the time	Some of the time	A lot of the time	Almost all the time	All the time
0	1	2	3	4	5

4. How strong have these cravings been? *(Circle one number)*

No urges	Slight	Moderate	Strong	Very strong	Extremely strong
0	1	2	3	4	5

Figure 20. Hunger and food craving score (HCS)

5.2.2. Method

We checked whether the data from the HCS was suitable for principal components analysis by doing two tests (UCLA ATA, 2011). Firstly, the Kaiser-Meyer-Olkin Measure of Sampling Adequacy should have a minimum cut off value of 0.6. Secondly, Bartlett's Test of Sphericity should show that the correlation matrix is significantly different from an identity matrix (an identity matrix consists of all the diagonal elements being one and all off diagonal elements being zero).

We then extracted the main components this questionnaire sought to address, using principal components analysis with a direct oblimin rotation in SPSS 17. This is the standard method when the factors are allowed to correlate (a non-orthogonal/oblique solution). As discussed in chapter three (section 3.1.2) hunger and food craving have been shown to be interdependent. Components were included using the Kaiser criterion i.e. if they had an Eigenvalue greater than one.

We reduced the data by creating a 'component score' from the mean scores of answered questions showing good internal consistency ($r > 0.8$). These mean scores were used in further analyses.

To confirm the internal consistency of component 1, the measure of craving for sweet or fatty foods, we calculated Cronbach's alpha. We did this for one day's data each week, to see if the internal consistency of the questionnaire changed over time.

5.2.3. **Results**

The Kaiser-Meyer-Olkin Measure of Sampling Adequacy and the Bartlett's Test both met the criteria for suitability to perform a principal components analysis (Table 34). There were two principal components identified, which together accounted for 80% of the variance (Table 35, Figure 21).

The first component had a high correlation (>0.8) on all the questions relating to cravings for sugary or fatty foods both in the pattern (Table 36) and structure matrix (Table 37). I called this component 'food desire', the score of which was a mean of answers to questions 2a, 2b, 2c, 3 and 4 (Figure 20). The second component was most highly correlated with a desire for healthy food (r=0.9) both in the pattern and structure matrix. It was also more weakly correlated with 'genuine hunger' (r=0.7). I called this component 'food need' and it was scored solely on healthy food desire as the plot in rotated space showed 'genuine hunger' to be midway between component 1 and 2 (Figure 22).

There was good internal consistency of the elements that made up food desire at various point in time (Table 38).

Kaiser-Meyer-Olkin Measure of Sampling Adequacy		0.6
Bartlett's Test of Sphericity	Approx. Chi-Square	63.0
	df	21.0
	Sig.	<0.001

Table 34. Kaiser-Meyer-Olkin and Bartlett's Test for the HCS

	Initial Eigenvalues			Rotation Sums of Squared Loadings[a]
Component	Total	% of Variance	Cumulative %	Total
1	4.3	62.1	62.1	4.3
2	1.2	17.6	79.7	1.5
3	0.7	10.4	90.1	
4	0.5	7.2	97.3	
5	0.1	2.0	99.3	
6	0.0	0.6	99.9	
7	0.0	0.1	100.0	

Table 35. Total variance explained by component extraction from the HCS

	Component	
	1	2
Hunger	0.542	0.730
Sweetcraving	0.875	0.167
Sweetfatcraving	0.864	0.251
Sweetsavourycraving	0.788	0.037
Timecravingsugarandfat	0.972	0.156
Strengthofcraving	0.969	0.173
Healthyfoodcraving	-0.002	0.899

Table 36. Pattern matrix for components 1 and 2

	Component	
	1	2
Hunger	0.424	0.653
Sweetcraving	0.873	0.009
Sweetfatcraving	0.846	0.097
Sweetsavourycraving	0.808	-0.109
Timecravingsugarandfat	0.976	-0.020
Strengthofcraving	0.970	-0.003
Healthyfoodcraving	-0.170	0.930

Table 37. Structure matrix for components 1 and 2

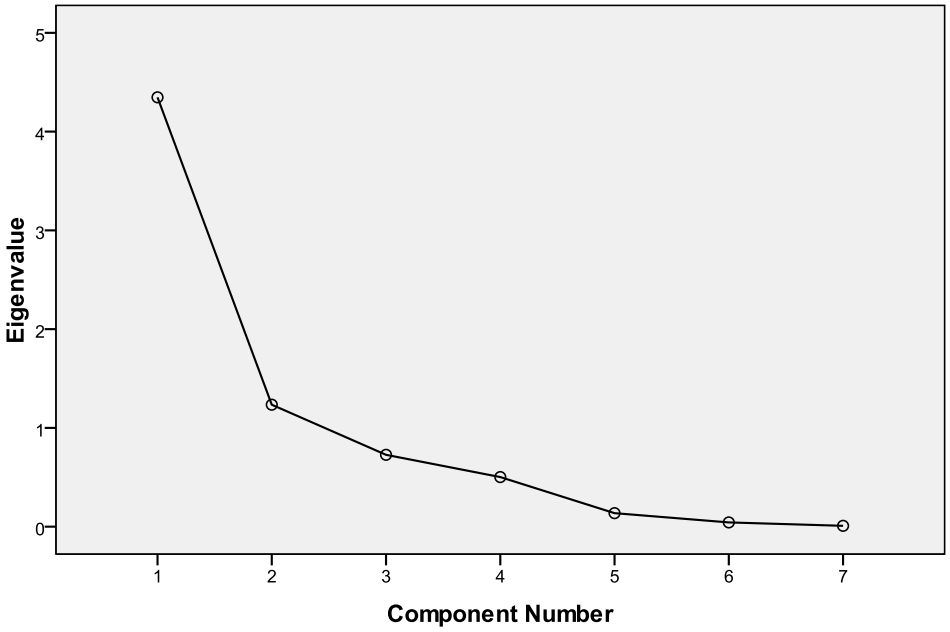


Figure 21. Scree plot of components in the HCS

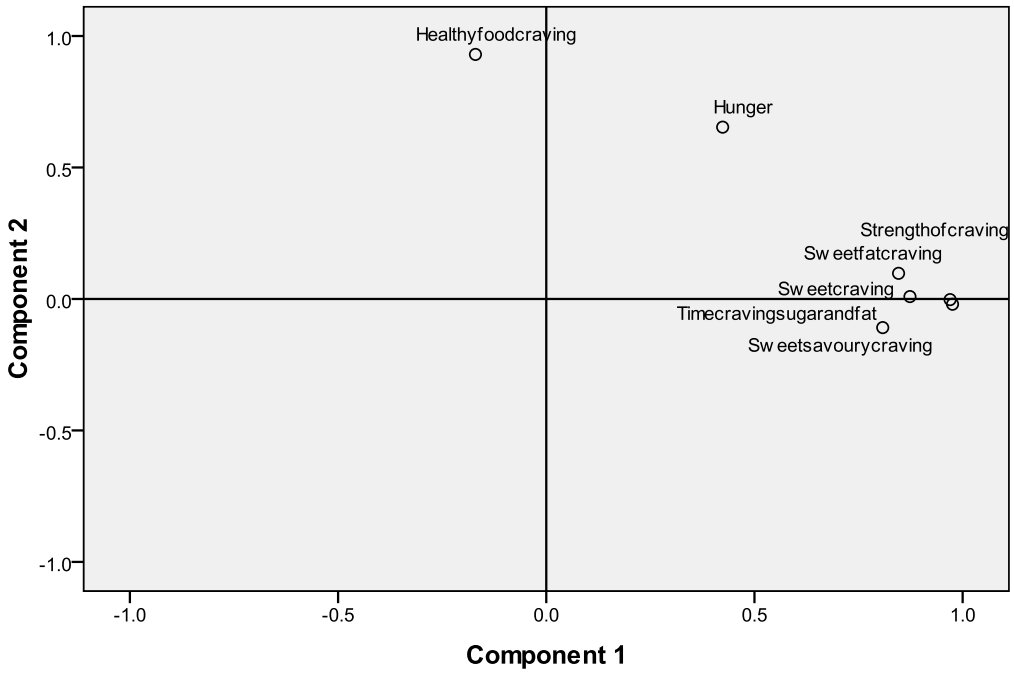


Figure 22. Component plot in rotated space using oblimin rotation

Day since quit date	cronbach's alpha
1	0.9
7	0.9
14	0.9
27	0.8

Table 38. Cronbach's alpha for Component 1 'food desire' over time

5.2.4. Discussion

The HCS captured two different motivations to eat, the first was a craving for sweet or fatty foods and the second was desire to eat healthy foods. The high correlation between the elements in the first component, lent itself well to data reduction. This suggests that it may not be necessary to capture craving for sweet, sweet and fatty or sweet and savoury foods separately as discussed in Toll's paper (Toll et al., 2008). Rather, grouping the desire for these foods together may be just as reliable measure. The second component was unexpected; it did not fit well with the notion of genuine hunger. Although hunger can be differentiated from craving as a drive for any food type and the healthy foods defined here were in direct contrast to the fatty and sugary foods usually craved (White, 2002). However, the expected defining question on hunger was strongly correlated to both components so we are still some way from defining this as a separate entity from food craving.

One limitation of developing a brief questionnaire, such as this, was that we could not measure all dimensions of food craving such as perceived positive affect (Toll et al., 2008, Nijis et al., 2007), loss of control, preoccupation and emotional craving (Nijis et al., 2007). Instead, we focused on intensity of craving, the feeling most likely to lead to impulsive behaviour rather than preoccupation; the behavioural aspects were left to speak for themselves as outcomes on smoking and weight. In addition, we used the words 'crave and want' in contrast with 'genuine and need' without further explanation of their meaning, so they were open to interpretation. For some people the distinction between the two may have been unclear.

Future efforts to differentiate between hunger and food craving require us to backtrack a little. We need to expand our questionnaire further before reducing it to the brief tool that we needed. Our questions and definitions need to incorporate more dimensions of hunger and craving which clarify the differences between the two. It would be helpful to start with a qualitative study to understand whether and how people conceptualise, express notions of craving or desire for food, and differentiate these from more physiological notions of hunger.

The value of developing this tool goes beyond smoking cessation studies; measuring food craving is being developed for research into the causes and treatments of obesity, mood disorders and addictions. However, none of these have sought to differentiate between physiological hunger and the more impulsive based food craving, which could be confused.

5.3. Measure of confidence in trial arm

5.3.1. Introduction

Blinding of participants is the usual method to avoid participants' expectations affecting the apparent response to treatment (Altman et al., 2001). Participants who know the treatment they receive may have favourable or unfavourable expectations of it. If they are assigned to a treatment they do not think will work or a control group, they may become disheartened and drop out early.

It was impossible to blind the different dietary interventions in DeMiST so participants were asked, prior to randomisation, which treatment they were most confident would be successful. We used this to determine whether expectation of success in the allocated treatment was associated with attrition.

5.3.2. Method

We coded participants according to whether they were randomised into the arm which they thought would be most successful or not. We then compared the association between this and the mean length of retention in the study using unadjusted linear regression in SPSS 17.

5.3.3. Results

Most participants (10/16, 63%) thought the IDAP arm had the greatest chance of success, (5/16, 31%) thought the VLCD would be most effective and one participant thought the SBS arm would be most successful. Sixty-three percent of participants (10/16) received the arm they thought would be successful and 37% (6/16) did not.

Unadjusted linear regression showed no significant association between considering a treatment would be successful and length of time staying in the treatment programme (Table 40). The mean difference showed those who did not receive the allocation they thought would be successful stayed in the study -0.3 weeks [-3.2, 2.6] less than those who did. However, confidence intervals around this mean difference were large. In addition, semi-structured interviewing revealed some very strong

feelings of disappointment in those receiving SBS, which was interpreted as a control group, a treatment that they did not feel met their needs (chapter four).

	Regression coefficient	Standard error	p value	95% LCI	95% UCI
(Constant)	9.3	0.8		7.5	11.1
Received allocation thought successful	-0.3	1.3	0.826	-3.2	2.6

Reference category: did not receive the treatment thought successful

Table 39. Unadjusted linear regression coefficient with 95% confidence intervals for association between participants who received the allocation they considered to be successful and the length of time they stayed in study

5.3.4. Discussion

There was no evidence that participants dropped out of DeMiST early because they did not receive the treatment they thought had the most chance of success. As discussed previously in section 4.2.3.2 there are many trials which have examined the association of receiving preferred treatment on attrition, overall these have not found an association.

However, our qualitative findings suggest that participants had strong feelings of disappointment when they did not receive their favoured treatment but other reasons for attrition were given, for example life circumstances becoming difficult and failure to stop smoking (chapter four).

6. DeMiST RESULTS: CHANGES IN CIGARETTE CRAVING, SMOKING STATUS AND PHYSICAL MEASURES BY TRIAL ARM

6.1. **Introduction**

The primary objective of DeMiST was to determine acceptability and feasibility of running a dietary intervention trial in smoking cessation clinics, which was discussed in chapter four.

Chapter six contains the results of the quantitative measurements collected to meet the secondary and tertiary outcomes, the measurement of which have been described in detail in chapter three. This fulfils objective seven: to report on the effects of the dietary interventions on urges to smoke and whether this is a result of change in desire for food or ketosis, and objective eight of the thesis: to report on the effects of dietary interventions on body weight and chronic disease risk factors in quitting smokers.

We have included analysis for data up to the end of treatment. Data was not available at all time points, in particular, six month and 12 month follow up data was not available at the time of completing this PhD so long term outcomes were not included.

The outcomes assessed were:

- The effects of each intervention on cigarette cravings and whether this was mediated by hunger or ketosis,
- Smoking cessation rates in each intervention arm,
- Weight gain according to treatment arm. In addition, we included a sub-group analysis splitting by those who abstained (abstainers) and those who lapsed back to smoking but did not abandon their quit attempt (lapsers)?
- The effects of each intervention on body composition, cardiovascular risk factors, blood glucose and lung function.

We were unable to recruit sufficient people to test the hypothesis that cravings would be worsened by hunger, but would improve with ketosis. Nevertheless, we have analysed the data using the same methods, as we would have done if we had been able to recruit full numbers. The reasons for this were two-fold. Firstly, they allowed me to show that I can carry out such analyses for the purposes of the PhD and secondly allow us to identify large effects that may provide preliminary evidence for these interventions.

As described in the protocol (section 3.7) we analysed data in completers to investigate efficacy of interventions if they were taken as planned. Sub-analyses and modelling excluded those who were not adherent to the VLCD (verified by the absence of urinary ketones). Then we carried out intention to treat analyses (ITT), which accounted for people who began treatment but dropped out.

ITT gives a pragmatic estimate of benefit were the intervention to be used in clinical practice (rather than the potential benefit in those who receive treatment exactly as planned). Without ITT analyses falsely positive results are common, as those with poor outcomes may drop out of the intervention and bias the results (Hollis and Campbell, 1999). Where there were missing values, we imputed baseline observation carried forward (BOCF).This assumed that all those who dropped out of the trial early relapsed to smoking and regained lost weight. Where there was missing data but participants had not dropped out, a mean of their weight measured immediately before and after was imputed. Imputation from available longitudinal data for a particular person is considered the most reliable way of dealing with missing data (Engels and Diehr, 2003).

As described in the protocol (section 3.7) we focused on outcomes at the following key time points. Firstly we did so regardless of smoking status and then in abstainers and lapsers only. Change in anthropometrics (measurements of weight, waist and hip) were investigated:

- From baseline to prequit week, to give an idea of the effects of diet before quitting,
- From baseline to the first week post quit date – when abstinence rates are likely to be highest and differences between the trial arms can be most clearly seen3.4.3,
- At four weeks post quit date which defines the end of Stage 1 of treatment and the Russell standard of abstinence
- At the end of Stage 2 of treatment (12 weeks post quit) when the control group will have received the IDAP intervention.

Multilevel modelling of the trajectory of weight change and change in fat mass used all the weekly time points to investigate the effects of trial arm and smoking status. In addition we investigated the mediating effects of change in fat intake and HCI score on change in fat mass as discussed in the previous chapter .

We modelled the trajectory of cigarette cravings using daily measures during the first four weeks of treatment. We paid particular attention, as per protocol, to the change from baseline cigarette craving score in the first 24 hours and during the first week when differences between trial arms were expected to be at their highest. In the multilevel model this was taken into account using a time*trial interaction. Multilevel modelling was carried out using MLwiN 2.20 software.

The most sensitive approach for detecting differences in cravings between trial arms is to adjust for baseline cravings as a covariate (West et al., 2006). However as the sample size was so small we used change in craving score rather than baseline score as a covariate, to minimise the number of variables in the model. Multilevel modelling between individuals at level two is limited by the level two sample size and follows the same rules as single level regression.

To minimise overfitting we did not test all the explanatory and mediating variables in one model, as we would have liked, instead we tested them individually in separate models as described in later sections. Even so, in such a small sample we could not

Trial arm	All	SBS	IDAP	VLCD
N	16	6	6	4
Age	46(14)	56 (7)	37 (17)	46 (4)
Fagerstrom Score	5(2)	5 (2)	5(2)	6 (1)
Number of cigarettes per day	23(8)	21 (7)	19 (6)	30 (8)
MPSS-C	3.7(0.8)	3.5(0.5)	3.8(0.3)	4.0(2.1)
Forced Vital Capacity (FVC) (L)	3.6(1.0)	3.3 (0.7)	3.5 (0.7)	4.5 (1.6)
Forced Expiratory Volume in 1 sec (FEV1) (L)	2.9(0.8)	2.6 (0.6)	3.0 (0.6)	3.2 (1.3)
FEV1/FVC ratio (%)	80(9)	80 (6)	85 (7)	71 (11)
Total Cholesterol (TC) (mmol/L)	5.6(1.5)	5.5 (1.4)	5.4 (1.6)	6.2 (2.0)
HDL-cholesterol (mmol/L)	1.2(0.3)	1.2 (0.3)	1.3 (0.3)	1.0 (0.2)
LDL-cholesterol (mmol/L)	3.0(1.2)	2.5 (1.2)	3.2 (1.5)	3.5
TC:HDL ratio	4.8(1.5)	4.8 (1.3)	4.3 (1.6)	6.2 (0.8)
Triglyceride (mmol/L)	1.3(0.7)	1.6 (0.9)	1.0 (0.4)	1.6 (0.9)
Glucose (mmol/L)	4.7(0.4)	4.6 (0.4)	4.7 (0.4)	5.1 (0.2)
White blood cells (WBC) ($x10^9$/L)	7.4(2.7)	5.7 (4.1)	7.8 (1.6)	9.3 (0.7)
Mean Corpuscular Volume (MCV)	92(4)	92 (3)	93 (5)	91 (2)
Haemoglobin (Hb) g/dl	14.4(1.3)	14.2 (0.7)	14.2 (1.7)	15.5 (1.2)
Platelets ($x10^9$/L)	277(91)	275 (63)	282 (123)	269 (59)
C-Reactive Protein (mg/L)	4.3(3.6)	6.8 (2.2)	1.8 (1.8)	6.5 (6.4)
CO (ppm)	22(8)	19 (9)	24 (9)	25 (7)
Blood pressure (mmHg)	126/79(16/10)	128/82 (13/5)	124/76 (23/13)	123/81 (9/10)
Weight (Kg)	79.7(13.8)	81.3 (11.4)	73.5 (15.4)	86.7 (14.1)
Men (Kg)	91.6(5.5)	91.5	-	91.7(7.7)
Women (Kg)	77.0(13.8)	79.3(11.4)	73.4(15.4)	81.6(20.9)
BMI (Kg/m^2)	29.52(5.60)	30.3 (4.3)	27.6 (5.3)	31.3 (8.2)
Hip circumference (cm)	106(12)	107(7)	104 (16)	109 (12)
Waist circumference (cm)	96(13)	97 (9)	91 (16)	102 (14)
Fat Mass (Kg)	28.8(9.7)	31.3 (7.5)	27.4 (12.0)	27.3 (10.7)
Fat Free Mass (Kg)	50.9(10.2)	50.1(10.0)	46.1(4.3)	59.4(13.5)
Total Body Water (Kg)	37.0(6.9)	36.7 (7.3)	33.7 (3.2)	42.6 (8.5)
BMR (Kcal)	1573(257)	1515 (236)	1494 (165)	1765 (348)
Healthy Choice Index (HCI) Score	52(6)	54 (8)	53 (3)	47 (6)
Food desire	2.1(1.0)	2.3(1.3)	1.8(0.8)	2.3(1.1)
Food need	1.9(0.8)	1.8(0.8)	2.0(1.2)	2.0(<0.1)

Table 40. Baseline characteristics of all participants by trial arm (mean(SD))

rule out over-fitting and so conducted the analysis predominately to demonstrate my ability to do so and ability to interpret these analyses. Therefore, we interpreted our coefficients and model plots cautiously with careful reference to how well the models fitted the raw data.

