Genetic Test Feedback for Risk of Weight Gain – Motivational and Behavioural Effects

Thesis submitted for the degree of
Doctor of Philosophy

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DECLARATION

I, Susanne Meisel, declare that the work presented in this thesis is my own. Where work has been derived from other sources, I confirm that this has been indicated.

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ABSTRACT

The value of genetic test feedback for common conditions is widely debated. This is principally because of the lack of impact on behaviour change of feedback for genes with small effect sizes, but also because of concern about the risks of fatalistic responses to positive test results or false reassurance from negative results. This thesis describes research using feedback for one gene, FTO, implicated in the development of obesity, as a model to investigate motivational and emotional reactions to testing for genetic susceptibility. It comprises a series of six studies examining the benefits and harms associated with genetic test feedback. They incorporated a mixture of qualitative and quantitative methodologies, used hypothetical and real genetic feedback, and tested predominantly normal-weight students and overweight/and obese individuals from a web panel.

Fatalism or false reassurance in response to FTO genetic test feedback was not observed in any of the studies. Genetic test feedback was consistently perceived as motivating, and negative emotional effects of a higher-risk FTO gene result were minimal. Overweight and obese individuals found the test result helpful for alleviating guilt and stigma; although in response to an unexpected lower-risk genetic test result, some were disappointed.

University is notoriously a life stage with risk of weight gain but not all students gain weight. One study examined associations between genetic risk status and weight gain, and found that students with at least one higher-risk allele were more likely to gain weight. The final study was a randomised controlled trial examining the effect of giving FTO feedback alongside simple weight control advice to first year students. Short-term (one month) results showed that weight control intentions were significantly higher in those randomised to receive *FTO*

feedback and weight control advice than weight control advice alone, but there was no effect on weight or reported behaviour change.

Although the studies in this thesis had many limitations, the findings indicate that people are unlikely to misinterpret or overstate the impact of genetic test results, at least in the context of a single gene implicated in a multifactorial condition. However, effects on behaviour remained elusive. This indicates the need for future research to learn how to harness the potential of genetic information to promote personalised prevention.

Table of Contents

Table of Figures

Table of Tables

List of Abbreviations

ACMG	American College of Medical Genetics
ALSPAC	Avon Longitudinal Study of Parents and Children
AN	anorexia nervosa
APOE	Apolipoprotein E, implicated in Alzheimer's disease
BMI	Body-Mass-Index., used to assess a person's weight status; calculated weight (kg)/ height $(m)^2$
BN	bulimia nervosa
BOLD	blood-oxygen-level dependent
CEBQ	Child Eating Behaviour Questionnaire
CONSORT	Consolidated Standard of Reporting Trials
DNA	Deoxyribonucleic acid
DTC	Direct to consumer genetic tests
EAH	Eating in the absence of hunger
EDE	Eating Disorder Examination
ES	Effect Size
FAP	Familial adenomatous polyposis
FDA	Food and Drug Administration
FH	Familial Hypercholesterolemia
FPS-S	Fat Phobia Scale –Short form
FTO gene	Fat mass and-obesity associated gene (originally named Fused Toe and Obesity associated because deletion results in fused toes in). The FTO gene codes for the FTO enzyme (N6 methyl-adenosine demethylase, an mRNA demythelase).
GIANT	The **G**enetic **I**nvestigation of **AN**thropometric **T**raits (**GIANT**) consortium
GINA	Genetic Information and Nondiscrimination Act
GP	General Practitioner

HBM	Health Belief Model
HSE	Health Survey for England
IASO	International Association for the Study of Obesity
IOTF	International Obesity Task Force
MC4R	Melanocortin 4 receptor
NHS	National Health Service
NPV	Negative Predictive Value
NWCR	National Weight Control Registry
PA	Physical activity
PCA	Principal Component Analysis
PPV	Positive Predictive Value
SD	Standard Deviation
SES	Socioeconomic status
SNP	Single Nucleotide Polymorphism
SPSS	Statistical Package for Social Sciences
RCT	Randomized controlled trial
TEDS	**T**wins **E**arly **D**evelopment **S**tudy
TEFQ	Three Factor Eating Questionnaire
UCL	University College London
UK	United Kingdom
US	United States
WBIS	Weight Bias Internalization Scale
WHO	World Health Organization

Chapter 1: Obesity, *FTO* and the environment

1.1 The Burden of Obesity

Obesity is of major concern for health care providers and policy makers, because it raises the risk of serious health conditions such as diabetes, hypertension, cardiovascular disease, and certain types of cancer; contributing significantly to morbidity and mortality and driving healthcare costs substantially upward (World Health Organization (WHO), 2000; James, 2008).