6.2. Results

6.2.1. Baseline characteristics

As we were unable to randomise more than fourteen participants into DeMiST 1 and two participants into DeMiST 2 it was not possible to analyse DeMiST 1 and 2 separately and then combine them in a meta-analysis as we had planned. Instead to maximise the data we had we combined the results and adjusted for baseline differences.

Participants were overweight (Table 40), white European population in middle age, heavy smokers and predominantly female. The majority had a mortgage or owned their home, and were in employment. Half were educated up to secondary school level and a quarter had a professional qualification (Table 41).

If we had recruited the full sample size, no difference in baseline characteristics between the groups would have been expected, as randomisation determined allocation into each trial arm. Randomisation, based on the theory of probability, generates similar numbers in the three trial arms that have an approximately equal distribution of known and unknown potential confounders. Therefore, any differences

should be due to chance alone rather than a reflection of selection bias (Altman et al., 2001).

Trial arm	All	SBS	ITDA	VLCD
Gender				
Male	19%	1/6	-	2/4
Female	81%	5/6	6/6	2/4
Ethnicity				
White	100%	6/6	6/6	4/4
Pakistani		-	-	-
Bangladeshi		-	-	-
Indian		-	-	-
Black-African		-	-	-
Black Caribbean		-	-	-
Black-other		-	-	-
Chinese		-	-	-
Other groups – Asian		-	-	-
Other groups – other		-	-	-
Car ownership				
No car		-	-	-
I car	69%	2/6	6/6	3/4
2 or more cars	31%	4/6	-	1/4
Home ownership				
Owning it/Buying it	56%	5/6	2/6	2/4
Renting it	38%	1/6	4/6	1/4
Not disclosed	6%	-	-	1/4
Educational level				
Secondary	50%	3/6	2/6	3/4
Sixth Form	6%	1/6	-	-
	25%	1/6	3/6	-
University/Polytechnic	13%	-	1/6	1/4
Still In Full-time		-	-	-
None of the above	6%	1/6	-	-
Employment				
In paid employment	75%	3/6	5/6	4/4
Unemployed	13%	2/6	-	-
Looking after home	13%	1/6	1/6	-
Retired		-	-	-
Full-time Student		-	-	-
Medical history				
Depression/Anxiety	20%	1/6	1/6	1/4

Table 41. Baseline characteristics all participants and by trial arm (Frequency)

However, with our small sample and combining DeMiST 1 and DeMiST 2 participants there were moderate differences between trial arms such as age and gender (Table 40, Table 41). These may have influenced change in weight so we adjusted for these in analyses of weight and body fat changes.

6.2.2. Cigarette craving

Baseline MPSS-C in smokers, measured before they attempted to quit was approximately four in all trial arms (Table 40), scored from a range of zero to six. There was a mean fall after 24 hours post quit date in the SBS arm (-1.1), a rise in the IDAP, (0.8) and no change in the VLCD arm. Mean differences between these arms was clinically, but not statistically different (Table 42). After one week, there was a reduction in score of approximately two in all arms. After one month, MPSS-C had reduced most in the VLCD arm and least in the SBS arm (Table 42).

Trajectories of mean change in daily MPSS-C score varied considerably in each trial arm, perhaps less so in the SBS arm. MPSS-C appeared to fall most towards the end of the month in those on the VLCD (Figure 23).

We can see from the trajectories in individuals that this variability was not clearly associated with 7 day point prevalent abstinence or daily smoking (cigarette smoking was recorded daily in individuals: 21, 26, 30, 31, 32) (Figure 24).

Change from baseline in:	SBS (n=5)	IDAP (n=3)	VLCD (n=2)	VLCD-SBS	IDAP-SBS	VLCD-IDAP
After 24 hours MPSS-C	-1.1 (0.7)	0.8 (1.7)	0.0 (0.7)	1.1[-1.7, 3.9]	1.9[-0.6, 4.4]	-0.8[-4.0, 2.3]
After 7days MPSS-C	-1.8(0.8)	-2.0(0.9)	-2.0(2.1)	-0.2[-2.9, 2.5]	-0.2[2.6, 2.2]	0.0[-3.0, 3.0]
After 1month MPSS-C	-1.1(1.0)	-2.5	-4.5	-3.4	-1.4	-2.0

Table 42. Mean change(SD) in trial arms and mean difference [95% CI] between trial arms in MPSS-C after 24 hours, 7 days and 1 month post quit date (ANOVA with Gabriel post hoc tests)

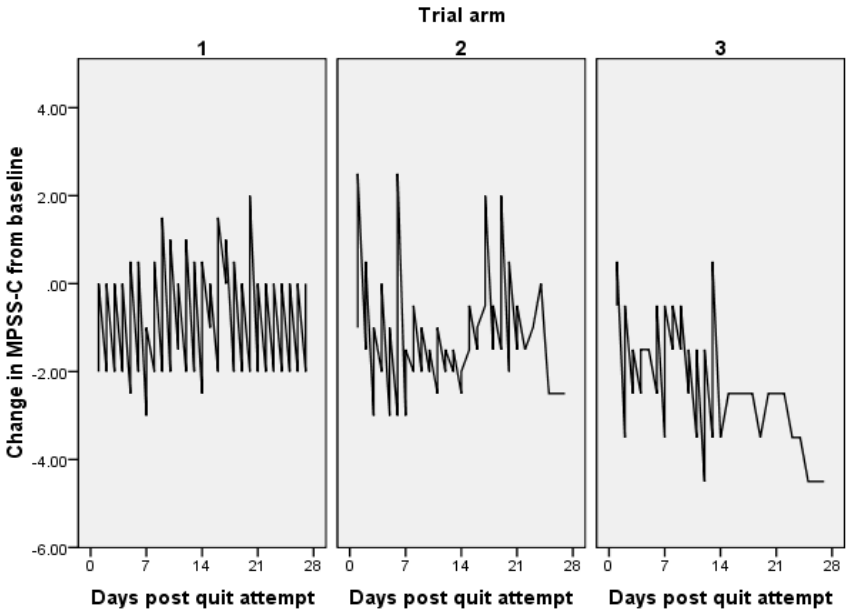


Figure 23. Mean change in MPSS-C score in each trial Arm (1=SBS, 2=IDAP, 3=VLCD)

1= Abstinent 0=Lapsed

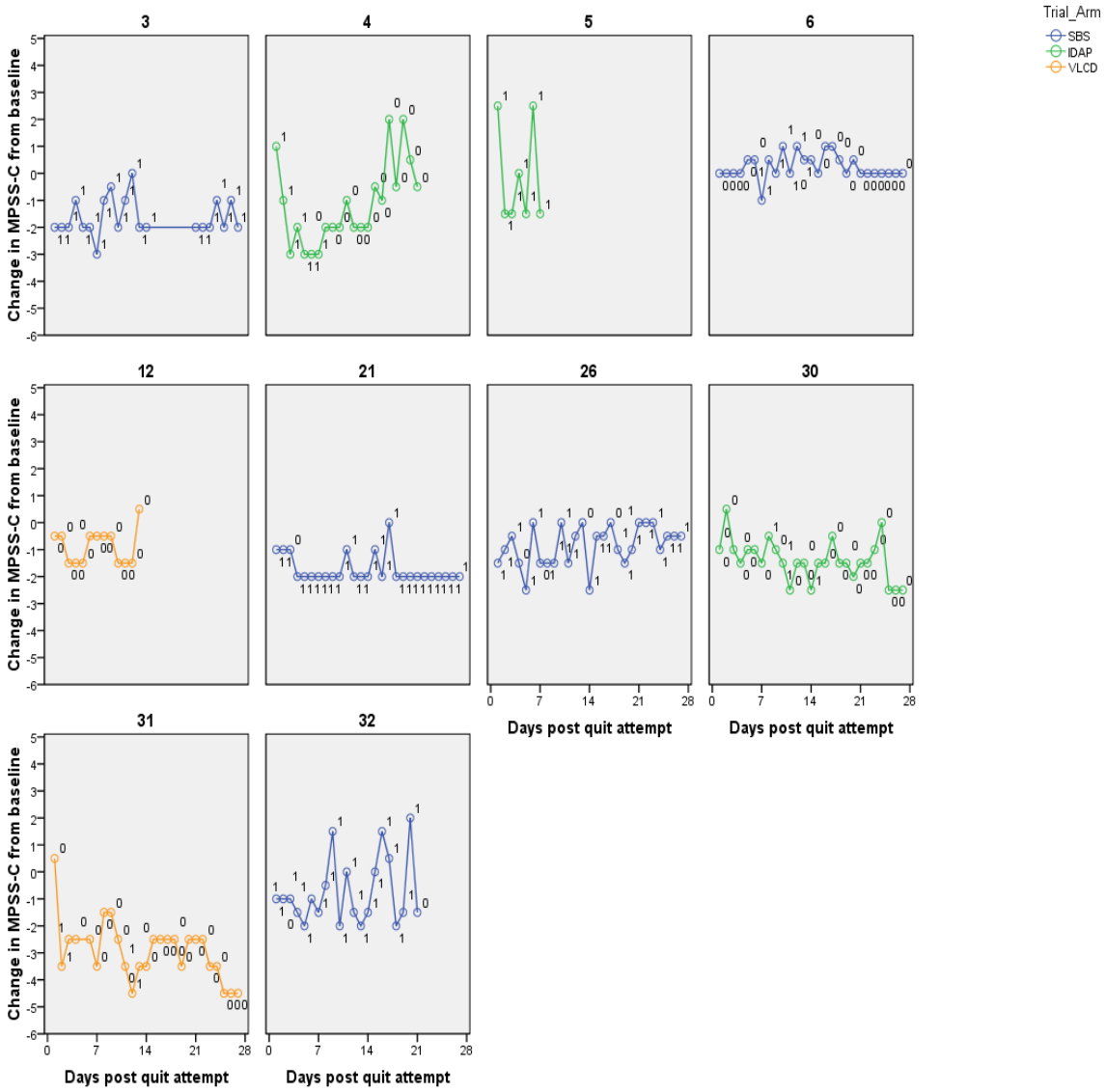


Figure 24. Trajectories of Cigarette craving for individuals

6.2.3. Modelling of trajectories of cigarette craving by trial arm

We used seven random effects models to investigate differences in change in MPSS-C score by trial arm, adjust for smoking status, and explored the mediating effects of food desire and food need on cigarette cravings. Ketosis characterised those adhering to the VLCD. Model one was an unadjusted linear function of change in craving score over time, we added trial arm variables to create model two. We compared these models using chi squared to see if adjusting for trial arm improved the fit of the model. We then created models to investigate the mediating effects of food desire (model 3), food need (model 4), and abstinent/lapsed status (model 5) on the differences of trial arm.

There was no statistically significant improvement in fit when we included trial arm (Model 1 to 2,Table 43). However, the coefficient for trial arm showed that each day mean craving score in the VLCD arm was 1.0 less than in the SBS arm (the SBS arm was the reference category in which MPSS-C score fell by a mean 0.9 from baseline) (Model 2, Table 44). If this were the true difference between the VLCD and SBS diets then this would be of clinical relevance. By comparison the Danielsson trial showed craving score fell by 0.5 in VLCD compared to the control arm, which was associated with improved abstinence (Danielsson et al., 1999)(section 3.1).

Adding food desire (Model 2 to 3, Table 43) and food need (Model 2 to 4, Table 43) significantly improved the fit of the model. However, including these variables

did not mediate/explain the difference in cigarette craving by trial arm. Mediation would be shown if the coefficients for trial arm reduced substantially by including these terms, but as Table 44 shows this did not happen. The VLCD coefficient remained approximately -1.0.

The magnitudes of the coefficients for food desire (0.1 (Model 3)) and food need (0.1(Model 4)) were too small to be clinically relevant (Table 44). These represented a 0.1 increase in craving score with a one unit increase on a six point scale (zero being the least desired and five being the most desired) of food desire and a five point scale (zero to four) of food need.

Adjusting for complete abstinence and lapses to smoking a cigarette significantly improved the model fit (Model 2 to 5, Table 43), and suggested that total abstinence was associated with a reduction in MPSS-C score of 0.4. However it did not explain the difference in craving between trial arms as the coefficients for trial arm changed very little (Model 2 compared to model 5, Table 44).

We allowed the effects of trial arm to vary over time as the plots of the mean trajectories by trial arm suggested these might differ (Figure 23). To do this we included a time by trial interaction term (model 7). This significantly improved the fit of the model (Table 43) and the model fit better with the observed data. Piasecki, in 2003, found that the best fitting curve for cigarette cravings was a quadratic one, so we added in a trial arm by time squared interaction. This did not

significantly improve the fit further (Model 8, Table 43) and including this risked overfitting the model. However, visually comparing both the linear model (Figure 25) and the quadratic model slopes (Figure 26) to the observed mean (Figure 23) showed that the quadratic model appeared to fit best. However, these models did not capture or explain the dramatic peaks and troughs which varied within and between individuals (Figure 24).

Model Steps	-2LL	-2LL	Chi	df	p
1 to 2	619.49	616.98	2.51	2	0.285
2 to 3	616.98	504.31	112.68	1	0.000*
2 to 4	616.98	585.06	31.92	1	0.000*
2 to 5	616.98	613.08	3.090	1	0.048*
2 to 6	616.98	606.12	10.86	2	0.001*
2 to 7	606.12	603.75	2.36	2	0.125

*statistically significant improvement in fit of model to data $p<0.05$.

Model 1: change in craving score, according to linear function of time.
Model 2: model 1 plus trial arm.
Model 3: model 2 adjusted for food desire.
Model 4: model 2 adjusted for food need.
Model 5: model 2 adjusted for abstinence.
Model 6: model 2 plus trial arm*time interaction.
Model 7: model 6 plus trial arm*time^2 interaction.

Table 43. Difference in fit between models 1 to 7 for trajectory of change in cigarette craving

Model	1	S.E.	2	S.E	3	S.E	4	S.E.	5	S.E.	6	S.E.	7	S.E.
Fixed Part														
cons	-1.116	0.282	-0.913	0.343	-0.747	0.354	-0.932	0.334	-0.561	0.374	-1.081	0.335	-1.321	0.387
Days post quit date (Time)	-0.002	0.009	-0.003	0.009	-0.011	0.008	-0.001	0.009	-0.007	0.009	0.01	0.011	0.061	0.044
IDAP			-0.007	0.542	0.016	0.640	-0.027	0.526	-0.149	0.523	0.062	0.554	0.466	0.642
VLCD			-0.994	0.616	-1.022	0.620	-0.912	0.593	-1.282	0.607	-0.098	0.635	-0.106	0.736
Food desire					0.054	0.108								
Food need							-0.112	0.096						
Abstinent									-0.388	0.195				
IDAP*Time											-0.003	0.021	-0.094	0.081
VLCD*Time											-0.08	0.024	-0.076	0.088
Time*time													-0.002	0.002
Time*time*IDAP													0.003	0.003
Time*time*VLCD													0	0.003
Random Part														
Level: Participant ID														
cons/cons	0.656	0.314	0.494	0.242	0.501	0.255	0.443	0.22	0.449	0.222	0.421	0.207	0.409	0.202
Level: Time														
cons/cons	0.895	0.088	0.896	0.088	0.733	0.077	0.885	0.089	0.883	0.087	0.856	0.084	0.847	0.083
-2*loglikelihood:	619.491		616.981		504.306		583.057		613.079		606.124		603.766	
Units: Participant ID	10		10		9		10		10		10		10	
Units: Time	217		217		190		206		217		217		217	

*statistically significant improvement in fit of model to data $p<0.05$. Model 1: change in craving score, according to linear function of time. Model 2: model 1 plus trial arm. Model 3: model 2 adjusted for food desire. Model 4: model 2 adjusted for food need. Model 5: model 2 adjusted for abstinence. Model 6: model 2 plus trial arm*time interaction. Model 7: model 6 plus trial arm*time^2 interaction.

Table 44. Coefficients of multilevel models 1 to 7 for cigarette cravings

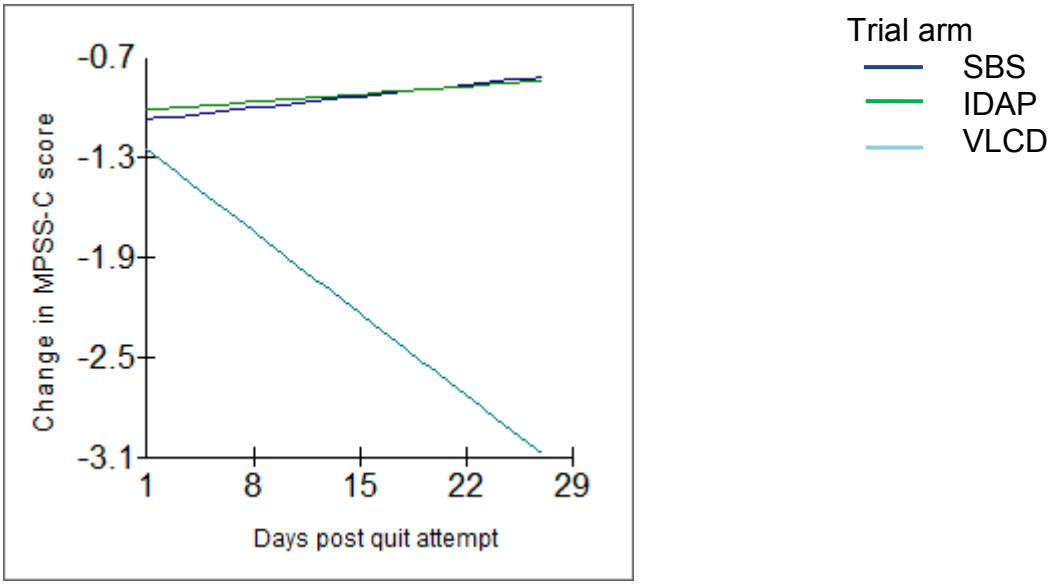


Figure 25. Plot of fixed effects of trial arm dependent on time on MPSS-C from model 7

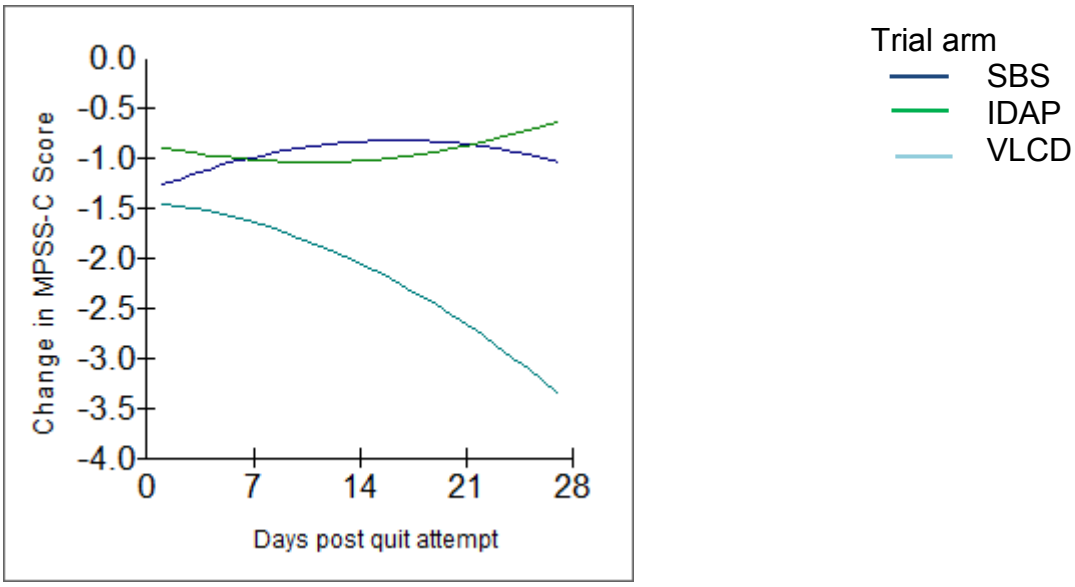


Figure 26. Plot of fixed effects of trial arm dependent on time squared on MPSS-C from model 10

6.2.4. Change in food desire and food need by trial arm

In examining whether the effects of trial arm on cravings are mediated by food desire and/or food need, we have made two assumptions. One that food desire and/or food need is dependent on trial arm and two that cigarette craving is dependent on desire and/or food need, but so far, we have not examined these independently. We do so in this section with the use of seven models. (Food desire and food need were measured using the HCS).

6.2.5. Is food desire and /or food need affected by trial arm?

Model 1 is the change in food desire over time; we tested with chi square whether the fit of this model improved by adding in the explanatory variable, trial arm (Model 2). We found that the improvement in fit did not reach statistical significance (Table 45), but the difference in hunger score between trial arms, as shown by the coefficients were quite large. On a scale of 1 to 6, food desire was reduced during this time by a mean 0.7 points in the SBS arm. Whereas in the IDAP arm its increase was 1.3 points higher than in the SBS arm and in the VLCD arm it was 0.7 points higher than in the SBS (Table 46).

Model 3 is the change in food need over time; we tested with chi square whether the fit of this model improved by adding in the explanatory variable, trial arm (Model 4). We found that the improvement in fit did not reach statistical significance (Table 45), but the difference in food need score between trial arms,

as shown by the coefficients were again quite large. On a scale of 1 to 6, food need increased slightly in the SBS arm (0.4) but it was 1.7 points less in the IDAP arm than in the SBS arm and 0.7 points less in the VLCD than in the SBS arm (Table 46).

Model Steps	-2LL	-2LL	Chi	df	p
1 to 2	345.989	343.229	2.76	2	0.097
3 to 4	423.149	421.599	1.55	2	0.213

*statistically significant improvement in fit of model to data p<0.05.

Model 1: change in food desire, according to linear function of time.
Model 2: model 1 plus trial arm.
Model 3:change in food need, according to linear function of time.
Model 4: model 3 plus trial arm

Table 45. Difference in fit between models 1 to 4 for trajectory of change in food desire and food need

	Model 1	S.E.	Model 2	S.E.	Model 3	S.E.	Model 4	S.E.
Response	Food desire		Food desire		Food need		Food need	
Fixed Part								
cons	-0.351	0.356	-0.799	0.409	-0.081	0.391	0.371	0.51
Time	-0.007	0.005	-0.007	0.005	-0.024	0.006	-0.025	0.006
Cigarette craving								
IDAP			1.317	0.759			-1.017	0.827
VLCD			0.702	0.756			-0.733	0.946
Random Part								
Level: Participant ID								
cons/cons	1.089	0.521	0.8	0.385	1.465	0.665	1.255	0.571
Level: Time								
cons/cons	0.292	0.031	0.292	0.031	0.37	0.037	0.37	0.037
-2*loglikelihood:	345.989		343.229		423.149		421.599	
Units: Participant ID	9		9		10		10	
Units: Time	191		191		206		206	

Model 1: change in food desire, according to linear function of time.
Model 2: model 1 plus trial arm.
Model 3:change in food need, according to linear function of time.
Model 4: model 3 plus trial arm

Table 46. Coefficients of multilevel models 1 to 4 for food desire and food need

Therefore this shows that our measure of food craving (food desire) fell in the control (SBS) arm where people were allowed to eat freely, but by comparison it increased the most in the IDAP arm but was unaffected in the VLCD arm. Our measure of hunger (food need) was largely unchanged in the SBS arm, but fell by comparison in the VLCD arm and fell the most in the IDAP arm. So it would seem that food craving rather than actual hunger becomes the stronger motivation to eat and is felt most keenly in the IDAP arm.

6.2.6. Is cigarette craving affected by food desire and /or food need?

The fit of the model of cigarette craving over time was statistically significantly improved by adding in both food desire and food need as explanatory variables (Table 47). However, the coefficients of food desire and food need seemed too small to have any meaningful influence on craving (Table 48). So this lack of meaningful association accounts for the lack of evidence we found for food craving and hunger mediating the difference in cigarette craving by trial arm, and suggests the difference in craving by trial arm is caused by another mechanism.

Model Steps	-2LL	-2LL	Chi	df	p
5 to 6	619.491	506.875	112.616	1	<0.001*
5 to 7	619.491	585.359	34.132	1	<0.001*

*statistically significant improvement in fit of model to data p<0.05.
Model 5: change in cigarette craving, according to linear function of time.
Model 6: model 5 plus food desire.
Model 7: model 5 plus food desire

Table 47. Difference in fit between models 5 to 7 examining change in food desire and food need on the trajectory of change in cigarette craving

	Model 5	S.E.	Model 6	S.E.	Model 7	S.E.
Fixed Part						
cons	-1.114	0.285	-0.979	0.303	-1.124	0.271
time	-0.002	0.009	-0.01	0.008	0	0.009
food desire			0.038	0.108		
food need					-0.101	0.097
Random Part						
Level: Participant ID						
cons/cons	0.656	0.314	0.688	0.343	0.574	0.279
Level: time						
cons/cons	0.895	0.088	0.733	0.077	0.885	0.089
-2*loglikelihood:	619.491		506.875		585.359	
Units: Participant ID	10		9		10	
Units: time	217		190		206	

Model 5: change in cigarette craving, according to linear function of time.
Model 6: model 5 plus food desire.
Model 7: model 5 plus food desire

Table 48. Coefficients of multilevel models 5 to 7 for which examine food desire and food need on cigarette craving

6.2.7. Change in smoking status - time to relapse

All those in the IDAP and VLCD arms had either relapsed to smoking or dropped out and assumed relapsed back to smoking by 12 weeks (Table 49) although we know that one person became abstinent later on in the VLCD arm, after initial weight loss (ID 31, Figure 32).

The median time to relapse was early at 1 and 2 weeks in the IDAP and VLCD arms respectively (Table 49, Figure 27). The hazard ratios from Cox regression using the SBS arm as the reference category show those in the IDAP arm were almost 4 times more likely to relapse than those in the SBS arm. And those in the VLCD arm were 8 times more likely to relapse than those in the SBS arm. These differences did not reach statistical significance, but we cannot exclude type two error as the sample size was small and confidence intervals wide giving imprecise results.

Trial Arm	Median time to relapse (weeks)	Number of relapses/Total number in arm	HR [95%CI] for relapse to smoking
SBS		2/6	Reference Category
IDAP	1	6/6	3.7 [0.7 , 18.8]
VLCD	2	4/4	7.8[1.2, 50.3]

Table 49. Number of relapses, median time to relapse and hazard ratios of relapse to smoking at 12 weeks according to trial arm

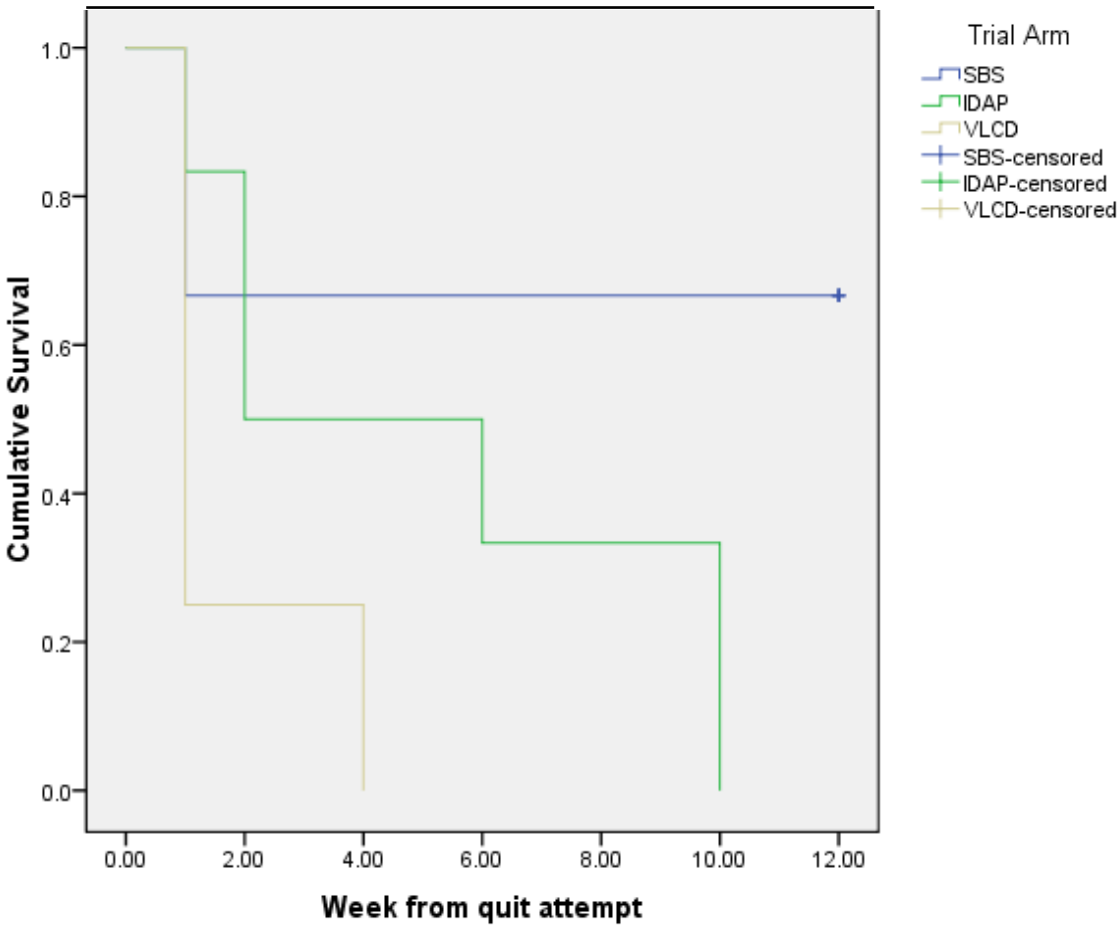


Figure 27. Kaplan Meier curve for survival of abstinence, until relapse to smoking within the first 12 weeks post quit attempt in each trial arm

6.2.8. Change in anthropometric, body composition and disease risk factors: completer analysis

Statistically significant differences between trial arms were unlikely considering the small sample size. The wide 95% confidence intervals (CIs) of many mean differences (Table 50) show imprecise estimates, so we cannot conclude these effects were due to chance alone. Therefore, we interpreted the findings in light of the possible clinical significance of means, bearing in mind the precision of the estimates. For example, we decided that a clinically important difference in weight change was approximately 0.5kg per week as this is considered a good rate of weight loss for the treatment of obesity in the NHS (NICE, 2006, SIGN, 2010).

The exception to this was for change in waist circumference, hip circumference and blood pressure; these were highly variable, with little obvious trend (Table 50). The 95% CIs for the mean differences between trial arms were so wide as to encompass biologically implausible changes over a week. In addition, the trial nurses reported difficulty obtaining accurate waist and hip measurements (chapter four), which adds to this uncertainty. Therefore, it would be unwise to draw any conclusions from such data, so although we have presented these measures for completeness, we will not discuss them further.

6.2.8.1. *Prequit change in weight, BMI and body composition*

Over the week prior to quitting, weight, BMI, and fat mass reduced by a clinically significant amount in the IDAP and VLCD arms, but by a clinically insignificant

amount in the SBS arm (week 0 in Figure 28, Figure 29). There was a fall in fat free mass, in particular total body water (which accounted for 82% of fat free mass loss) in the VLCD arm (week 0 in Figure 30, Figure 31). The standard deviations of these measurements were large, often exceeding the mean, sometimes several times over, which indicates that there was wide variation between individuals (Table 50).

The large loss of total body water seen in the VLCD arm is expected; initially glycogen stores become completely depleted by such severe energy restriction and water is released as glycogen is converted to glucose.

Those in the VLCD arm lost statistically significantly more weight than those in the SBS arm. The differences between the VLCD and SBS arm in change in fat mass, fat free mass and total body water were of clinical importance. Removing those who did not adhere to the VLCD from the analysis increased the difference between these two arms (Table 50).There was a clinically important difference in weight change and in particular fat mass change between the IDAP and SBS arm (0.4kg and 0.5kg respectively).

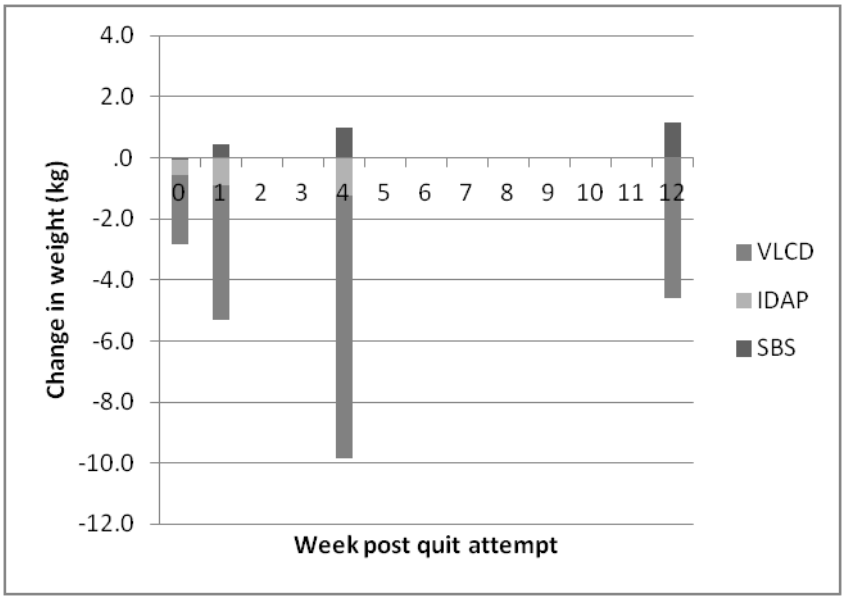


Figure 28. Bar chart of mean change in weight by trial arm, from baseline to week 0, +1, +4 and +12

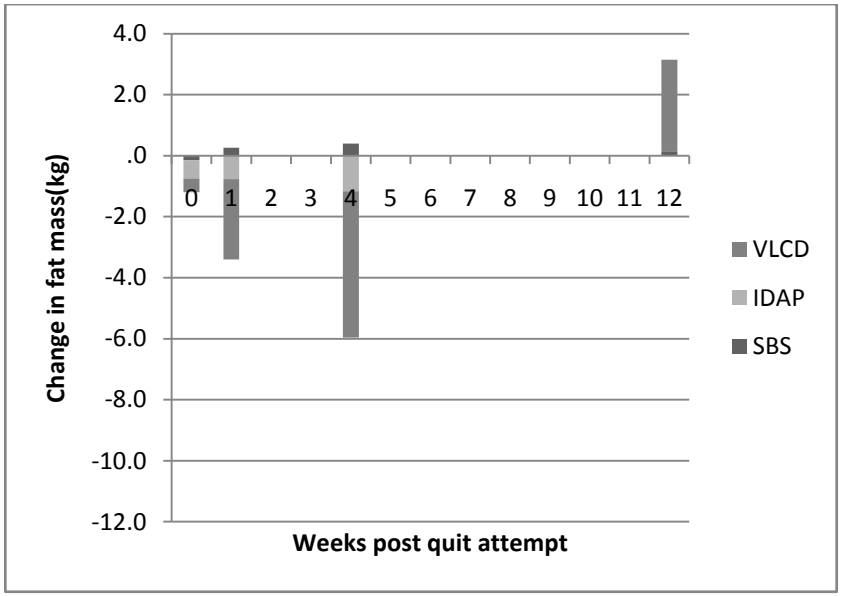


Figure 29. Bar chart of mean change in fat mass by trial arm, from baseline to week 0, +1, +4 and +12

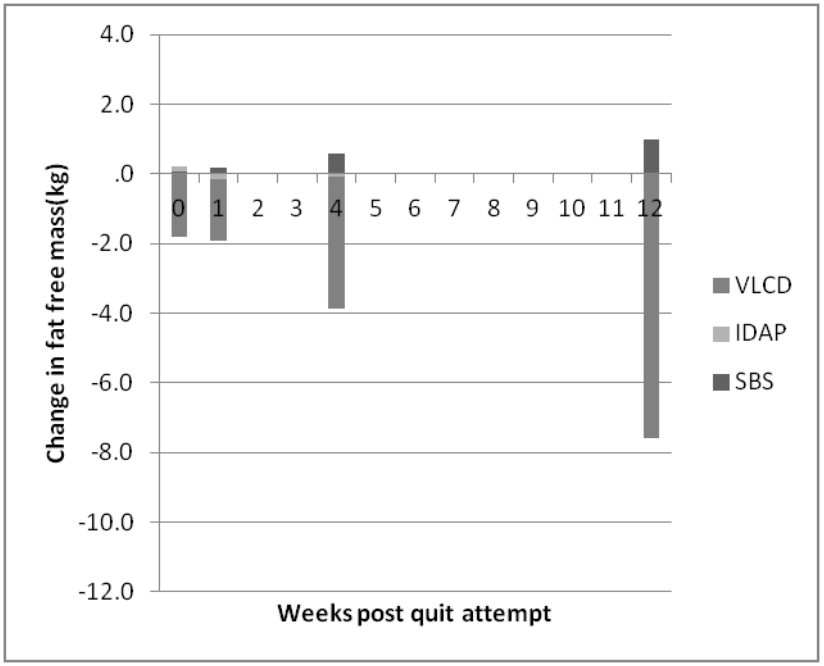


Figure 30. Bar chart of mean change in fat free mass by trial arm, from baseline to week 0, +1, +4 and +12

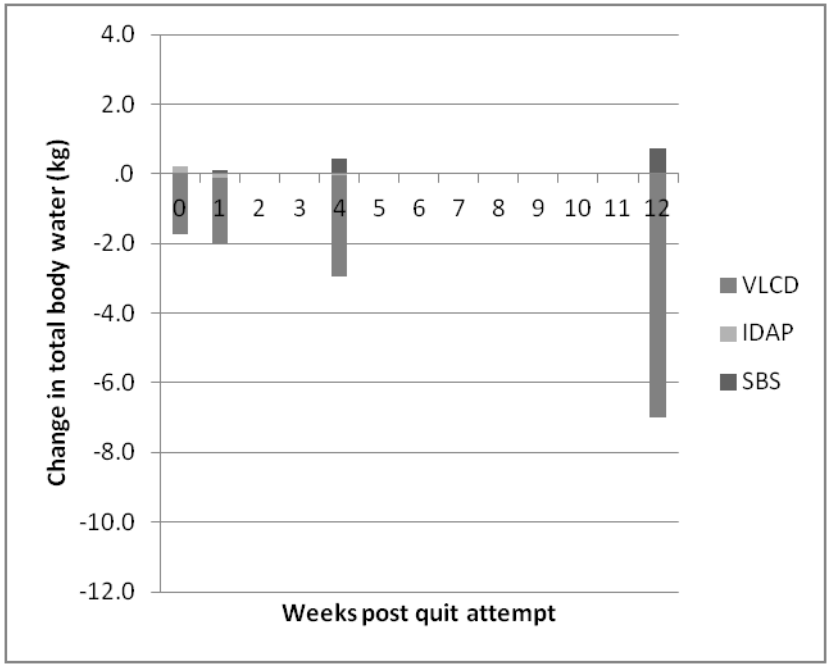


Figure 31. Bar chart of mean change in total body water by trial arm, from baseline to week 0, +1, +4 and +12

Change from baseline in:	SBS ($n^{\$}$=6)	IDAP ($n^{\$}$=6)	VLCD ($n^{\$}$=4)	VLCD(a)(n=2)	VLCD-SBS	VLCD(a)-SBS	IDAP-SBS	VLCD-IDAP	VLCD(a)-IDAP
Week 0									
Weight (kg)	-0.1(0.6)	-0.5(1.0)	-2.3(1.8)	-3.5(1.6)	-2.2[-4.1, -0.3]*	-3.4[-5.4, -1.5]*	-0.4[-2.1, 1.3]	-1.8[-3.7, 0.1]	-3.03[-4.99, -1.07]*
BMI (kg/m^2)	-0.01(0.21)	-0.18(0.36)	-0.84(0.70)	-1.25(0.77)	-0.83[-1.57, -0.10]*	-1.24[-2.04, -0.45]*	-0.17[-0.83, 0.49]	-0.66[-1.39, 0.07]	-1.07[-1.86,-0.27]
Systolic BP	-1(12)	-2(8)	4(11)	7(16)	4[-14, 22]	7[-17, 31]	-1[-18, 15]	6[-12, 23]	9[-15, 32]
Diastolic BP	-1(6)	0(3)	2(7)	6(6)	3[-7, 12]	7[-3, 17]	1[-7, 9]	2[-7, 10]	6[-4, 16]
Waist circumference (cm)	1(1)	-4(6)	-2(2)	-4	-3[-11,6]		-5[-12, 2]	2[-6, 10]	
Hip circumference (cm)	1(2)	3(7)	0(3)	1.00	0[-11, 11]		2[-7, 11]	-2[-12, 8]	
WHR	-0.00(0.02)	-0.07(0.13)	-0.02(0.27)	-0.05	-0.20[-0.22,0.18]		-0.7[-0.24,0.10]	-0.05[-0.14, 0.23]	
Fat mass (kg)	-0.2(0.7)	-0.6(0.5)	-0.5(1.5)	-0.8(1.1)	-0.3[-1.8,1.2]	-0.6[-2.0, 0.8]	-0.5[-1.8, 1.2]	0.2 [-1.3, 1.6]	-0.2[-1.6, 1.2]
Fat free mass (kg)	0.1(0.8)	0.1(0.9)	-1.8(2.0)	-2.7(0.4)	-1.9[-4.0, 0.2]	-2.8[-4.5, -1.0]*	0.1[-1.9, 2.0]	-2.0[-4.1, 0.2]	-2.8[-4.6, -1.1]*
Total body water (kg)	<0.0(0.6)	0.2(0.6)	-1.7(1.9)	-2.8(1.3)	-1.8[-3.6, 0.1]	-2.8[-4.3, -1.3]*	0.1[-1.5,1.8]	-1.9 [-3.7, -0.1]	-2.9[-4.4, -1.4]*
Week +1									
Weight (kg)	0.4(0.9)	-0.9(0.8)	-4.4(3.3)	-6.3(0.1)	-4.8[-8.1, -1.6]*	-6.7[-8.6,-4.9]*	-1.3 [-4.0, 1.4]	-3.5[-6.6, -0.4]*	-5.4[-7.2, -3.6]*
BMI (kg/m^2)	0.19(0.36)	-0.33(0.29)	-1.50(1.18)	-2.15(0.48)	-1.68[-2.86, -0.50]*	-2.34[-3.14, -1.54]*	-0.51[-1.50, 0.47]	-1.17[-2.30, -0.04]*	-1.82[-2.59, -1.06]*
Systolic BP	3(18)	-7(2)	-6(5)	-1(6)	-9[-33,16]	-11[-40, 18]	-10[-32,11]	1[-23,26]	-1[-30,29]
Diastolic BP	2(8)	-2(9)	-6(9)	-2(6)	-9[-26,9]	-4[-23, 15]	-4[-19, 11]	-5[-2, 12]	0[-19, 19]
Waist circumference (cm)	1(3)	-7(9)	-5(6)	-9	-6[-23, 12]		-8[-21, 2]	2[-14, 18]	
Hip circumference (cm)	2(1)	1(9)	1(4)	-2	-2[-25, 21]		-1[-20,18]	0[-19,18]	
WHR	-0.01(0.01)	-0.09(0.18)	-3.00	-0.07	-0.04[-0.49, 0.42]		-0.07[-0.45, 0.30]	-0.03[-0.34, 0.41]	
Fat mass (kg)	0.3(1.2)	-0.8(0.8)	-2.6(1.2)	-4.8	-2.9[-5.0, -0.8]*	-3.6[-5.3, -1.4]*	-1.0[-2.8, 0.7]	-1.9[-3.9, 0.1]	-2.5[-4.6, -0.4]*
Fat free mass (kg)	0.2(0.9)	-0.2(0.4)	-1.8(2.1)	-3.0	-1.9[-4.1, 0.3]	-3.2[-4.6, 1.7]	-0.3[-2.1, 1.5]	-1.6[-3.7, 0.5]	-2.9[-4.3, -1.5]*
Total body water (kg)	0.1(0.6)	-0.1(0.3)	-1.9(2.3)	-3.1	-2.0[-4.1, 0.2]	-3.2[-4.6, -1.7]*	-0.2[-2.0,1.5]	-1.8[-3.8, 0.3]	-2.9[-4.3, -1.5]*

$^{\#}$p<0.05 ANOVA *p<0.05 post-hoc Gabriel. Post hoc tests could not be performed in all cases due to small numbers. $^{\$}$Not complete numbers for all measurements, where no SD, mean is an individual measurement. (a)= those adherent to VLCD.