Obesity is defined as excess body fat that impacts on physical constitution, resulting from sustained positive energy balance (Martinez & Fruhbeck, 1996). It is commonly assessed using body mass index (BMI), which is the ratio of weight to height, calculated by dividing weight (kg) by height (m) squared. Established cut-off points are 25.0-29.9 kg/m^2 for overweight and ≥ 30.0 kg/m^2 for obesity (WHO, 2000); although these are somewhat arbitrary because weight itself is continuously distributed in the population assuming a bell-shaped curve. However, because of its easy use and relatively close correlation with body fat at ranges considered as hazardous for health, BMI remains the most widely used measure of weight status (Romero-Callo et al., 2008).

Obesity rates have been increasing at an alarming rate over the past 30 years, leading the WHO to declare it a 'global epidemic' in 2000 (WHO, 2000). Worldwide an estimated 1.46 billion adults are overweight or obese, with numbers in developing

countries rising rapidly (International Association for the Study of Obesity/International Obesity Task Force, 2010). In the United Kingdom (UK), the latest available figures show that over 60% of adults are overweight or obese (Health Survey for England, 2010). Importantly, to date, no country has demonstrated a reversal of the trend despite sustained efforts, highlighting not only the complexity of the problem, but also hinting at the prospective burden from ever increasing numbers of overweight and obese individuals.

1.2 Genetic and environmental influences in the development of obesity

The diverse causes of obesity are illustrated by the Obesity Systems Map shown in Figure 1.1 (Vandenbroeck et al., 2007) which includes over 100 variables spanning macro- and microenvironment, inter- and intrapersonal influences, and their interconnections which impact on obesity development. It is beyond the scope of this thesis to consider all of these influences, and for the empirical studies the primary focus will be on the interaction of one gene (*Fat mass and Obesity associated gene, FTO*) with the university environment in increasing risk of obesity; although I am aware that this is an overly simplistic account of the problem.

Figure 1.1 Foresight Obesity Systems Map (Vandenbroeck et al, 2007)

1.3 Genetic influences on obesity onset

1.3.1 Twin and adoption studies

Familial aggregation of obesity is common. For example, Whitaker and colleagues (2010) showed that child obesity levels increased in a graded linear fashion with degree of parental overweight. Children of two overweight or obese parents were twice and 12 times more likely to be obese than children of two normal weight parents.

However, it is difficult to distinguish the effects of shared familial environment, lifestyle, and genes in family studies. Twin studies are especially useful in teasing the relationship between genetic and environmental influence apart, because twins share either 100% of their genes (*monozygotic*), or 50% like normal siblings (*dizygotic*); both usually share, however, a very similar environment because they are born at the same time. Adoption studies also provide a powerful strategy for comparing genetic and environmental influences of obesity development.

If obesity is genetically determined, then monozygotic twins should show more similarities in their weight than dizygotic twins, and adopted children should show higher similarities in weight with their biological parents than with their adoptive parents. A recent meta-analysis of all twin and adoption studies confirmed the strong genetic effects on BMI in children throughout all age groups until onset of adulthood (Silventoinen et al., 2009). Heritability of obesity was estimated to be about 70%, taking into account that changing gene expression patterns across the lifespan may cause variation in heritability rates at different ages.

1.3.2 Mendelian and monogenic disorders linked with obesity

Further evidence for a strong genetic component in obesity onset comes from Mendelian diseases[1]. One example of a Mendelian disorder is Prader-Willi-Syndrome, which is, besides other factors, characterized by severe obesity (Ohta et al., 1999). Studying this syndrome closely in addition to studying individuals who suffer from other rare monogenic diseases has helped to establish a firm evidence base for the importance of genes in obesity onset. In Prader-Willi Syndrome, a deletion of a segment of the paternal Chromosome 15 (15q11.2-q12) has been found to cause disruption of the pathways responsible for energy homeostasis, leading to severe hyperphagia and obesity (Montague et al., 1997; Farooqi & O'Rahilly, 2009). Another example is the disruption of the leptin-melanocortin-pathway, which signals from adipose tissue to the hypothalamus to maintain energy balance (Farooqi & O'Rahilly, 2009; Montague et al., 1997). Similarly, mutations in the melanocortin-4-receptor (*MC4R*) gene disrupt energy homeostasis leading to increased food intake (Loos et al., 2008; Farooqi & O'Rahilly, 2005).