Table 50. Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week 0 and to week +1 in all completers by trial arm and mean difference [95% CI] in these between trial arm

6.2.8.2. *Change in weight, BMI and body composition, baseline to the end of the first week post quit date*

Weight gain in the SBS arm and weight loss in the IDAP arm was attributed to change in fat mass (week 1 in Figure 28, Figure 29) , but a large proportion of weight loss in the VLCD arm was due to change in total body water occurring during the first week (week 1 in Figure 30) (Table 50). During the second week on a VLCD people lose less water because glycogen stores are exhausted. Instead fat is metabolized for energy. Loss of body water during the second week may have occurred because people find it difficult to drink enough water.

When the SBS arm was compared with those adhering to the VLCD arm, there were statistically and clinically significant differences between the change in weight, BMI and fat mass (-6.7kg[-8.6, -4.9], -2.34kg/m^2[-3.14, -1.54], -3.6kg[-5.3, -1.4]). Such differences were also clinically important, but not statistically significant, between the SBS and IDAP arms (-1.3kg, -0.51kg/m^2, -1.0kg respectively) (Table 50).

6.2.8.3. *Change in weight, BMI and body composition baseline to the end of Stage 1*

Weight, BMI and fat mass had increased in the SBS arm and reduced in the IDAP and VLCD arms (week 4 in Figure 28, Figure 29). The differences between the intervention and control arms were clinically important and in favour of both interventions (Table 51). There was an increased loss of fat free mass, not explained by body water (-0.9kg) in those adhering to the VLCD (week 4 in Figure 30, Figure 31). This indicates an unexpected loss of lean

body tissue, although this has been a concern with VLCD formulas in the past, current formulas are tailored to minimise loss of lean tissue (section 3.11.1). However, useful conclusions cannot be drawn from data on one individual.

6.2.8.4. *Change in weight, BMI and body composition, baseline to the end of treatment*

No participants in the IDAP arm attended their end of treatment visit (reasons behind attrition have been explored in chapter four). One participant attended in the VLCD arm and four in the SBS arm. By this point in the trial both the SBS and VLCD arm had entered Stage 2 and had received IDAP advice.

In the SBS arm, there was a small further rise in weight (week 12 in Figure 28). Most of this was fat free mass, 73% of which was body water indicating some of the increase was lean body tissue (week 12 in Figure 30, Figure 31). Fat mass was slightly above baseline at this point (0.2kg) indicating that the gain seen after four weeks (0.6kg) had reduced during Stage 2 (week 12 in Figure 29, Table 51). In the VLCD arm approximately half of the weight lost was regained by the end of treatment, although the amount lost from baseline was still clinically significant (-4.6kg). Body composition analysis indicated that most of this weight regain was fat mass (+3.0kg) (week 12 in Figure 29) with an accompanying loss of fat free mass (-7.6kg) (week 12 in Figure 30) 92% of which was body water (-7.0kg) (week 12 Figure 31, Table 51). Changes in trends over time are explored more fully using multilevel modelling in section 6.2.18 .

Change from baseline in:	SBS ($n^{\$}$=5)	IDAP ($n^{\$}$=3)	VLCD (n=1)	VLCD-SBS	IDAP-SBS	VLCD-IDAP
Week+4						
Weight (kg)	1.0 (0.8)	-1.2 (1.7)	-8.6	-9.6#	-2.2#	-7.4#
BMI (kg/m^2)	0.38(0.31)	-0.49 (0.66)	-2.54	-2.92#	-0.87#	-2.05#
Systolic BP	4(11)	-17(9)	3	-1	-22	20
Diastolic BP	3(9)	-2 (9)	12	9	-5	14
Waist circumference (cm)	4(<0)	-8 (9)	-12	-16	-12	-4
Hip circumference (cm)	1	4 (11)	-3	-4	3	-7
WHR	0.03	-0.12 (0.18)	-0.09	-0.12	-0.15	0.03
Fat mass (kg)	0.4(1.5)	-1.2 (1.6)	-4.8	-5	-1.6	-3.6
Fat free mass (kg)	0.6(0.9)	-0.1 (0.5)	-3.8	-4.4#	-0.7#	-3.7#
Total body water (kg)	0.4(0.7)	-0.0 (0.3)	-2.9	-3.3#	-0.5#	-2.9#
Week +12						
Weight (kg)	1.2 (2.2)		-4.6	-5.8	-1.2	
BMI (kg/m^2)	0.45(0.78)		-1.79	-2.24	-0.45	
Systolic BP	1 (7)		-9	-10	-1	
Diastolic BP	-3(18)		12	15	3	
Waist circumference (cm)	-3(6)					
Hip circumference (cm)	2(1)					
WHR						
Fat mass (kg)	0.2(2)		3.0	2.9	-0.2	
Fat free mass (kg)	1.0(0.5)		-7.6	-8.6#	-1.0#	
Total body water (kg)	0.7(0.4)		-7.0	-7.7#	-0.7#	

#p<0.05 ANOVA Post hoc tests could not be performed due to small numbers $Not complete numbers for all measurements, where no SD, mean is an individual measurement.

Table 51. Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week +4 and to week +12 in all completers by trial arm and mean difference [95% CI] in these between trial arm

6.2.8.5. *Change in lung function, blood glucose and cardiovascular risk parameters at the end of treatment*

Data on change in lung function was only available for the SBS arm and showed lung function reduced by a clinically irrelevant amount over the course of treatment (Table 52). (Known large intra-individual variability in measured lung function means a clinically meaningful change in forced expiratory volume in 1 second (FEV1) should exceed 15% (Brusasco, 2009).

Blood glucose rose slightly in SBS and less so in IDAP, where dietary intervention had been present in both Stage1 and 2. Plasma lipid profile improved more in the IDAP arm than the SBS arm. The differences in change between these arms were clinically, although not statistically, significant as calculated as a percentage of the baseline value (Table 52) (10% and 18% improvement in TC:HDL ratio and triglycerides respectively). Most other markers of cardiovascular risk, elevated CRP, WBC, platelets, MCV and Hb (Lloyd-Jones et al., 2006, Libby et al., 2002, Davi & Patrono, 2007, Lowik et al, 1992) improved in both arms; generally more so in IDAP. Again, the sample size was too small to draw any conclusions from these changes, but these differences as a percentage of baseline values were clinically important (WBC and platelets improved by at 66% and 27% respectively). CRP reduced in both arms by more than 2.4mg/l (CRP above 2.4mg/l is associated with double the cardiovascular risk of CRP of 1mg/l (Lloyd-Jones et al., 2006)).

Change in:	SBS ($n^{\$}$=4)	IDAP ($n^{\$}$=1)	IDAP-SBS
Week +12			
Fasting blood glucose (mmol/L)	0.3(<0.1)	0.2	0.1
Forced Expiratory Volume in 1 sec (FEV1) (L)	-0.1(0.2)		
Forced Vital Capacity (FVC) (L)	-0.1(0.2)		
C-Reactive Protein (mg/L)	-3.5(0.7)	-4.0	0.7[-10.5, 11.5]
TC:HDL ratio	-0.3(0.6)	-0.8	0.5[-8.3, 9.3]
LDL-cholesterol (mmol/L)	-0.2	-0.3	0.1
HDL-cholesterol (mmol/L)	0.2(0.4)	0.3	-0.1[-6.5, 6.3]
Total Cholesterol (TC) (mmol/L)	-0.2(0.6)	0.0	-0.2[-10.1, 9.8]
Fasting triglycerides (mmol/L)	0.2(0.2)	-0.1	0.2[-2.2, 2.7]
White Blood Cells (WBC) ($x10^9$/L)	3.9(6.2)	-1.0	4.9[-90.9,100.6]
Platelets ($x10^9$/L)	-14(42)	-89	75[-585,735]
Mean Corpuscular Volume (MCV)	-1(1)	1	-2[-25, 21]
Haemoglobin (Hb) g/dl	-0.2(<0.1)	-0.4	0.2

$^{\$}$Not complete numbers for all measurements, where no SD, mean is an individual measurement.

Table 52. Mean Change (SD) in lung function and blood test results from baseline to week +12 in all completers by trial arm and mean difference [95% CI] in these between trial arm

6.2.9. Change in weight, BMI and body composition from baseline to 1 week post quit, in those achieving 7 day point prevalent abstinence

One, four and no participants fell into this category in the SBS arm, IDAP arm and adhering to the VLCD respectively. Comparison of abstainers in the SBS was only possible with those in the IDAP arm. A clinically important difference in change in weight (1.4kg), BMI (0.53kg/m^2) and fat mass (1.2kg) was seen between these groups. This was from gains in the SBS arm and losses in the IDAP arm. Fat free mass and body water reduced slightly in both groups but values did not represent clinically meaningful differences (Table 53).

6.2.10. Change in weight, BMI and body composition from baseline to 4 weeks of continued abstinence

Weight, BMI and fat mass continued to rise in the SBS arm and fall in the IDAP arm. The difference in the measures between the groups was clinically significant (-3.9kg, -1.52 kg/m^2 and -3.0kg respectively), although this was based on just one individual in the IDAP group (Table 53).

6.2.11. Change in weight, BMI and body composition from baseline to 12 weeks of continued abstinence

Twelve week abstinence data was only available for those in the SBS arm. In the preceding 4 weeks, participants in the SBS arm received the IDAP intervention. At 12 weeks participants BMI was the same as that recorded at 4 weeks post quit (Table 53). Fat mass was less than the 4 weeks post quit values, fat free mass and total body water had increased.

Change in:	SBS	IDAP	IDAP-SBS
Week +1			
n	4	5	
Weight (kg)	0.2(1.0)	-1.2(0.5)	1.4[0.2, 2.5]*
BMI (kg/m^2)	0.11(0.37)	-0.42(0.20)	0.53[0.08, 0.98]*
Systolic BP (mm/Hg)	3(21)	-7(2)	10[-24, 44]
Diastolic BP (mm/Hg)	2(9)	-2(9)	3[-11, 17]
Waist circumference (cm)	1.0(3.2)	-6.6(8.6)	7.6[-3.2, 18.4]
Hip circumference (cm)	2.3(1.1)	1.2(1.1)	1.1[-15.5, 17.6]
WHR	-0.01(0.01)	-0.09(0.01)	0.07[-0.27, 0.41]
Fat mass (kg)	0.3(1.4)	-0.9(0.8)	1.2[-0.4, 2.9]
Fat free mass (kg)	-0.1(0.8)	-0.2(0.4)	0.1[-0.8, 1.1]
Total body water (kg)	-0.1(0.6)	-0.2(0.3)	0.1[-0.6, 0.8]
Week+4			
n	4	1	
Weight (kg)	1.1(0.8)	-2.8	-3.9[-6.8, -1.0]*
BMI (kg/m^2)	0.43(0.34)	-1.09	-1.52 [-2.70, -0.32]*
Systolic BP	6(13)	-19	-25 [-69, 20]
Diastolic BP	4(10)	3	-1 [-36, 35]
Waist circumference (cm)	4(<0)	-9	-13
Hip circumference (cm)	1	-7	-8
WHR	0.03	-0.02	-0.05
Fat mass (kg)	0.8(1.4)	-2.3	-3.1[-8.2, 2.0]
Fat free mass (kg)	0.4(0.9)	-0.5	-0.9[-3.9, 2.2]
Total body water (kg)	0.2(0.6)	-0.3	-0.5[-2.7, 1.6]
Week +12			
n	4		
Weight (kg)	1.15(2.22)		
BMI (kg/m^2)	0.45(0.78)		
Systolic BP	1.25(6.84)		
Diastolic BP	-2.50(17.82)		
Waist circumference (cm)	-2.50(6.36)		
Hip circumference (cm)			
WHR			
Fat mass (kg)	0.15(2.18)		
Fat free mass (kg)	1.00(0.52)		
Total body water (kg)	0.73(0.43)		

*p<0.05 Students' t-test

Table 53. Mean Change (SD) in anthropometrics, body composition and blood pressure from baseline to week +1, +4 and +12 in completer abstainers by trial arm and mean difference [95% CI] in these between trial arm

6.2.12. Change in lung function, blood glucose and cardiovascular risk parameters by end of treatment in abstainers

Data on these parameters was only available for the four continuous abstainers in the SBS arm. Lung function reduced by a clinically insignificant amount (section 6.2.8.5). Most cardiovascular risk factors improved (TC:HDL cholesterol ratio reduced by 6% of baseline value) but triglycerides (rose by 14% of baseline value) and fasting blood glucose rose (Table 54).

Change in:	SBS (A) (n=4)	IDAP (L) (n=1)
Week +12		
Glucose (mmol/L)	0.3(0.00)	0.2
Forced Expiratory Volume in 1 sec (FEV1) (L)	-0.1(0.2)	
Forced Vital Capacity (FVC) (L)	-0.1(0.2)	
C-Reactive Protein (mg/L)	-3.5(0.7)	-4.0
TC:HDL ratio	-0.3(0.6)	-0.8
LDL-cholesterol (mmol/L)	-0.2	-0.3
HDL-cholesterol (mmol/L)	0.2 (0.4)	0.3
Total Cholesterol (TC) (mmol/L)	-0.2(0.6)	0.0
Triglycerides (mmol/L)	0.2(0.2)	-0.1
WBC ($x10^9$/L)	3.9(6.2)	-1.0
Platelets ($x10^9$/L)	-14(42)	-89
MCV	-1.15(1.48)	0.80
HB	-0.2(0.0)	-0.4

A=Abstainers L=Lapsers

Table 54. Mean Change (SD) in lung function and blood test results from baseline to week +12 in SBS abstainers and IDAP lapsers

6.2.13. Change in weight and body composition in lapsers from baseline to 1 week post quit date

There was data on one lapser each in the SBS and IDAP arms and two on the VLCD. Weight increased in the SBS arm by a clinically meaningful amount (1.2kg). By comparison, weight fell dramatically in the VLCD arm (-6.3kg) and increased moderately in the IDAP arm (0.4kg). These accounted for clinically meaningful differences in weight between the trials arms but much of these weight changes were attributable to body water (67%, 25% and 49% in the SBS, IDAP and VLCD arms respectively) (Table 55).

6.2.14. Change in weight and body composition in lapsers from baseline to four weeks post quit date (end of treatment, Stage 1)

There was data on one participant in the SBS arm, two in the IDAP arm and one in the VLCD arm who were still trying to quit but were not doing so successfully. The person in the SBS arm had gained weight (0.5kg) but had lost fat mass (-1.1kg), in the IDAP arm weight (fat mass(-0.6kg)) was lost. The individual in the VLCD arm had lost a large amount of weight (-8.6kg), which included fat mass (-4.8kg), fat free mass (-0.9kg) and total body water (-2.9kg). Differences between the VLCD and SBS arm were clinically important, but not between the IDAP and SBS arms (the sample was too small to generate confidence intervals for these differences between the trial arms) (Table 55).

6.2.15. Change in weight body composition and disease risk factors in lapsers from baseline to end of treatment

There were anthropometric data available on one lapsed individual in the VLCD arm who gained fat mass by this time (section 6.2.8.4). Data for lung function and blood test results were available for one individual who was in the IDAP arm. Lung function showed no clinically relevant change (Section 6.2.8.5). Blood glucose rose slightly, triglycerides fell by 5% of baseline value, TC:HDL cholesterol fell by 19% of baseline value (both LDL cholesterol fell and HDL cholesterol rose). CRP fell by 4mg/L, and platelets fell by 27% of baseline value, which are clinically meaningful changes (Table 54).

There was a smaller rise in blood glucose and a greater improvement in cardiovascular markers in the individual who followed IDAP, but continued to smoke, than in the individuals in the SBS arm who stopped smoking. But the sample is far too small to draw any meaningful conclusions (Table 54).

Change from baseline in:	SBS ($n^{\$}$=1)	IDAP ($n^{\$}$=1)	VLCD ($n^{\$}$=2)	VLCD-SBS	IDAP-SBS	VLCD-IDAP
Week +1						
Weight (kg)	1.2	0.4	-6.3(0.1)	-7.5	-0.8	-6.7
BMI (kg/m^2)	0.5	0.15	-2.15(0.48)	-2.65	-0.35	-2.3
Systolic BP	4		-1(6)	-4.8		
Diastolic BP	4		-2(6)	-6		
Waist circumference (cm)			-9			
Hip circumference (cm)			-2			
WHR			-0.07			
Fat mass (kg)	0.1	0.1	-4.8	-4.9	0	-4.9
Fat free mass (kg)	1.1	0.2	-3.0	-4.1	-0.9	-3.2
Total body water (kg)	0.8	0.1	-3.1	-3.9	-0.7	-3.2
Week +4						
Weight (kg)	0.5	-0.5(1.5)	-8.6	-9.1	-1.0	-8.2
BMI (kg/m^2)	0.21	-0.19(0.58)	-2.54	-2.75	-0.4	-2.35
Systolic BP	-1	-17(12)	3	4	-16	20
Diastolic BP	-1	-5(11)	-4	-3	-4	1
Waist circumference (cm)		-8(12)	-12			-5
Hip circumference (cm)		9(7)	-3			-12
WHR		-0.18(0.22)	-0.09			0.09
Fat mass (kg)	-1.1	-0.6(1.8)	-4.8	-3.7	0.5	-4.2
Fat free mass (kg)	1.6	0.2(0.4)	-3.8	-5.4	-1.5	-4.0
Total body water (kg)	1.2	0.1(0.3)	-2.9	-4.1	-1.1	-3

$^{\$}$Not complete numbers for all measurements, where no SD, mean is an individual measurement.

Table 55 Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week +1 and to week +4 in completer lapsers by trial arm and mean difference [sample to small for 95% CI] in these between trial arms

6.2.16. Individual trajectories of change in weight and fat mass

The measures of weight and fat mass over time were of most clinical interest here. As there are only a small number of participants, we have presented the change in weight and fat mass trajectories of all individuals (Figure 32). By doing so – annotating the time points of abstinence, lapses, dietary change and colour coding them by trial arm – we can see these effects within each individual. This helps with understanding and interpreting the data in subsequent analyses.