[1] These diseases are characterised by three distinct inheritance patterns that were discovered by the Monk Gregor Mendel: 1. dominant, 2. recessive, 3. sex-linked. In dominant inheritance patterns, a mutation in a single gene is sufficient to cause illness. Recessive inheritance patterns, on the other hand, require the mutation to be present in both genes to be expressed. If only one copy is present, the disease can be transmitted, but the individual will not fall ill. This is also the case for the sex-linked disorders. There, the mutation lies on a gene on the X-chromosome. As men only have one X-chromosome (they receive a Y from the father), they will be affected by the disease regardless of whether it follows a dominant or recessive inheritance pattern; in contrast, women have two X-chromosomes, one of which will be inactivated, so that they do not fall ill if the disease is X-linked recessive. They can however, transmit the faulty gene to their offspring.

1.3.3 Linkage studies and genome-wide association studies (GWAS)

Although studies of Mendelian disorders have been valuable in understanding some of the mechanisms responsible for obesity onset, single-gene disorders represent only a minority of cases, and therefore cannot account for the high prevalence of obesity in the population. It is now recognised that so-called 'common obesity' is a complex, multifactorial disorder in which many genes of small effect and with high population prevalence each act to affect weight only marginally, which is known as *Common Disease/Common Variant Hypothesis* (Lander, 1996). Genes with small effect may also interact with one another, other genes, and the environment, to increase susceptibility to weight gain.

Previously it was difficult to detect small effects of specific genes because the genome was not fully sequenced, and there were no methods available to search it on a large scale. With the development of genetic technologies over the last decade which allow for scanning the entire genome, it has become clear that gene variations (*alleles*) exist at many specific locations in the genome. Genes can now be scanned for *Single Nucleotide Polymorphisms (SNP*s) to find common risk alleles which contribute to disease development. Because effects are so small, large sample sizes are required to have sufficient power to detect them and mustering these has become possible only relatively recently through decreased sequencing costs.

1.4 *FTO* and other genes implicated in obesity development

In 2007, Frayling and colleagues reported a common variant in the *FTO* gene *(rs9939609)*, located on Chromosome 16, which leads to an average increase in weight

of three kilograms in homozygotes. With one risk allele, individuals tend to be on average 1.7kg heavier compared with those having none. About 37% of the Caucasian population carry one higher risk allele of *FTO,* and 16% carry two. This finding has been replicated by several research groups (Cauchi et al., 2009; Haworth et al., 2008; Loos & Bouchard, 2008; Scuteri et al., 2007; Dina, 2008) and in other ethnic groups, albeit frequency distributions and specific SNPs may vary (Yajnik et al., 2009; Grant et al., 2008; Tan et al., 2008; MI et al., 2009; Hotta et al., 2008).

In 2008, Loos and colleagues confirmed another locus near the *MC4R* gene *(rs17782313)* as adding small amounts to weight (about 0.2 kg per allele). Although this is a small increase in body weight per se, it results in an 8% increase for the chance of being overweight and a 12% increase in chance of being obese, in individuals homozygous for the higher risk allele. Willer and colleagues (2009) then identified six new loci associated with obesity, in addition to replicating the already well-known loci for *FTO* and near *MC4R*.

A recent study from the **G**enetic **I**nvestigation of **AN**thropometric **T**raits (**GIANT**) consortium, an international collaboration that seeks to identify loci that are implicated in body size and shape, confirmed 18 new loci implicated in obesity in a genome-wide association meta-analysis encompassing 46 studies with close to 250,000 individuals, (Speliotes et al., 2010). In total, there have now been more than 56 genes identified which influence obesity onset; leading to an estimated BMI difference of 2.7 points under the additive model in individuals having 38 or more higher risk variants compared with individuals having 21 or less (Speliotes et al., 2010). However, despite these new findings, genes discovered to date can only explain about

1.45% of the variance in weight (about 2%-4% of heritability) and *FTO* remains the gene with the largest effect size, explaining about 1% of the variance in BMI (Frayling et al., 2007).