For most participants in the SBS arm weight increased over time (ID 3, 21, 32) and slowed or fell following the start of IDAP in Stage 2 (ID 3, 6, 26 32). One individual lapsed back to smoking (although their intention was not to abandon their quit attempt at this point) and weight began to fall (ID 6).

Weight initially fell (ID 4, 10, 8 and 30) in the IDAP arm and then rose again towards the end of treatment (ID 10, 18 and 30).

In the VLCD arm two participants abandoned their diet early and also failed to quit and left the programme (ID 7 and 21). Two participants continued the diet and lost a lot of weight until re-feeding (ID 12 and 31); Neither had quit by this point. One of these two (ID 31) quit after initial weight loss and during the re-feeding stage.

The change in fat mass paralleled and largely accounted for the change in weight. This was true for all individuals in all trial arms (Figure 33), except for one person. This person (ID 31) put on a large amount of fat mass during Stage 2 of the VLCD intervention. This coincided with the time that they quit smoking. Therefore, they had a greater fat mass at the end of treatment (week +12) than at baseline. Quitting in the other trial arms was not associated with this dramatic increase in fat mass.

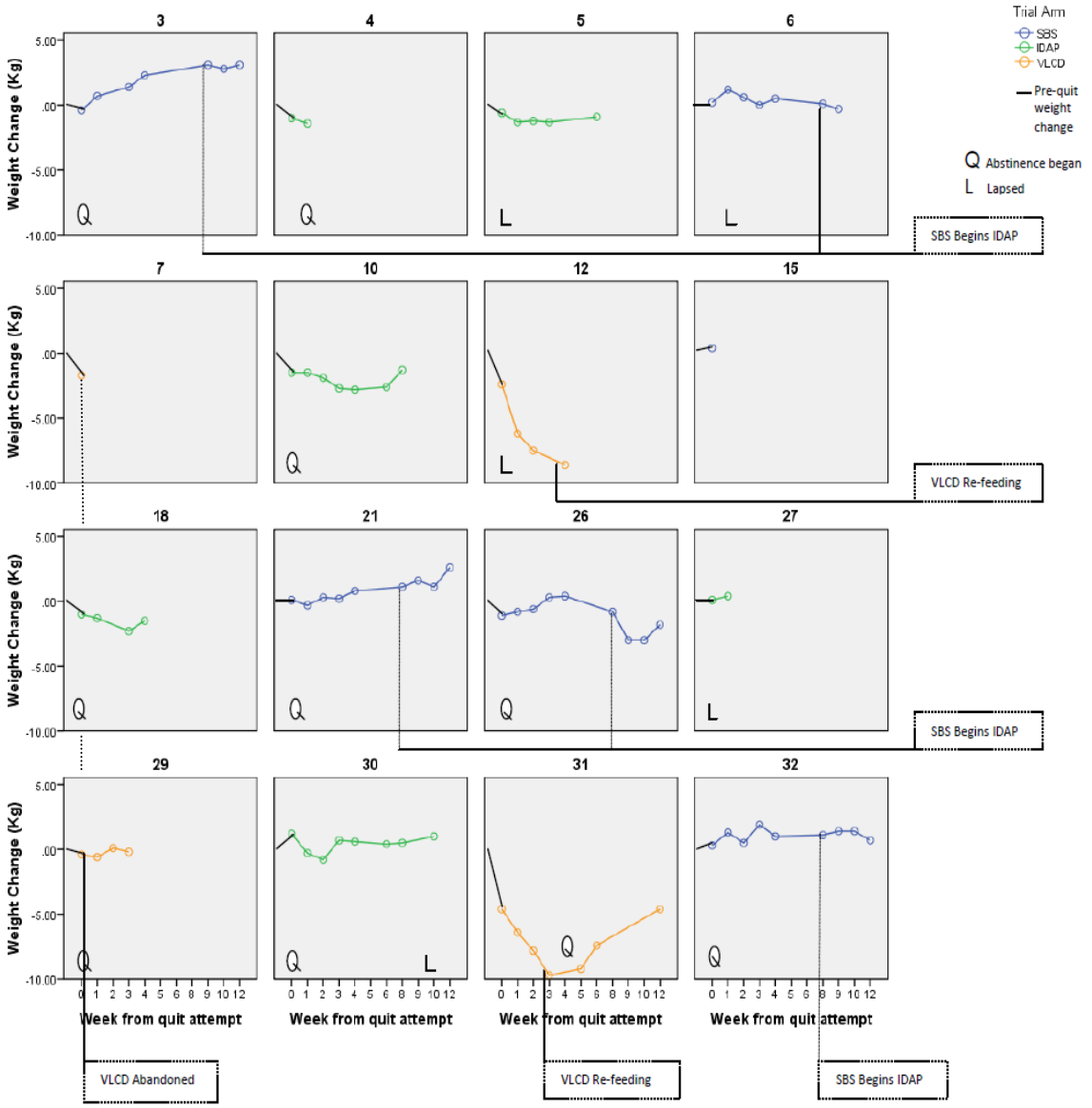


Figure 32. Individuals' change in weight over weeks -1 to +12, annotated by trial arm, change in smoking status and dietary change

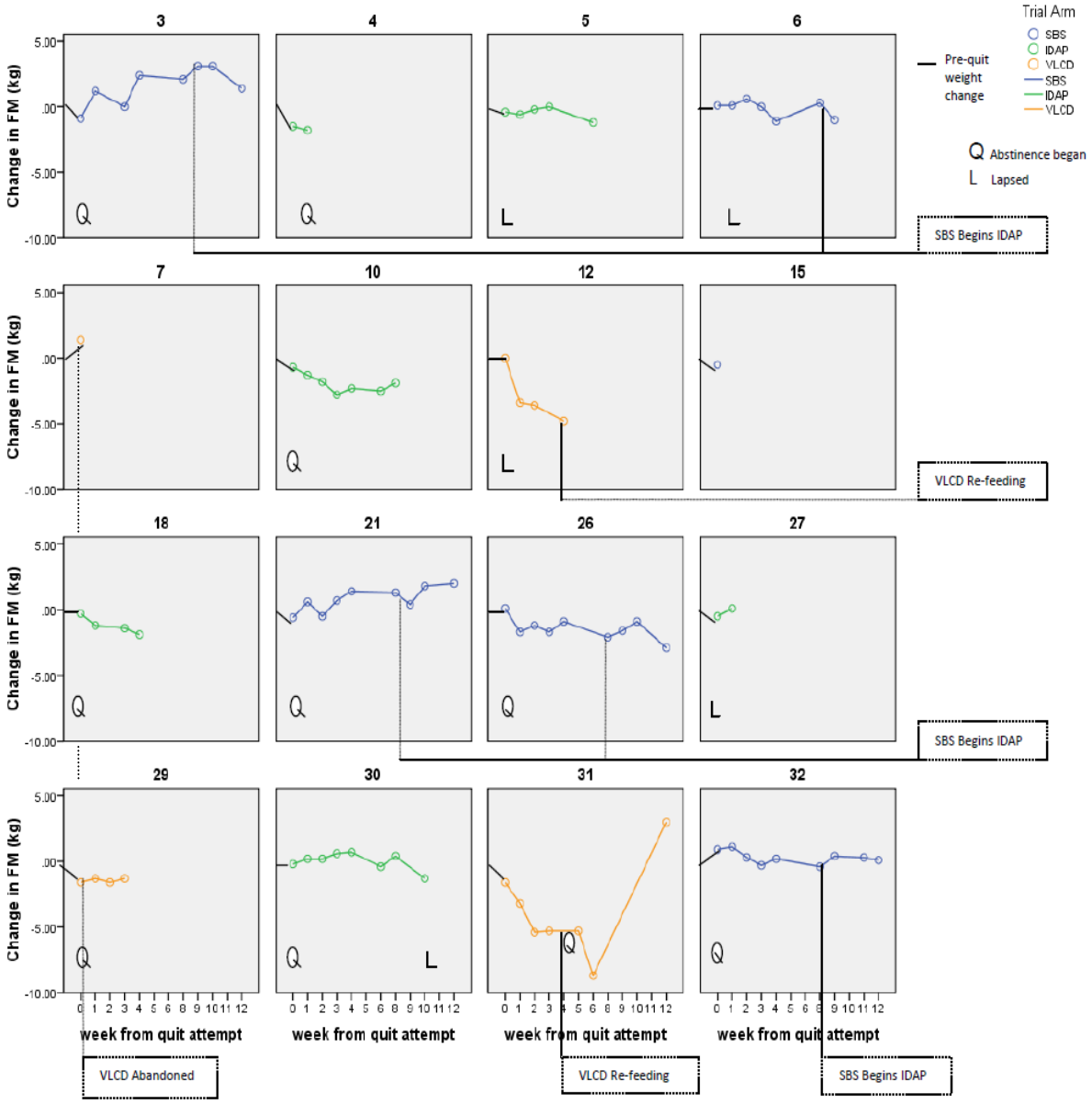


Figure 33. Individuals' change in fat mass over weeks -1 to +12, annotated by trial arm, change in smoking status and dietary change

6.2.17. Change in mean weight and fat mass by trial arm

In Stage 1 weight and fat mass rose in the SBS arm, fell moderately in the IDAP arm and fell dramatically in the VLCD arm. During Stage 2 weight began to fall in the SBS arm, rise in the in the IDAP arm and rise dramatically in the VLCD arm. Fat mass began to level off in the SBS arm, continued to fall in the IDAP arm and rose significantly beyond baseline in the VLCD arm (Figure 34,Figure 35).

6.2.18. Modelling of weight and fat mass trajectories by trial arm

We modelled the effects of trial arm to adjust for the effects of abstinence or lapsing, gender and age. We built up the multilevel model in several stages. From the mean plots of weight and fat mass over time we could see that the effects of trial arm were not linear. So we modelled a quadratic and then cubic function of time. The fit significantly improved from the linear to the quadratic model, but not to the cubic model for both weight (Model 1-2 and 2-3,Table 56) and fat mass (Model 1-2 and 2-3,Table 57).

The effects of trial arm, with SBS as the reference category, were interpreted from the coefficients for each trial arm in a model containing a quadratic function of time and trial arm (Models 4 in Table 58, Table 59). Over the 12 weeks, the mean differences for weight and fat mass change between the IDAP and SBS arm were

-1.3kg and -0.9kg respectively. Between the VLCD and SBS arm they were -7.1kg for weight -3.4kg for fat.

Adjusting for point prevalent abstinence (with lapsing as the reference category) significantly improved the fit of the models for both weight and fat mass (models 4 to models 5). The coefficients showed weight and fat mass was 0.4kg higher in those who were abstinent. But this did not explain the differences by trial arm, the coefficients for trial arm hardly changed (Models 5,Table 58 & Table 59).

Adjusting for age significantly improved the fit of the models, such that a one year increase in age was associated with a 40g increase in weight and fat mass. Therefore, someone who was 60 years old might gain 0.8kg more than someone who was 30 years old. But this did not explain differences between trial arms as the trial arm coefficients were unaltered (model 6, Table 58 & Table 59). Adjusting for gender (female was the reference category) did not significantly improve the fit of the model or explain difference by trial arm, but the coefficients suggested that males gained 0.7kg more and had 0.9kg more fat mass than females (model 7, Table 58 & Table 59).

The mean plots of change in weight (Figure 34) and fat mass (Figure 35) by trial arm suggest that rate of change was different within each trial arm, this was expected as during Stage two participants received the IDAP intervention at different times (week 5 in VLCD and Week 8 in SBS). To account for these changes we included a time by trial arm interaction, which showed a large, significant reduction in -2loglikelihood and hence improvement in the fit of the model (model 8 Table 58 & Table 59). Plotting the fixed effects of these models (Figure 36 & Figure 37) showed that they fit the mean plots well (Figure 34 & Figure 35).

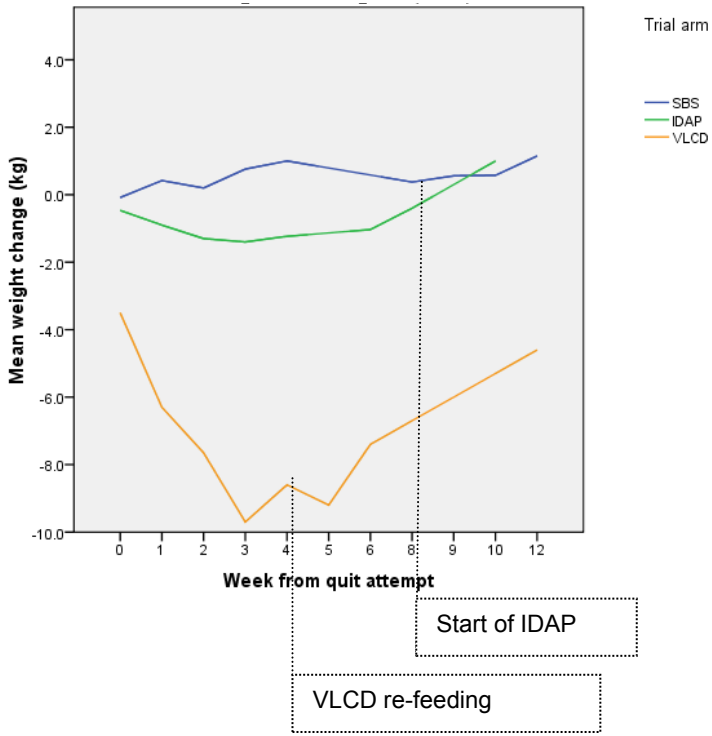


Figure 34. Mean weight change by trial arm over weeks post quit

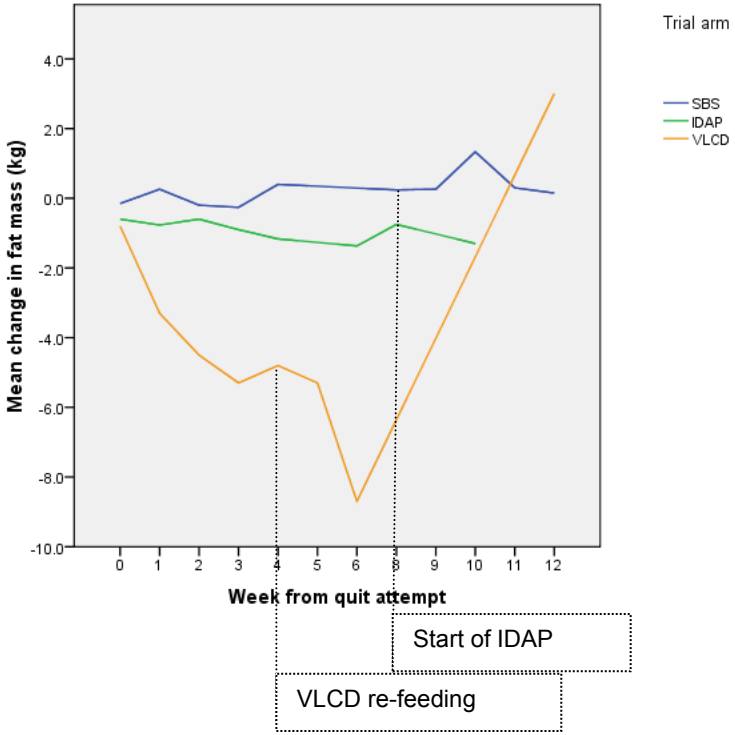


Figure 35. Mean fat mass change by trial arm over weeks post quit

Model Steps	-2LL	-2LL	Chi	df	p
1 to 2	294.314	287.966	6.348	1	0.012*
2 to 3	287.966	287.656	0.31	1	0.578
2 to 4	287.966	258.986	28.98	2	<0.001*
4 to 5	258.986	257.891	1.095	1	0.295
4 to 6	258.986	254.871	4.115	1	0.043*
4 to 7	258.986	257.765	1.221	1	0.269
4 to 8	258.986	221.629	37.357	4	<0.000*

*statistically significant improvement in fit of model to data using Chi-squared test. Model 1: weight change according to linear function of time. Model 2: weight change according to quadratic function of time. Model 3: weight change according to cubic function of time. Model 4: weight change according to quadratic function of time and trial arm. Model 5: weight change according to quadratic function by time, trial arm, adjusted for point prevalence abstinence. Model 6: weight change according to quadratic function by time, trial arm, adjusted for age Model 7: weight change according to quadratic function by time, trial arm, adjusted for gender Model 8: weight change according to quadratic function by time, trial arm, and trial arm by time interaction.

Table 56. Difference in fit between models of change in weight over time

Model Steps	-2LL	-2LL	Chi	df	p
1 to 2	311.09	300.862	10.228	1	0.001*
2 to 3	300.862	300.846	0.016	1	0.899
2 to 4	300.846	287.133	13.713	2	<0.001*
4 to 5	287.133	283.265	3.868	1	0.049*
4 to 6	287.133	283.394	3.739	1	0.053
4 to 7	287.133	285.014	2.119	1	0.145
4 to 8	287.133	223.007	64.126	4	<0.001*

*statistically significant improvement in fit of model to data using Chi-squared test. Model 1:fat mass change according to linear function of time. Model 2: fat mass change according to quadratic function of time. Model 3: fat mass change according to cubic function of time. Model 4: fat mass change according to quadratic function of time and trial arm. Model 5: fat mass change according to quadratic function by time, trial arm, adjusted for point prevalence abstinence. Model 6: fat mass change according to quadratic function by time, trial arm, adjusted for age Model 7: fat mass change according to quadratic function by time, trial arm, adjusted for gender Model 8: fat mass change according to quadratic function by time, trial arm, and trial arm by time interaction.

Table 57. Difference in fit between models of change in fat mass over time

	Model 1	S.E.	Model 2	S.E.	Model 3	S.E.	Model 4	S.E.	Model 5	S.E.	Model 6	S.E.	Model 7	S.E.	Model 8	S.E.
Fixed Part																
cons	-1.206	0.687	-0.858	0.692	-0.793	0.699	0.744	0.42	0.622	0.441	2.575	0.918	0.895	0.421	0.175	0.414
Time	0.035	0.037	-0.265	0.122	-0.377	0.235	-0.268	0.118	-0.328	0.13	-0.266	0.117	-0.277	0.118	0.172	0.129
Time*time			0.027	0.011	0.055	0.05	0.028	0.01	0.032	0.011	0.027	0.011	0.028	0.010	-0.011	0.011
Time*time*time					-0.002	0.003										
IDAP							-1.323	0.535	-1.294	0.547	-1.738	0.505	-1.417	0.511	-0.736	0.591
VLCD							-7.133	0.734	-6.988	0.763	-7.312	0.642	-6.950	0.709	-4.585	0.824
Point prevalence(PP)									0.361	0.345						
Age (years)											-0.038	0.017				
Gender													-0.713	0.616		
IDAP*time															-0.526	0.223
VLCD*time															-1.787	0.262
IDAP*time*time															0.054	0.023
VLCD*time*time															0.148	0.022
Random Part																
Level: Participant ID cons/cons	6.078	2.418	5.971	2.367	5.924	2.349	0.582	0.31	0.623	0.326	0.389	0.232	0.490	0.276	0.607	0.284
Level: Time cons/cons	1.274	0.22	1.164	0.201	1.16	0.2	1.145	0.197	1.117	0.192	1.139	0.196	1.152	0.193	0.670	0.116
-2*loglikelihood:	294.314		287.966		287.656		258.986		257.928		254.817		257.765		211.629	
Units: Participant ID	14		14		14		14		14		14		14		14	
Units: week from quit	81		81		81		81		81		81		81		81	

Model 1: weight change according to linear function of time. Model 2: weight change according to quadratic function of time. Model 3: weight change according to cubic function of time. Model 4: weight change according to quadratic function of time and trial arm. Model 5: weight change according to quadratic function by time, trial arm, adjusted for point prevalence abstinence. Model 6: weight change according to quadratic function by time, trial arm, adjusted for age Model 7: weight change according to quadratic function by time, trial arm, adjusted for gender Model 8: weight change according to quadratic function by time, trial arm, and trial arm by time interaction.