However, novel methods of genome analysis, such as Genome-wide Complex Trait Analysis (GCTA), which estimates the proportion of phenotypic variance in a population explained by genome- or chromosome-wide SNPs (Yang et al., 2011) may improve heritability estimates, and studies are already beginning to emerge in this area. For example, Llewellyn and colleagues (2013) used GCTA to quantify the additive genetic effect of common obesity-related SNPs on BMI SDS scores using data from the Twins Early Development study (TEDS) and found that GCTA could explain about 30% of the variance in BMI SDS scores; substantially improving estimates attained with 'traditional' analysis methods.

1.4.1 Function of FTO

FTO's function (*Fto* when referred to in animals) is only beginning to be uncovered. Although gene expression occurs in many bodily tissues, including adipose tissue, *FTO* and *fto* expression rates are highest in brain, especially in the hypothalamus and adjacent nuclei associated with energy homeostasis and feeding behaviour (Gerken et al., 2007; Frayling et al., 2007; Olszewski et al., 2009).

FTO's structure and resemblance to homologues involved in nucleic acid repair or modification, and the preferential binding to single-stranded RNA over double-stranded DNA of the FTO protein, suggested early on that it may be concerned with nucleic acid demethylation (Jia et al. 2008). This assumption was supported by the

presence of FTO in the cell nucleus (Gerken et al., 2007). More recently, Jia and colleagues (2011) confirmed in in vitro experiments that the FTO protein is responsible for demethylation of N6-methyladenosine (m^6A) in RNA.

FTO expression rates also appear to be sensitive to environmental conditions. *Fto* expression was up-regulated following food deprivation, but no change in expression was observed when animals were fed a hyper-caloric diet over a period of time without prior food deprivation (Fredriksson, 2008); further suggesting a role in energy homeostasis. Therefore, attention has turned to investigating the effects of *FTO* on food intake, eating behaviour and energy expenditure to discover whether the association of *FTO* with BMI is mediated by these variables. The body of literature pertaining to animal studies is large, but because the current thesis is concerned with *FTO*'s effects in humans, and evidence from animal studies cannot be directly applied to humans, the current review is restricted to studies involving people. A table of all studies reviewed in the following section is included in Appendix 1.

1.4.2 FTO, food intake and dietary preferences

Fifteen studies investigated associations of *FTO* with energy or macronutrient intake, with only three studies focusing exclusively on energy intake without also investigating macronutrient content (Johnson et al., 2009; Wardle, Llewellyn, Sanderson, & Plomin, 2008; Dougkas, Yaqoob, Givens, Reynolds, & Minihane, 2013). Nine used population-based cohorts involving several thousand participants (Park et al., 2013; Brunkwall et al., 2013; Bauer et al., 2009; Holzapfel et al., 2010; McCaffery et al., 2012; Timpson et al., 2008; Sonestedt et al., 2009; Hasselbalch et al., 2010; Johnson et al., 2009). Consequently, these studies assessed food intake and food preferences using food

frequency questionnaires or diet diaries; in the latter, participants recorded food and drink intake over one, three or seven days. Only three studies measured food intake in experimental designs; these are described in detail below.

Cecil and colleagues (2008) measured *ad libitum* food intake 1.5 hours after ingesting a high energy (389kcals), low energy (187 kcals) or no energy (water) preload in a sample of 76 schoolchildren aged four to ten years. Foods offered at the test meal provided a selection of cold sweet and savoury items adding up to 1900 kcals. Foods were weighed before and after consumption, and energy content was determined using caloric values provided by the manufacturer. Children with at least one higher risk *FTO* allele ingested food with significantly higher energy density, but not higher weight, than children with the lower risk genotype after receiving the no energy and low energy preload, with a similar trend for the high energy preload. This effect remained significant after controlling for age and BMI.