Table 58. Coefficients of multilevel models for weight change

Model	1	S.E.	2	S.E.	3	S.E.	4	S.E.	5	S.E.	6	S.E.	7	S.E.	8	S.E.
Fixed Part																
cons	-0.962	0.417	-0.415	0.441	-0.397	0.463	0.485	0.430	0.344	0.459	2.201	0.906	0.695	0.423	-0.115	0.408
Time	0.044	0.044	-0.411	0.143	-0.442	0.281	-0.401	0.140	-0.48	0.155	-0.399	0.139	-0.412	0.140	0.095	0.125
Time*time			0.041	0.012	0.049	0.06	0.04	0.012	0.046	0.013	0.040	0.012	0.041	0.012	-0.005	0.011
Time*time*time					0	0.003										
IDAP							-0.886	0.522	-0.856	0.537	-1.264	0.492	-1.019	0.481	-0.508	0.583
VLCD							-3.459	0.711	-3.289	0.748	-3.627	0.623	-3.267	0.655	-0.859	0.813
Point prevalence(PP)									0.436	0.405						
Age (years)											-0.036	0.017				
Gender													-0.924	0.585		
IDAP*time															-0.214	0.220
VLCD*time															-2.178	0.259
IDAP*time*time															0.006	0.023
VLCD*time*time															0.208	0.021
Random Part																
Level: Participant ID cons/cons	1.657	0.784	1.665	0.769	1.66	0.769	0.44	0.288	0.486	0.307	0.263	0.216	0.301	0.233	0.586	0.279
Level: Time cons/cons	1.95	0.334	1.687	0.289	1.687	0.289	1.669	0.284	1.641	0.281	1.667	0.283	1.684	0.286	0.662	0.113
-2*loglikelihood:	311.09		300.862		300.846		287.133		283.265		283.394		285.014		223.007	
Units: Participant ID	14		14		14		14		14		14		14		14	
Units: week from quit	82		82		82		82		81		81		81		82	

Model 1:fat mass change according to linear function of time. Model 2: fat mass change according to quadratic function of time. Model 3: fat mass change according to cubic function of time. Model 4: fat mass change according to quadratic function of time and trial arm. Model 5: fat mass change according to quadratic function by time, trial arm, adjusted for point prevalence abstinence. Model 6: fat mass change according to quadratic function by time, trial arm, adjusted for age Model 7: fat mass change according to quadratic function by time, trial arm, adjusted for gender Model 8: fat mass change according to quadratic function by time, trial arm, and trial arm by time interaction.

Table 59. Coefficients of multilevel models for change in fat mass

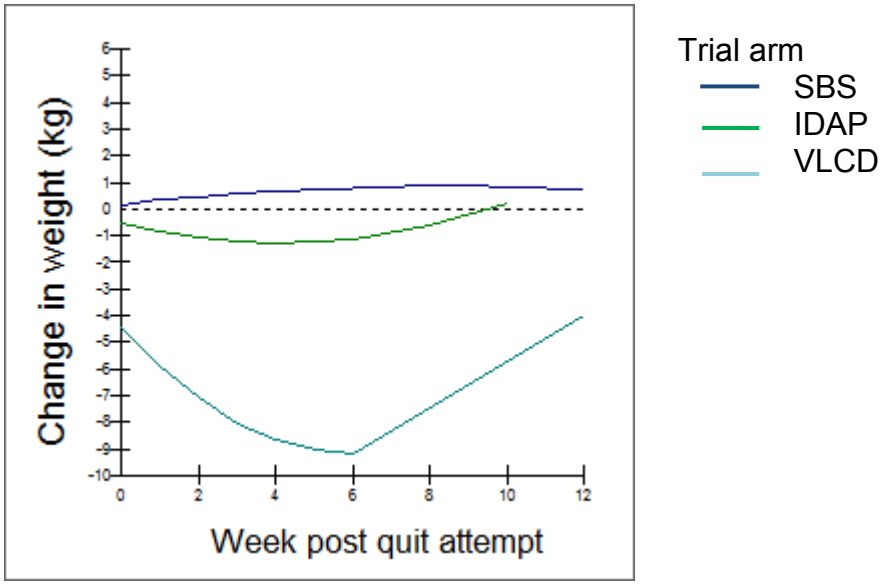


Figure 36. Plot of fixed effects of weight change trajectories by trial arm (model 8)

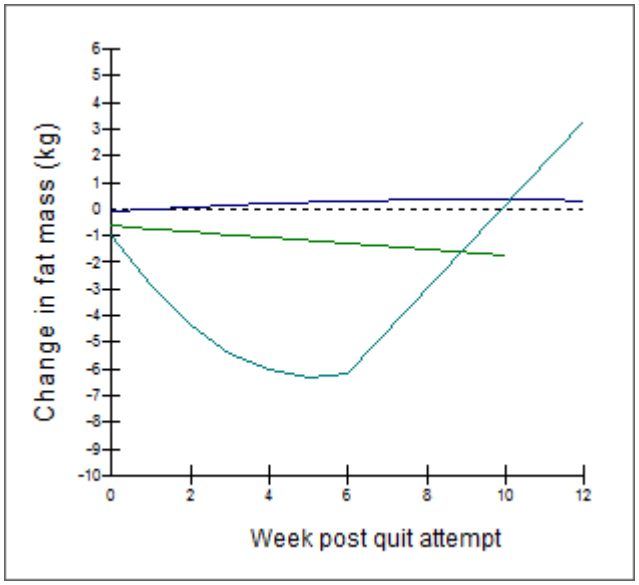


Figure 37. Plot of fixed effects of fat mass change trajectories by trial arm (model 8)

6.2.19. Change in fat intake and HCI score as mediators of change in body fat

As described in chapter five we had data on change in fat intake and HCI score for some individuals. So we tested these as mediators within a multilevel model of change in body fat for these individuals.

The HCI could only detect large differences in fat intake (there was a 32% level of agreement). So we classed the guideline daily amount of fat (70g (females)) with corresponding lower and upper levels of agreement as a medium level of fat intake, anything below and above this was classed as low and high respectively. Change in fat intake from baseline to the end of treatment was defined as a move between these categories. All our participants either stayed within the same category or moved from a high to medium or a medium to a low category of fat intake.

Adding change in fat intake and change in HCI score into the multilevel model for trajectory of fat mass did not significantly improve the fit of the models (Table 60)

but the coefficients were of clinical importance. A fall by one category of fat intake (with no change being the reference category) was associated with a decrease in body fat mass of 1.0kg. The change in the coefficients for trial arm showed that this explained 22% of the reduction in body fat in the IDAP arm but had a negligible effect in the VLCD arm (Table 61).

An increase of one point in HCI score was associated with an increase in fat mass of 0.056kg (56g), or to put it another way an increase of 10 was associated with a increase of 0.6kg. But it did not explain the change in fat mass by trial arm, the coefficient for the VLCD arm hardly changed and the coefficient for the IDAP arm got larger (Table 61).

Model Steps	-2LL	-2LL	Chi	df	p
1 to 2	132.926	131.781	1.145	1	0.285
1 to 3	132.926	132.444	0.482	1	0.488

Table 60. Change in fit of models for the trajectory of change in fat mass

Model	1	S.E.	2	S.E.	3	S.E.
Fixed Part						
cons	0.877	0.618	0.969	0.615	0.692	0.669
week from quit day	-0.392	0.246	-0.422	0.243	-0.389	0.244
Week from quit^2	0.051	0.021	0.052	0.021	0.05	0.021
IDAP	-0.968	0.601	-0.651	0.66	-1.39	0.85
VLCD	-4.623	0.696	-4.64	0.686	-4.385	0.771
Drop by one fat intake category			-1.013	0.939		
Change in HCI score					0.056	0.081
Random Part						
Level: Participant ID						
cons/cons	0	0	0	0	0	0
Level: week from quit day						
cons/cons	2.35	0.554	2.277	0.537	2.319	0.547
-2*loglikelihood:	132.926		131.781		132.444	
Units: Participant ID	5		5		5	
Units: week from quit day	36		36		36	

Models: trajectory of change in fat mass by trial arm (1) adjusted for change in fat intake (2) adjusted for change in HCI score (3)

Table 61. Coefficients for multilevel models for trajectory of change in fat mass

6.2.20. Change in anthropometrics and body composition: Intention to treat (ITT) analysis

As described in section 6.1, to get an idea of the pragmatic effects of our trial we carried out an ITT analysis. We input BOCF for missing values of those who dropped out and means of before and after values for intermittent missing data.

All results are presented in the tables that follow but only the key similarities and differences between the results from ITT and completer analysis are described in the sections below.

6.2.20.1. *Prequit change in weight, BMI and body composition*

No one had dropped out by week 0 so results for the ITT analysis were the same as those from completer analysis without removed of those who were not adhering to the VLCD (Table 62).

6.2.20.2. *Change in weight and body composition from baseline to one week post quit date*

Differences in change in weight and fat mass between IDAP and the SBS arm was the same for ITT and completer analysis (1.3kg and 1kg respectively). Differences in changes in weight and fat mass between VLCD and SBS arms were less marked but still statistically and clinically significant (3.7kg and 2.2kg respectively) (Table 62).

Change from baseline in:	SBS (n=6)	IDAP (n=6)	VLCD (n=4)	VLCD-SBS	IDAP-SBS	VLCD-IDAP
Week 0						
Weight (kg)	0.1(0.6)	-0.5(1.0)	-2.3(1.8)	-2.2[-4.1, -0.3]*	-0.4[-2.1, 1.3]	-1.8[-3.7, 0.1]
BMI (kg/m^2)	-0.01(0.21)	-0.18(0.36)	-0.84(0.70)	-0.83[-1.57, -0.10]*	-0.17[-0.83, 0.49]	-0.66[-1.39, 0.07]
Systolic BP	-1(12)	-2(8)	4(11)	4[-14, 22]	-1[-18, 15]	6[-12, 23]
Diastolic BP	-1(5)	<-1(3)	2(7)	3[-6, 11]	1[-6, 8]	2[-7, 10]
Waist circumference (cm)	1(1)	-4(6)	-2(2)	-3[-10, 5]	-5[-11, 1]	2[-5, 10]
Hip circumference (cm)	<0(1)	3(7)	<0(2)	<0[-8, 8]	2[-5, 9]	-2[-10, 5]
WHR	-0.00(0.02)	-0.07(0.13)	-0.02(0.02)	-0.15[-0.16, 0.13]	-0.07[-0.20, 0.06]	0.06[-0.09, 0.20]
Fat mass (kg)	-0.2(0.7)	-0.6(0.5)	-0.5(1.5)	-0.3[-1.8, 1.2]	-0.5[-1.8, 0.9]	0.2[-1.3, 1.6]
Fat free mass (kg)	0.1(0.8)	0.1(0.9)	-1.8(2.0)	-1.9[-4.0, 0.2]	0.1[-1.9, 2.0]	-2.0[-4.1, 0.2]
Total body water (kg)	<0.0(0.6)	0.2(0.6)	-1.7(1.9)	-1.8[-3.6, 0.1]	0.1[-1.5, 1.8]	-1.9[-3.7, -0.1]*
Week +1						
Weight (kg)	0.4(0.9)	-0.9(0.8)	-3.3(3.5)	-3.7[-6.8, -0.5]*	-1.3[-4.1, 1.6]	-2.4[-5.6, 0.8]
BMI (kg/m^2)	0.16(0.33)	-0.33(0.29)	-1.12(1.22)	-1.28[-2.41, -0.15]*	-0.48[-1.50, 0.53]	-0.80[-1.93, 0.33]
Systolic BP	3(17)	-6(3)	-5(5)	-7[-26, 12]	-9[-26, 8]	2[-17, 20]
Diastolic BP	2(7)	-1(8)	-5(8)	-7[-20, 6]	-3[-15, 9]	-3[-16,10]
Waist circumference (cm)	1(3)	-6(8)	-3(5)	-4[-15, 8]	-6[-16, 3]	3[-9, 14]
Hip circumference (cm)	1(1)	1(8)	<0(2)	<0[-9, 8]	<0[-8, 8]	-1[-9, 8]
WHR	-0.00(0.01)	-0.07(0.16)	-0.03(0.04)	-0.02[-0.20, 0.16]	-0.07[-0.23, 0.09]	0.05[-0.13, 0.22]
Fat mass (kg)	0.2(1.1)	-0.8(0.8)	-2.0(1.6)	-2.2[-4.2, -0.2]*	-1.0[-2.8, 0.8]	-1.2[-3.2, 0.8]
Fat free mass (kg)	0.1(0.8)	-0.2(0.4)	-1.3(2.0)	-1.5[-3.4, 0.4]	-0.3[-2.0, 1.4]	-1.2[-3.1, 0.7]
Total body water (kg)	0.1(0.6)	-0.1(0.3)	-1.4(2.1)	-1.5[-3.4, 0.4]	-0.2[-1.9, 1.5]	-1.3[-3.2, 0.6]

#p<0.05 ANOVA *p<0.05 post-hoc Gabriel. Post hoc tests could not be performed in all cases due to small numbers.

Table 62. Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week 0 and to week +1 in ITT population by trial arm and mean difference [95% CI] in these between trial arm.

6.2.20.3. *Change in weight, BMI and body composition from baseline to the end of Stage 1*

By four weeks post quit date differences in change in weight and fat mass between VLCD and SBS arms were less marked but still statistically and clinically significant (5.4kg and 1.5kg respectively). Differences in change in weight and fat mass between IDAP and SBS arms were less marked but still of some clinical importance (1.6kg and 1.0kg respectively) (Table 63).

6.2.20.4. *Change in weight and body composition from baseline to the end of treatment*

By the end of treatment, differences in change in weight and fat mass between VLCD and SBS arms were again less marked but still clinically significant (1.9kg and 0.7kg respectively). Differences in change in weight and fat mass between IDAP and SBS arms were small (0.8kg and 0.1kg respectively) (Table 63). However, they arose essentially from lack of weight gain in the IDAP compared to the SBS arm. At three months post quit we would expect an increase of almost 3kg in untreated abstinent smokers (Aubin et al., under review) but the weight gain in the SBS arm was a third of this, which may have been due to the IDAP intervention in Stage 2. However little weight gain in these both arms may just reflect the weights of many participants who dropped out, and were assumed to have relapsed to smoking and their baseline weight. Splitting the analysis into abstainers and lapsers helps address this.

Change from baseline in:	SBS (n=6)	IDAP (n=6)	VLCD (n=4)	VLCD-SBS	IDAP-SBS	VLCD-IDAP
Week+4						
Weight (kg)	0.8(0.8)	-0.8(1.3)	-4.5(5.2)	-5.4[-10.0, -0.7]*	-1.6[-5.8, 2.6]	-3.7[-8.4, 1.0]
BMI (kg/m^2)	0.32(0.32)	-0.30(0.48)	-1.56(1.86)	-1.88[-3.56, -0.20]*	-0.62[-2.13, 0.89]	-1.25[-2.93, 0.42]
Systolic BP	4(10)	-9(11)	1(2)	-3[-19, 13]	-12[-27, 2]	9[-7, 26]
Diastolic BP	2(8)	-1(6)	-1(2)	-3[-14, 8]	-3[-13, 6]	<1[-11, 11]
Waist circumference (cm)	1(2)	-4(7)	-3(6)	-4[-14, 5]	-5[-14, 3]	1[-8, 10]
Hip circumference (cm)	<0(0)	2(7)	-1(2)	-1[-9, 7]	2[-5, 8]	-3[-10, 5]
WHR	0.00(0.01)	-0.06(0.13)	-0.02(0.04)	-0.03[-0.18, 0.12]	-0.07[-0.20, 0.07]	0.04[-0.11, 0.19]
Fat mass (kg)	0.3(1.4)	-0.7(1.2)	-2.5(2.9)	-2.9[-6.0, 0.3]	-1.0 [-3.8, 1.8]	-1.8[-5.0, 1.3]
Fat free mass (kg)	0.5(0.9)	<0.0(0.3)	-1.0(1.9)	-1.5[-3.3, 0.4]	-0.5[-2.2, 1.2]	-0.9[-2.8, 1.0]
Total body water (kg)	0.4(0.6)	0.1(0.3)	-1.9(2.3)	-2.3[-4.4, -0.2]*	-0.3[-2.2, 1.6]	-2.0[-4.1, 0.1]
Week +12						
Weight (kg)	0.8(1.8)	0.0(0.0)	-1.2(2.3)	-1.9[-4.7, 0.8]	-0.8[-3.2, 1.7]	-1.2[-3.9, 1.6]
BMI (kg/m^2)	0.30(0.65)	0.00(0.00)	-0.45(0.90)	-0.75[-1.78, 0.28]	-0.30[-1.22, 0.62]	-0.45[-1.48, 0.58]
Systolic BP	1(5)	0(0)	-2(5)	-3[-10,4]	-1[-7, 5]	-2[-9, 5]
Diastolic BP	-2(14)	0(0)	3(6)	-5[-11, 20]	-2[-13, 16]	3[-13, 19]
Waist circumference (cm)	-1(3)	0(0)	0(0)	0.1[-3, 4]	0.8[-2, 4]	0[-3, 3]
Hip circumference (cm)	0(0)	0(0)	0(0)			
WHR	0.00(0.00)	0.00(0.00)	0(0)			
Fat mass (kg)	0.1(1.7)	0.0(0.0)	0.8(1.5)	0.7[-1.6, 2.9]	-0.1[-2.1, 1.9]	0.6[-1.5, 3.0]
Fat free mass (kg)	0.7(0.7)	0.0(0.0)	-1.9(3.8)	-2.6[-5.8, 0.7]	0.7[-3.0, 2.3]	-1.9[-5.2, 1.4]
Total body water (kg)	0.5(0.5)	0.0(0.0)	-1.8(3.5)	-2.2[-5.2, 0.8]	-0.5[-3.2, 2.2]	-1.8[-4.7, 1.2]

#p<0.05 ANOVA *p<0.05 post-hoc Gabriel. Post hoc tests could not be performed in all cases due to small numbers.

Table 63. Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week +4 and to week +12 in ITT population by trial arm and mean difference [95% CI] in these between trial arm

6.2.21. Change in weight and body composition in abstainers only: intention to treat (ITT) analysis

ITT results for abstainers followed a very similar pattern to the completer analysis for changes after one, four (Table 64) and 12 weeks post quit (Table 66) in the SBS and IDAP arms. Differences between IDAP and SBS arms were very slightly less marked at the end of seven day point prevalence abstinence than in the completer analysis (Table 64 vs Table 50). In the ITT analysis clinically important differences between the IDAP and SBS group after four weeks of continuous abstinence were seen for weight and fat mass (0.5kg and 0.9kg respectively) (Table 64).

6.2.22. Change in weight and body composition in lapsers only: intention to treat (ITT) analysis

Differences in change in weight and fat mass between the IDAP and SBS arms in the ITT analysis for lapsers did not differ from the completer analysis at the end of one week post quit date, and were very similar after four weeks post quit date (Table 65). These differences in change in weight and fat mass between the VLCD and SBS arms were the same after one week post quit date but approximately half that seen in completer analysis at the end of week four (Table 65 versus Table 51)

In lapsers the only change still apparent by 12 weeks was in the VLCD arm which showed a smaller, although still clinically important, reduction in weight (-1.3kg) and an increase in fat mass (0.8kg) (Table 68).

Change from baseline in:	SBS (n=5)	IDAP (n=5)	VLCD (n=2)	VLCD-SBS	IDAP-SBS	VLCD-IDAP
Week +1						
Weight (kg)	0.2(0.8)	-1.2(0.5)	-0.3(0.4)	-0.5 [-2.0, 1.1]	-1.3[-2.5, -0.2]*	0.9[-0.7, 2.4]
BMI (kg/m^2)	0.09(0.32)	-0.42(0.20)	-0.09(0.13)	-0.18[-0.78, 0.42]	-0.51[-0.98, -0.04]*	0.33[-0.27, 0.93]
Systolic BP	2(18)	-8(2)	-1(1)	-3[-32, 26]	-10[-32, 13]	-3[-23, 36]
Diastolic BP	1(8)	-2(9)	-8(11)	-9[-29, 11]	-3[-19, 13]	-6[-26, 14]
Waist circumference (cm)	1(3)	-7(9)	0(0)	-0.80[-15.02, 13.42]	-7.40[-18.42, 3.62]	6.60[-7.62, 20.82]
Hip circumference (cm)	1(1)	1(9)	2(2)	1[-13, 15]	<1[-10, 11]	1[-13, 14]
WHR	-0.01(0.01)	-0.09(0.18)	-0.2(0.03)	-0.01[-0.29, 0.26]	-0.08[-0.30, 0.13]	0.07[-0.21, 0.35]
Fat mass (kg)	0.2(1.2)	-0.9(0.8)	-0.6(0.9)	-0.9[-3.2, 1.4]	-1.2[-3.0, 0.6]	0.3[-2.0, 2.6]
Fat free mass (kg)	-0.1(0.7)	-0.2(0.4)	0.4(0.5)	0.4[-0.9, 1.7]	-0.2[-1.2, 0.9]	0.6[-0.8, 1.9]
Total body water (kg)	<0.1(0.5)	-0.2(0.3)	0.3(0.4)	0.3[-0.7, 1.3]	-0.1[-0.9, 0.7]	0.4[-0.6, 1.4]
Week+4						
Weight (kg)	1.1(0.8)	-2.8			-3.9[-6.9, -1.0]$^{\#}$	
BMI (kg/m^2)	0.43(0.34)	-1.09			-1.51[-2.71, -0.32]$^{\#}$	
Systolic BP	6(13)	-19				
Diastolic BP	4(10)	3				
Waist circumference (cm)	2(2)	-9			-11[-19, -3]$^{\#}$	
Hip circumference (cm)	<1(<1)	-7			-7[-9, -6]$^{\#}$	
WHR	0.01(0.01)	-0.02			-0.03[-0.08, 0.2]	
Fat mass (kg)	0.8(1.4)	-2.3			-3.1[-8.2, 2.0]	
Fat free mass (kg)	0.4(0.9)	-0.5			-0.9[-3.9, 2.2]	
Total body water (kg)	0.2(0.6)	-0.3			-0.5[-2.7, 1.6]	

*p<0.05 ANOVA post-hoc Gabriel. $^{\#}$p<0.05 students t test

Table 64. Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week +1 and to week +4 in ITT abstainer population by trial arm and mean difference [95% CI] in these between trial arm

Change from baseline in:	SBS (n=1)	IDAP (n=1)	VLCD (n=2)	VLCD-SBS	IDAP-SBS	VLCD-IDAP
Week +1						
Weight (kg)*	1.2	0.4	-6.3(0.14)	-7.5	-0.8	-6.7
BMI (kg/m^2)	0.5	0.15	-2.15(0.48)	-2.65	-0.35	-2.3
Systolic BP	4	0	-8(6)	-12	-4	-8
Diastolic BP	4	0	-2[6]	-6	-4	-2
Waist circumference (cm)	0	0	-5(6)	-5	0	-5
Hip circumference (cm)	0	0	-1(1)	-1	0	-1
WHR	0	0	-0.03(0.05)	-0.03	0	-0.03
Fat mass (kg)*	0.1	0.1	-3.3(0.1)	-3.4	0	-3.4
Fat free mass (kg)	1.1	0.2	-3.0(0.3)	-4.1	-0.9	-3.2
Total body water (kg)	0.8	0.1	-3.1(1.3)	-3.9	-0.7	-3.2
Week+4						
Weight (kg)	0.3(0.4)	-0.4(0.9)	-4.5(5.2)	-4.8[-13.0, 4.5]	-0.7[-8.5, 7.2]	-4.1[-10.6, 2.3]
BMI (kg/m^2)	0.10(0.15)	-0.15(0.33)	-1.56(1.86)	-1.66[-4.60, 1.27]	0.25[-3.06, 2.56]	-1.41[-3.71, 0.89]
Systolic BP	-1(1)	-7(11)	1(2)	1[-18, 21]	-6[-25, 13]	7[-8, 23]
Diastolic BP	-1(1)	-2(6)	-1(2)	-1[-12, 11]	-2[-13, 11]	1[-8, 10]
Waist circumference (cm)	0(0)	-3(7)	-3(6)	-3[-19, 13]	-3[-18, 12]	0[-13, 13]
Hip circumference (cm)	0(0)	4(6)	-1(2)	-1[-12, 10]	4[-7, 14]	-4[-13, 4]
WHR	0(0)	-0.07(0.15)	-0.22(0.04)	-0.22[-0.29, 0.35]	-0.07[-0.29, 0.25]	0.05[-10.57, 2.34]
Fat mass (kg)	-0.6(0.8)	-0.4(1.0)	-2.5(2.9)	-2.0[-6.9, 2.9]	-0.7[-4.5, 4.9]	-2.2[-6.0, 1.7]
Fat free mass (kg)	0.8(1.1)	0.1(0.2)	-1.0(1.9)	-1.8[-4.9, 1.4]	-0.7[-3.7, 2.3]	-1.0[-3.5, 1.4]
Total body water (kg)	0.6(0.9)	0.2(0.3)	-1.9(2.3)	-2.5[-6.2, 1.2]	-0.4[-4.0, 3.1]	-2.1[-5.0, 0.9]

*p<0.05 ANOVA post hoc tests could not be performed in all cases due to small numbers.

Table 65. Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week +1 and to week +4 in ITT lapser population by trial arm and mean difference [95% CI] in these between trial arm

Change from baseline in:	SBS (n=4)
Week +12	
Weight (kg)	1.2(2.2)
BMI (kg/m^2)	0.45(0.78)
Systolic BP	1(7)
Diastolic BP	-3(18)
Waist circumference (cm)	-1(4)
Hip circumference (cm)	0(0)
WHR	0(0)
Fat mass (kg)	0.2(2.2)
Fat free mass (kg)	1.0(0.5)
Total body water (kg)	0.7(0.4)

Table 66. Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week +12 ITT abstainer population by trial arm

Change from baseline in:	SBS(n=1)	IDAP(n=1)	VLCD (n=2)	VLCD-SBS	IDAP-SBS	VLCD-IDAP
Week +12						
Weight (kg)	0.0(0.0)	0.0(0.0)	-1.2(2.3)	-1.2[-4.4, 2.1]	0[-3.0, 3.0]	-1.2[-3.6, 1.3]
BMI (kg/m^2)	0.00(0.00)	0.00(0.00)	-0.5(0.9)	-0.45[-1.72, 0.83]	0[-1.18, 1.18]	-0.45-1.41, 0.51]
Systolic BP	0(0)	0(0)	-2(5)	-2[-9, 4]	0[-6, 6]	-2[-7, 3]
Diastolic BP	0(0)	0(0)	3(6)	3[-6, 12]	0[-8, 8]	3[-3, 9]
Waist circumference (cm)	0(0)	0(0)	0(0)			
Hip circumference (cm)	0(0)	0(0)	0(0)			
WHR	0.00(0.00)	0.00(0.00)	0.00(0.00)			
Fat mass (kg)	0.0(0.0)	0.0(0.0)	0.8(1.5)	0.8[-1.4, 2.9]	0[-2.0, 2.0]	0.8[-0.9, 2.4]
Fat free mass (kg)	0.0(0.0)	0.0(0.0)	-1.9(3.8)	-1.9[-7.3, 3.5]	0[-5.0, 5.0]	-1.9[-6.0, 2.2]
Total body water (kg)	0.0(0.0)	0.0(0.0)	-1.8(3.5)	-1.8[-6.7, 3.2]	0[-4.6, 4.6]	-1.8[-5.5, 2.0]

Table 67. Mean (SD) change in anthropometrics, body composition and blood pressure from baseline to week +12 in ITT lapser population by trial arm and mean difference [95% CI] in these between trial arms

6.2.23. Change disease risk factors from baseline to end of treatment in lapsers

In contrast to completer analysis, the ITT analysis showed that all changes in the disease risk factors we measured were of negligible clinical importance (Table 68). It was not possible to examine the difference between arms in abstainers because only participants in SBS arm maintained abstinence. In the SBS arm the changes from baseline here were less than those seen in completer analysis and were minimal (0.2mmol rise in blood glucose, a 6% rise in triglycerides, an 8% rise in HDL cholesterol and fall of 4% in LDL cholesterol and TC:HDL ratio (Table 69).

Change in:	SBS	IDAP	VLCD	VLCD-SBS	IDAP-SBS	VLCD-IDAP
Week +12						
Glucose (mmol/L)	0.1(0.2)	<0.1(0.1)	0.0(0.0)	-0.1[-0.3, 0.1]	-0.1[-0.2, 0.1]	<0.1[-0.2, 0.2]
Forced Expiratory Volume in 1 sec (FEV1) (L)	-0.1(0.14)	0.0(0.0)	0.0(0.0)	0.1[-0.1, 0.2]	0.1[-0.1, 0.2]	0[-0.2. 0.2]
Forced Vital Capacity (FVC) (L)	-0.1(0.2)	0.0(0.0)	0.0(0.0)	0.1[-0.1, 0.2]	0.6[-0.1, 0.2]	0[-0.2, 0.2]
C-Reactive Protein (mg/L)	-1.2(1.8)	-0.7(1.6)	0.0(0.0)	-1.2[-1.5, 3.8]	0.5[-1.9, 2.9]	0.7[-2.0, 3.3]
TC:HDL ratio	-0.1(0.3)	-0.1(0.3)	0.0(0.0)	0.1[-0.4, 0.6]	<0.1[-0.5, 0.4]	0.1[-0.3, 0.6]
LDL-cholesterol (mmol/L)	<0.1(0.1)	0.0(0.0)	0.0(0.0)	<0.1[-0.1, 0.2]	<0.1[-0.5, 0.1]	0.1[-0.3, 0.6]
HDL-cholesterol (mmol/L)	0.1(0.2)	0.1(0.1)	0.0(0.0)	-0.1[-0.3, 0.2]	<0.0[-0.2, 0.2]	-0.1[-0.3, 0.2]
Total Cholesterol (TC) (mmol/L)	-0.1(0.3)	0.0(0.0)	0.0(0.0)	<0.1[-0.3, 0.4]	<0.1[-0.3, 0.3]	0.0[-0.3, 0.3]
Triglycerides (mmol/L)	0.1(0.1)	<0.1(<0.0)	0.0(0.0)	-0.1[-0.2, 0.1]	-0.1[-0.2, 0.1]	<0.1[-0.1, 0.1]
WBC ($x10^9$/L)	1.3(3.4)	-0.2(0.4)	0.0(0.0)	-1.3[-5.0, 2.4]	-1.5[-4.8, 1.9]	-1.3[-3.5, 3.9]
Platelets ($x10^9$/L)	-4.7(20.3)	-14.8(36.3)	0.0(0.0)	4.7[-40.4, 49.7]	-10.2[-50.7, 30.3]	14.8[-30.2, 59.9]
MCV	-0.38(0.89)	0.13(0.33)	0.00(0.00)	0.38[-0.64, 1.41]	0.52[-0.41, 1.44]	-0.13[-1.16, 0.89]
HB	-0.1(0.1)	-0.1(0.2)	0.0(0.0)	0.1[-0.1, 0.8]	0.0[-0.2, 0.2]	0.1[-0.1, 0.3]

Table 68. Mean Change (SD) in lung function and blood test results from baseline to week +12 in all ITT by trial arm and mean difference [95% CI] in these between trial arms

Change in:	SBS (A) (n=4)	SBS (L) (n=2)	IDAP (L) (n=6)	VLCD(L) (n=4)
Week +12				
Glucose (mmol/L)	0.2(0.2)	0.0(0.0)	<0.1(0.1)	0.0(0.0)
Forced Expiratory Volume in 1 sec (FEV1) (L)	-0.1(0.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)
Forced Vital Capacity (FVC) (L)	-0.1(0.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)
C-Reactive Protein (mg/L)	-1.8(2.1)	0.0(0.0)	-0.7(1.6)	0.0(0.0)
TC:HDL ratio	-0.2(0.4)	0.0(0.0)	-0.1(0.3)	0.0(0.0)
LDL-cholesterol (mmol/L)	-<0.1(0.1)	0.0(0.0)	-0.1(0.1)	0.0(0.0)
HDL-cholesterol (mmol/L)	0.1(0.3)	0.0(0.0)	0.1(0.1)	0.0(0.0)
Total Cholesterol (TC) (mmol/L)	-0.1(0.4)	0.0(0.0)	0.0(0.0)	0.0(0.0)
Triglycerides (mmol/L)	0.1(0.1)	0.0(0.0)	<0.1(<0.1)	0.0(0.0)
WBC ($x10^9$/L)	1.9(4.2)	0.0(0.0)	-0.2(0.4)	0.0(0.0)
Platelets ($x10^9$/L)	-7.0(25.8)	0.0(0.0)	-14.8(36.3)	0.0(0.0)
MCV	-0.58(1.08)	0.00(0.00)	0.13(0.33)	0.00(0.00)
HB	-0.1(0.1)	0.0(0.0)	-0.1(0.2)	0.0(0.0)

A=Abstainers
L=Lapsers

Table 69. Mean change (SD) in lung function and blood test results from baseline to week +12 in ITT abstainers and ITT lapsers by trial arm

6.2.24. **Adverse Events**

There were no serious adverse events during the trial. Most adverse events (7) occurred in the SBS arm, 5 of which may have been related to NRT use. There was one adverse event in the IDAP arm related to NRT and there were 4 adverse events in the VLCD arm, 2 of which were related to the VLCD formula (Table 70).

AE ID	visit	Trial arm	PARTICIPANT ID	Diagnosis Syndrome	Start Date	Stop Date	Intensity	Serious	Cause: Study Med?	Action taken (study Med)	Outcome
1	+1	2	27	Sore/heavy/ inflamed arm at site of patch	04/06/2010	08/06/2010	moderate	No	Yes (NRT)	Intervention discontinued	Recovered
2	0	3	29	unable to tolerate lipotrim formula	11/06/2010	13/06/2010	mild	No	Yes (Lipotrim)	Intervention discontinued	Recovered
3	+4	1	21	headache	28/07/2010	29/07/2010	moderate	No	Possibly (NRT)	Reduced patch*	Recovered
4	+4	1	21	central chest pain	29/07/2010	29/07/2010	moderate	No	Possibly (NRT)	Reduced patch*	Recovered
5	+4	1	21	nausea	29/07/2010	29/07/2010	mild	No	Possibly (NRT)	Reduced patch*	Recovered
6	+4	1	21	backache	28/07/2010	29/07/2010	moderate	No	Unlikely	None	Recovered
7	+4	1	21	pain in right forearm	28/07/2010	29/07/2010	mild	No	Unlikely	None	Recovered
8	+4	1	21	visual disturbance	28/07/2010	29/07/2010	moderate	No	Possibly (NRT)	Reduced patch*	Recovered
9	+4	1	21	cold sweating /flushing	28/07/2010	29/07/2010	mild	No	Possibly (NRT)	Reduced patch*	Recovered
10	+1	3	31	Headaches	16/09/2010	23/9/2010	mild	No	Yes (Lipotrim)	None	Recovered
11	+2	3	31	Headache & sore throat	26/09/2010	30/9/2010	mild	No	Unlikely	None	Recovered
12	+3	3	31	Flu-like symptoms.	30/09/2010	2/10/2010	mild	No	Unlikely	None	Recovered

***Unlikely related to NRT as been on patches for 4 weeks by this time, no ECG changes. Med = medication**

Table 70. Adverse Events (AE) during DeMiST

6.3. Discussion

6.3.1. Limitations

The greatest limitations for our findings came from the small sample size. Firstly, randomisation of few participants led to an unequal balance of characteristics in the intervention arm, these presented a possible source of confounding. However where it was appropriate and possible we adjusted for these; we adjusted for age and gender in the analysis of change in weight and fat mass. Secondly, there was insufficient quantitative data to draw conclusions as lack of statistical significance may have been due to type two error rather than lack of real effect. Thirdly, although some effects did reach statistical and clinical significance the sample was too small to be representative of the population as a whole. Fourthly, a larger sample size is needed to overcome measurement error. This may have been the case for bioelectrical impedence measures of body fat. We used a standard operating procedure and trained nurses to standardise measurements and kept participants appointment times consistent. However natural variations in body water throughout the day or throughout the menstrual cycle may have increased random error. Also, the large variability in waist and hip measurements meant we had to discount these.

6.3.2. Summary and interpretation of cigarette cravings by trial arm

We found no evidence that cravings in people on IDAP were different from the control group (Stage 1 of SBS). There was however, evidence that VLCD reduced cravings by a clinically relevant degree. This is similar to the findings of Danielsson

that also showed a reduction in cravings in those on a VLCD (Danielsson et al., 1999).

We examined whether the effect of the diets on cigarette cravings was mediated by food desire and/or food need. Food desire, in particular, increased in the IDAP arm, but there was no evidence that either food desire or food need accounted for the difference in cigarette cravings between trial arms. Those adhering to the VLCD were in ketosis and this may have explained the reduction in cravings in the VLCD arm.

Periods of abstinence were associated with lower cigarette craving scores. Abstinence varied by trial arm, but there was no evidence that these differences in abstinence accounted for the difference in cigarette cravings seen between trial arms.

The best fitting model of cigarette cravings over time was a quadratic function that varied by trial arm but this did not capture or explain the dramatic peaks and troughs within and between individuals. This variability in withdrawal patterns among individuals has previously been reported by Piasecki in 2003. He described and mathematically defined ‘symptomatic volatility’ to model the deviations of the observed data from an individual’s predicted quadratic model of craving. He suggested that it is these peaks which make an individual suceptible to relapse. He also showed that lapsing to smoking can result in either a peak or a trough. We also saw that abstinence was associated with drop in cigarette craving. We expected the

opposite to be true. But as discussed by Piasecki, higher cravings may be associated with lapsing, as desire to smoke may become too great to resist, rather than smoking reducing desire. In other words the association may have been due to cause rather than effect. To explore this further a time lagged model is needed to differentiate between cause and effect, investigating whether an increase in craving preceeds lasping and whether lapsing leads to a reduction in craving.

To better explore the relationships between lapsing and cigarette craving, food need and food desire with cigarette craving we need a more sensitive measure of cigarette cravings, food cravings and hunger over time. This could be done using ecological momentary assessment (Shiffman et al., 2002), together with a record of when cigarettes are smoked. Then, perhaps the most useful way to model these data would be a time lagged model on the symptomatic volatility of cigarette cravings.

6.3.3. Summary of and interpretation of smoking status by trial arm

Participants were 4 and 8 times more likely to relapse in the IDAP and VLCD arms respectively, than those in the SBS arm. These values were not statistically significant and the small sample size and wide 95% confidence intervals around the means makes the findings uncertain.

Cravings may predict relapse, data from an observational study (n=1500), where smokers enrolled in a smoking cessation trial assessed withdrawal symptoms four times a day over the two weeks prior to and two weeks post quit date, showed a postive association between mean craving score and relapse (Piper et al, 2011). So our findings that relapse is higher and cravings are lower in the VLCD arm seem contradictory, although our study was not powered to detect difference in abstinence rates.

6.3.4. Summary and interpretation of physical measures by trial arm

Weight and fat mass reduced in the IDAP arm and increased in the SBS arm. These effects lessened as the intervention continued and the SBS arm went into Stage 2. The differences between these trial arms were of clinical importance at all time points. Reduction in dietary fat intake explained 22% of the reduction in body fat mass.

Weight, fat mass and total body water reduced dramatically in the VLCD arm, by four weeks post quit there was also evidence of some loss of lean body mass, which is of clinical concern. Most lost weight was regained in Stage 2 of the VLCD but weight gain was less than in the SBS arm. Fat mass in the VLCD arm exceeded its baseline value at 12 weeks post quit date and this gain was greater than in the SBS arm.

Subgroup analysis by abstinence status showed that participants who lapsed or relapsed to smoking lost greater weight than those who stopped smoking. This is consistent with previous cohort studies (O'Hara et al., 1998) and our own analysis of the Oxford Patch data (section 2.4.3) which shows those who relapse to smoking return to their smoking weight.

IDAP showed the most promise of a clinically important effect on weight and body fat in particular, and this was greatest when given at the time of quitting. The Cochrane review also showed that an individually tailored dietary intervention prevented more weight gain compared to usual care 12 months, than did a VLCD or general healthy eating education (Parsons et al., 2009). We found IDAP was not associated with any adverse events, but people were more likely to relapse to smoking in this arm, however our study was inadequately powered to investigate abstinence rates. The Cochrane review showed no significant difference in abstinence rates at 12 months between those on this type of intervention and usual care, but the sample size from which this was calculated was still too small to be certain. IDAP now needs to be compared to usual care in an adequately powered trial to detect long term change in body composition and effects on relapse.

6.3.5. Summary and interpretation of disease risk factors by trial arm

There were no data on these parameters in the VLCD arm. We had some on lung function in the SBS arm which showed no important change during the trial.

By the end of treatment blood glucose rose slightly in both the SBS and IDAP arms. In general, cardiovascular risk factors improved in both these arms but more so in the IDAP arm. The exception was triglycerides, these fell in the IDAP arm but rose in the SBS arm. It was interesting to note that the data from the IDAP arm was from a lapsed individual and the data from the SBS arm was from abstainers, but even so, parameters improved most in the IDAP arm. The sample was too small to draw conclusions. However, it does draw attention to the benefit:risk ratio of smoking cessation on short term increase in disease risk factors that were discussed at length in the introduction to this thesis. The investigation of which needs further investigation with the aim of targeting and reducing these risks in quitting smokers.

6.3.6. Failure to attend and intention to treat analysis

This trial, as expected from other smoking cessation trials (Marteau et al., 2010), had a large proportion of participants not attending their appointments and assumed relapsed to smoking. More participants completed the programme in the SBS arm, and they were less likely to relapse to smoking although this was an underpowered measure. It is possible that the incentive of weight control support at eight weeks, after they stopped smoking, helped to keep them motivated and adhering to the programme. Whereas, by then, the other arms already received most of their intervention and incentive to return for visits was reduced.

High non-attendance rates meant a large number of missing data had to be imputed for intention to treat analysis. Although I used BOCF that assumed no effect (i.e. a return to smoking and original weight) this did not allow for the possibility of weight gain following relapse after a quit attempt. However, available data suggests that this is unlikely as 'relapsers' return to their smoking weight (Lycett et al., 2011a, O'Hara et al., 1998). Not accounting for this worst case scenario may have made the results from the ITT analysis appear more favourable than they were.

The ITT analysis provided a similar pattern of results, but with a diluted effect, on physical measures compared to completer analysis. Clinically important differences in favour of the IDAP and VLCD interventions compared to the SBS arm were found. However, changes in disease risk factors were no longer clinically important in the ITT analysis.

7. SUMMARY OF CONCLUSIONS. REFLECTIONS AND FUTURE DIRECTION

I presented many of the findings of this doctoral research and its implication for clinical practice and future research as a plenary at the annual UK National Smoking Cessation Conference in June 2011 (Appendix 46).

Chapter seven fulfils objective nine of the thesis : to discuss the implications of findings from this doctoral research to advance understanding in this field and lead to improved clinical practice.

7.1. **The Oxford patch cohort analysis**

We began this thesis by discussing the problem of smoking cessation related weight gain. We sought to add to current knowledge by investigating long term weight gain in a cohort of smokers and abstainers where abstinence was biochemically validated and continuous over eight years. We then investigated the baseline characteristics associated with this weight gain. Key points are summarised in Table 71 with respect to what was already known at the start of our research, what our research has added and reflections on what this means for public health, clinical practice and further research. Further detail is discussed in the text below.

We found that smokers who quit smoking gain, over eight years, 7kg more than if they had continued to smoke, while those who quit for a substantial period and then resume smoking seem to resume their 'smoking weight'. We were the first researchers to find a J-shaped relation between baseline BMI and weight gain in quitters. We also found evidence to suggest that moderate alcohol consumption at the time of quitting is associated with less weight gain in quitters over eight years. A complex relationship exists between alcohol consumption and weight gain and this has long been a source of controversy, so far it has rarely been explored in quitting smokers.

Our cohort included well-defined continuous abstainers, over a full eight years, however this group of abstainers was relatively small (n=85) and did not measure all potential confounders. Therefore, further studies are needed to confirm our findings, but if these are confirmed, they have important implications for the management of weight during smoking cessation, in particular to identify those individuals who are at most risk and at most need of weight control interventions.

From a personal point of view, this cohort analysis helped me develop my skills in multiple regression analysis and I learnt to identify the strengths and limitations of our data. This was helped by the peer review process when I submitted these findings for publication and had to justify the value of my findings despite limitations of a high level of attrition, some self reported data and unmeasured confounders. All these things I will consider in designing future studies.

Area of investigation	Previous Evidence	Our method	Our contribution to further evidence	Implications for further research	Implications for public health/clinical practice
Risks of post cessation weight gain	Some of the benefit of smoking cessation such as reduced decline in lung function, is offset by weight gained	Literature review	Several large prospective cohort studies show that the risk of type two diabetes during the first five years of quitting exceeds that of continuing smokers.	Full systematic review and meta-analysis of these studies is required to quantify the risk of diabetes during the years after quitting smoking	Quitting smokers may benefit from screening for diabetes during this time.
Extent of post cessation weight gain	5kg at one year post cessation, 8-9 at four and five years post cessation	Oxford Cohort analysis	9kg at eight years post cessation. Large standard deviations of our estimates show variable weight gain. 2kg gain in continuing smokers, which is similar to relapsed smokers over this time. Only 25% of those who quit remain a healthy weight 8 years later.	Further long term prospective cohort studies are needed with comparison to the continuing and never smoking population to further determine the extent and duration of post cessation weight gain	Mean weight gain over 8 years is 7kg above continuing smokers, for some it is a lot more. Those who quit smoking are a population at risk of accelerated weight gain
Association of baseline BMI with post cessation weight gain	Evidence is inconclusive	Oxford Cohort analysis	We showed for the first time a J shaped relation between baseline BMI and weight gain which may account for some previous inconsistencies.	Confirmatory analysis needed in a larger cohort, with more potential confounders measured and adjusted for.	If confirmed those who are already obese, should be targeted for interventions to prevent further weight gain on smoking cessation
Association of baseline alcohol consumption with post cessation weight gain	One study showed weight gain is greater at 5 years with lower baseline alcohol consumption	Oxford Cohort analysis	Higher baseline alcohol consumption is associated with less weight gain at eight years.	Confirmatory analysis needed in a larger cohort, with more potential confounders measured and adjusted for.	If confirmed advice to avoid alcohol during smoking cessation may need to be revised for those at greatest risk of weight gain. Or non drinkers may need to be targeted for weight gain prevention strategies.

Table 71. Summary of findings and academic contribution from the analysis of the Oxford patch data

7.2. The DeMiST trial

We considered how we could add to the evidence base to advance clinical practice to prevent or treat post cessation weight gain. The Cochrane review (Parsons et al., 2009) showed evidence that two separate dietary strategies may prevent weight gain and not reduce abstinence and may even increase it. The interventions were an individualised dietary and physical activity plan (IDAP) and a very low calorie diet (VLCD). We therefore designed a three armed randomised controlled feasibility trial comparing these interventions to usual care within NHS stop smoking clinics. To do this we used a variety of research methods to answer a number of questions. Key aspects of our findings on feasibility, process measures and clinical outcomes, and how these contribute to the current evidence are summarised in Table 72, Table 73 and Table 74 respectively with some further detail described below.

7.2.1. Acceptability

To investigate the acceptability of the trial to participants we measured response and recruitment rates. We found that using a VLCD excluded many potential participants. We demonstrated that it is difficult to recruit into a trial which offers help to control weight together with smoking cessation, from GP practices and advertisement by fliers in newspapers. We were recruiting in an area with access to free smoking cessation services, so many of those keen to have stop smoking support may have already done so. It may also be that people are not keen to tackle weight control and smoking cessation together.

Our plan is to move to a full scale trial of the IDAP intervention for weight control versus usual care during smoking cessation. To improve recruitment we plan to recruit from a population who are already enrolled in an NHS stop smoking service. A recent trial in Scotland did so and recruited 90% of smokers entering the service into a trial to prevent weight gain through education about healthy eating (Hankey et al., 2010).

We carried out qualitative interviews to understand participants' views of the interventions and trial design. Reasons for acceptability of the IDAP arm seemed to be a conservative approach to weight loss, whereas in the SBS lack of acceptability was because participants wanted a weight control intervention sooner than offered in the control arm. Participants attracted to this kind of trial were not persuaded that tackling this 'step by step' was appropriate. Acceptability seemed also to depend on whether the allocated intervention met participants' individual needs rather that the inherent properties of a particular trial arm. However, our conclusions are tentative as we were unable to meet our purposive sample. Nevertheless there are several ways we could incorporate meeting participants' needs within our future trial design to test these findings. We could run a pragmatic trial where participants are randomised into control or a pragmatic intervention arm in which participants are offered one of several strategies from which to choose and/or swap between. However, this still leaves us with a control arm which some might find unacceptable. We could run a preference trial, where participants without preference are randomised into control or intervention and those with a preference are allowed to choose. However, systematic review

evidence shows that this does not improve retention within an intervention, although it may improve recruitment rates at the outset (King et al., 2005).

We also asked participants prior to randomisation which intervention they thought would be most successful. We found no evidence that those who got the intervention they believed in followed the programme for longer than those who did not. Aside from the small sample, this evidence is clouded because our question did not assess whether this was a general belief about the efficacy of the intervention in a population, or whether it was a belief that it would work for them personally.

Further investigations of ways to improve retention in behavioural treatment programmes are needed. One way might be to counsel participants to deal with difficulties and disappointments that might arise during a clinical trial.

During the exploration of acceptability, I developed skills in semi-structured interview techniques and learnt that there is a fine balance between insufficient probing which can lead to false assumption, and too much probing which can sway participants' opinion. The complexity of analysing qualitative data with its many levels of meaning and interlinking themes has reminded me of the necessity to keep to a clearly focused research question.

7.2.2. Feasibility

Fidelity checks within clinics showed that nurses were competent to run the trial and deliver the clinical interventions according to the protocol. We have therefore demonstrated that we were able to train nurses to provide these specialist dietary interventions within NHS stop smoking clinics. The nurses debriefing session and fidelity checks provided suggestions to increase nurses' confidence in delivering the interventions and to streamline the practicalities of the full scale trial. In particular, we will reduce the number of clinical parameters measured. The nurses found some of these clinical measures difficult. Although they performed them adequately, the complexity undermined their confidence in their work. In a phase three trial, where less supervision is likely, there is the potential that this lack of confidence could lead to stress and reduced competence.

Area of investigation	Previous Evidence	Our method	Our contribution to further evidence	Implications for further research	Implications for public health/clinical practice
Recruitment to a stop smoking and weight control trial through invitations from GPs	When we began our research this has not been tried in an NHS setting	Demist feasibility trial	Recruitment to such a trial through invitation via GP practices is difficult	We should try recruiting those already enrolled in the stop smoking services	If recruitment continues to be unsuccessful, we may need to question whether there is a real need for the development and provision of a service which combines smoking cessation and weight control.
Acceptability of randomisation into SBS	Preference trials have shown recruitment can be increased if individuals are given a choice although there is little effect seen on attrition.	Demist feasibility trial	Despite attempts to appease those in the control group with belated dietary intervention participants still found randomisation to the control arm unacceptable. Although there was no evidence to suggest that those randomised to the control arm left the programme earlier than the other arms.	Further research should consider ways to help participants prepare for difficulties and disappointments within clinical trials in order to improve retention in these	
Feasibility of a VLCD for quitting smokers	One trial showed a VLCD was feasible for us in this population in a research setting	Demist feasibility trial	VLCD was not a practical option for use in typical NHS stop smoking services	Alternative ketogenic diets could be explored	It is unlikely that VLCDs will form standard care for preventing smoking cessation related weight gain.
Feasibility of delivery of IDAP by stop smoking nurses	When we began our research this has not been tried in an NHS setting	Demist feasibility trial	This was feasible	This model could now be trialed on a larger scale.	

Table 72. Feasibility Findings from DeMiST and their contribution to current evidence

7.2.3. Process measures

7.2.3.1. The Healthy Choice Index (HCI)

We developed the healthy choice index and assessed its validity against a seven day food diary where food quantity was estimated but not weighed. We measured the limits of agreement for nutrient intake. We found that while the HCI was a useful prompt for setting dietary goals within the IDAP intervention it was not a valid measure of nutrient intake. The one exception to this was total fat, where it was able to distinguish between low, medium and high intakes. Our results showed that a fall by one category of fat intake over 12 weeks was associated with a decrease in body fat mass of 1.0kg. This explained 22% of the reduction in body fat seen in the IDAP arm.

The assessment of dietary fat was based on more questions than any of the other nutrients which may have influenced the validity of this measure. Future efforts should focus on refining the questions in the HCI to improve sensitivity to detect change in the other nutrients. It could then be used in an adequately powered sample to test its validity. Before it can be used as a full nutrient assessment tool within clinical trials, investigating its repeatability and sensitivity to dietary change associated with a change in clinical outcomes is also needed.

7.2.3.2. The Hunger and Craving Score (HCS)

We designed the HCS to capture two different motivations to eat, that resulting from a homeostatic response to lack of food and the more hedonistic food craving. There have been independent measures of hunger and cravings developed before (section 3.1.2). Also, laboratory experiments have measured 'implicit wanting' and 'explicit liking' as a response to food cues before and after test meals (Finlayson et al., 2008). However, we know of no questionnaire to distinguish between these two motivations in free living conditions.

We carried out principal components analysis on our HCS to reduce our data for further analysis. We found that we could distinguish between a craving for fatty and sugary food and desire for healthy food, but that the item measuring hunger could be perceived as either. We found no evidence that either of these motivations to eat was associated with urge to smoke, but we cannot be sure that this did not arise from the limitations of our questionnaire.

More work on this is needed to better differentiate between hunger and food craving. A new good starting point would be a qualitative study to understand how people conceptualise and express notions of craving or desire for food, in contrast to more physiological notions of hunger. It would have value in investigating not only hunger and food cravings during smoking cessation, but also their role in obesity development.

Area of investigation	Previous Evidence	Our method	Our contribution to further evidence	Implications for further research
Hunger and food craving in quitting smokers	No questionnaire available to distinguish between food need and food craving in the usual living conditions Laboratory studies showed that hunger may increase cravings for cigarettes	Development of Hunger Craving Score (HCS)	It was possible to distinguish between two motivations to eat using a questionnaire, but the nature of 'hunger' was still unclear Despite cigarette cravings and food craving being different between trial arms we found no evidence that desire for food mediated cravings for cigarettes	There was considerable overlap of these motivations which require further exploration before these can be measured accurately. This was a process measure which needs confirmation in a larger trial
Dietary change in quitting smokers	There was no validated tool which can be used to assess diet and prompt dietary change in clinical practice	Development of Healthy Choice Index (HCI)	The HCI was validated for assessing high, medium and low intakes of dietary fat, but not of other nutrients. Change in fat as calculated by the HCI partially accounted for reduction in fat mass in the IDAP arm The nurses found it a useful tool to initiate discussion regarding dietary behaviour change	This tool needs revision and further investigation of its validity as a dietary assessment tool. Its role in helping to prompt and monitor change in fat intake needs to be confirmed.

Table 73. Findings of the investigation of process measures in DeMiST their implication for further research

7.3.1. Effects of trial arms on urges to smoke

We found no evidence that IDAP reduced cravings compared with control (Stage 1 of SBS) but there was evidence that the VLCD, in which adherent participants were ketotic, reduced cravings by a score of one on the MPSS similar to previous findings (Danielsson et al., 1998). However, our modelling did not capture or explain the dramatic peaks and troughs within and between individuals, which may be the most likely cause of relapsing (Piasecki et al., 2003). Also it was not a time lagged model to allow us to investigate whether hunger clearly preceeded uges to smoke. Our daily measures were also not frequent enough to capture a variation in urges over the course of a day. This could be investigated in future studies using ecological momentary assessment (Shiffman et al., 2002).

Analysis of our repeated measures data in DeMiST developed my skill and confidence in multilevel modelling.

7.3.2. Effects of trial arms on relapse

Participants were four and eight times more likely to relapse in the IDAP and VLCD arms respectively, than those in the SBS arm, but our sample size was too small for us to be certain. If cravings predict relpase (Piper at al., 2011) this finding does not support our findings or those of Danielsson et al. (1998) that cravings are reduced on a VLCD. The Cochrane review (Parsons et al, 2009) also showed that abstinence rates were not statistically significantly worse in an individualised

dietary intervention compared to usual care, and abstinence rates were better in those receiving a VLCD than a control condition.

7.3.3. Effects of trial arms on smoking cessation related weight gain

Completer analysis of all those attempting to quit showed weight and fat mass reduced in the IDAP arm and increased in the SBS arm. These effects lessened as the intervention continued, and the SBS arm went into Stage 2, and received their dietary advice. The differences between these trial arms were of clinical importance at all time points. Intention to treat analysis showed a similar pattern but the differences were smaller.

In those achieving four week continuous abstinence weight rose in the SBS arm by 1.1(0.8)kg, this is comparable with weight gain of 1.3kg at four weeks shown by meta-analysis of those in control arms of smoking cessation trials (Aubin et al., unpublished). By contrast weight fell by 2.8kg in the IDAP arm but this was based on one individual. Two studies have weight data at four weeks in continuous abstainers who were given individualised dietary advice, one showed weight increased by 0.6(1.6)kg (n=72) (Perkins et al, 2001) and the other showed virtually no mean weight increase 0.08(2.4)kg (n=26) (Hall et al., 1992). However, the standard deviations for these means were large indicating a wide variability, so with more people we may find that mean weight loss in IDAP is not quite so big.

There were no continuous abstainers in the VLCD arm at four weeks, but during this time participants had quit and lapsed. Overall weight loss was dramatic. However, there was some evidence of loss of lean body mass by four weeks and excessive gain in body fat by 12 weeks, which is of clinical concern, but our sample was too small to be conclusive. Many other studies, in the general population, have investigated changes in body composition on a VLCD and these have been reassuring (COMA, 1987). However Danielsson et al. (1998) carried out the only trial using a VLCD in quitting smokers and they not measure changes in body composition. So more research is needed if a VLCD is to be pursued for quitting smokers. However, because of the reasons summarised in the next section we do not feel this is a feasible option within typical NHS stop smoking services.

We did not have enough abstainers at the end of twelve weeks to compare changes in body composition by trial arm.

Area of investigation	Previous Evidence	Our method	Our contribution to further evidence	Implications for further research
Effect of intervention on weight control	Individual tailored advice and a VLCD looked most promising	Demist feasibility trial	VLCD may have unfavorable changes on body composition in this population. IDAP continues to look promising	IDAP needs to be trialed on a larger scale in comparison to usual care to determine its long term effect on weight gain in this population. Changes in body composition in quitting smokers need to be investigated further before a VLCD can be recommended in clinical practice
On cigarette cravings	VLCD looked promising	Demist feasibility trial	Cravings reduced in the VLCD arm compared to the control but were no different between the IDAP and SBS arm	See above
On relapse to smoking	VLCD looked promising, individual tailored advice looked neutral, general healthy eating education was identified as potentially problematic.	Demist feasibility trial	Those in the SBS arm were least likely to relapse, those in the VLCD arm were most likely to relapse	A trial large enough to test the equivalence of IDAP compared to usual care on smoking rates is needed. The evidence from the Danielsson trial (Danielsson et al., 1998) of reduced abstinence still stands as our trial was so small however the effects on body composition would need to be investigated before recommendations could be made

Table 74. Effects of DeMiST interventions on clinical outcomes and the implication for further research

7.3.4. What DeMiST means for clinical practice and future research

The sample was too small to draw firm conclusions for clinical practice. However, the value of VLCD use within NHS stop smoking clinics appears to be limited for several reasons. Firstly, only half of those randomised to the VLCD were able to adhere to it. Secondly, adverse events related to the VLCD were reported. Thirdly, lean body tissue reduced and fat mass increased beyond that of the control. Fourthly, the VLCD contraindications, including necessary monitoring which fell outside of the scope of stop smoking clinics, limited recruitment. This translates to its limited suitability as a treatment option for quitting smokers. We are therefore not keen to pursue further research of a VLCD within this population. However, the reduction in mean craving score found here, similar to those in the Danielsson study, cited in the Cochrane review (Parsons, 2009), should not be overlooked. It may be that there is a more practical, food based, ketogenic diet with the potential to reduce cigarette cravings, and we are keen to explore further.

IDAP showed the most promise at promoting weight loss in abstainers. Cravings in these individuals were no worse than those who were not actively trying to diet in the SBS arm. This goes a little way to alleviate concerns based on laboratory studies that dietary restriction leads to an increase in cigarette cravings. However, none of the individuals in the IDAP arm achieved 12 week abstinence; and it is not possible to tell whether this was an artifact of a small sample or an effect of dieting. Qualitative data showed that this was the least resisted arm of the trial. The Cochrane review (Parsons et al, 2009) also showed an individually tailored approach, with an energy prescription, was effective at preventing weight gain. It

also showed that this approach did not significantly reduce abstinence rates at 12 months, although the estimate was too imprecise to be sure that there is not a substantial harmful effect. We are now planning a large equivalence trial to investigate the long term effects of IDAP on smoking cessation related weight gain to determine whether abstinence rates in IDAP are equivalent to those in usual care.

In the meantime how should smoking cessation related weight gain be tackled in routine clinical practice? In the 2010 national survey of stop smoking advisors (n=484), we asked advisors what advice they give clients regarding preventing weight gain. Seventy-six percent reported they encourage healthy food choices (Appendix 47). Therefore, education about healthy eating is currently prevalent in practice, but it is not supported by evidence. We offered general healthy eating messages to those in the SBS arm, but they felt disgruntled and it did not prevent weight gain. The Cochrane review showed general healthy eating advice was ineffective in preventing weight gain and suggested that such an approach reduced abstinence. So, it seems prudent to discourage this practice.

For now, we advocate that smoking cessation advisors encourage patients not to embark on a dietary strategy to control weight until a quit attempt is established. Advisors can be reassured that there is no clear evidence, from a review of the literature, that allowing some weight gain will lead to relapse. However, given the evidence that this weight gain was unacceptable to some there is a need to be pragmatic. We would recommend quitting smokers who are keen to control their

weight follow the individually tailored dietary advice with an energy prescription. Many NHS dietitians currently provide this as a treatment for obesity. It appears the most promising and least likely to cause harm when quitting smoking. For now, the most expedient way is for a quitter to attend a weight loss service. In the future, if abstinence rates prove to be equivalent, stop smoking services could be trained to provide this dietary treatment as part of usual care. An alternative model is for weight management services to provide smoking cessation support. It need not only be an option for the weight concerned, but for all individuals as this weight gain attenuates some of the benefits of stopping smoking and may increase diabetes risk in the medium term.

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