Comparable results were obtained in a study by Wardle and colleagues (2008) who focused on the association of *FTO* and the phenotype known as 'eating in the absence of hunger' (EAH). In a home-based study, 131 children aged four to five years received a plate of highly palatable food (sweet and savoury biscuits) one hour after consuming a meal to satiety. Children were instructed to eat as much as they liked for the duration of 10 min and the amount eaten was determined by weighing the plate with the biscuits before and after task completion. Food intake was significantly higher in children carrying one or two *FTO* higher risk alleles than in children homozygous for the lower risk allele; following a linear trend. Results remained significant after adjusting for BMI.

However, a study by Dougkas and colleagues (2013) failed to show an association of *FTO* genotype and food intake in a sample of 40 overweight men (mean BMI: 27, SD = 2.0) who had consumed a dairy snack providing 201kcal (either semi-skimmed milk, a natural yoghurt, or cheese) or an isovolumetric amount of non-carbonated water (depending on treatment condition) 90 min prior to an *ad libitum* lunch. It is possible that individuals in this study were self-conscious and restrained their food intake because of stigma surrounding food intake in the overweight which was overriding any genetic tendencies to consume more food.

Studies from population-based cohorts provide mixed evidence for an association of *FTO* with energy intake. It was reported in the Avon Longitudinal Study of Parents and Children (ALSPAC), a cohort of 3641 children for which detailed three day parent completed dietary records were available (Timpson et al., 2008), and in a study with 150 adults aged between 21 and 64 years (54% overweight or obese) who completed detailed and verifiable (all food packaging was kept) seven day food records (Speakman, Rance, & Johnstone, 2008). However, in other studies it was not evident (Hasselbalch et al., 2010; McCaffery et al., 2012; Holzapfel et al., 2010; Bauer et al., 2009; Park et al., 2013; Brunkwall et al., 2013). It might be that the association of *FTO* with energy intake varies over the life course in accordance to its association with weight and BMI (Hardy et al., 2010), which is stronger in children since findings from these studies are largely in agreement. All but one paediatric study involving a sample of 1978 European and African-American adolescents (mean BMI: 22.8, SD not reported) using 24h diet recalls (Liu et al, 2010) reported an association of the higher risk *FTO* alleles with higher food intake. Alternatively, it is possible that under-

reporting and cognitive factors such as eating restraint are more prevalent in adult cohorts. Under-reporting of dietary intake has been well documented (e.g.Westerterp & Goris, 2002; Briefel, Sempos, McDowell, Chien, & Alaimo, 1997), particularly in the overweight or obese (e.g. Braam Ocké, Bueno-de-Mesquita, & Seidell, 1998; Johansson, Solvoll, Bjørneboe & Drevon, 1998), and may have had an influence in cohorts with a significant proportion of overweight and obese individuals. Several studies (but not all) investigated under-reporting and found that AA carriers were significantly more likely under-report total energy intake than TT carriers (e.g.Brunkwall et al., 2013; Sonestedt et al., 2009). Although these studies excluded the most severe cases of under-reporting, it may still have been widespread, albeit to a lesser extent.

However, population-based cohorts consistently report that individuals with AT or AA genotypes derive a greater percentage of their caloric intake from fat; irrespective whether subjects were adults or children (Sonestedt et al., 2009; Park et al., 2013; Timpson et al., 2008). Bearing in mind the limitations of self-reported dietary data, this finding is likely to be relatively robust.

1.4.2.1 *FTO and eating behaviour*

Nine studies have investigated the effects of *FTO* on aspects of eating behaviour other than energy-or macronutrient intake (Wardle et al., 2008; Ibba et al., 2013; Dougkas et al., 2013; Tanofsky-Kraff et al., 2009; Karra et al., 2013; den Hoed, Westerterp-Plantenga, Bouwman, Mariman, & Westerterp, 2009; Mueller et al., 2012; Jonassaint et al., 2011; Cornelis et al., 2013). Of those, five focused on responses to satiety sensitivity (Wardle et al., 2008; den Hoed et al., 2009; Ibba et al., 2013; Karra et al.,

2013; Dougkas et al., 2013) and four on aberrant eating behaviours such as loss of control over eating, emotional eating and cognitive restraint, either in general population samples (Tanofsky-Kraff et al., 2009; Cornelis et al., 2013) or in individuals with diagnosis of eating disorders (Mueller et al., 2012; Jonassaint et al., 2011). Five studies focused on children or adolescents (Jonassaint et al., 2011; Ibba et al., 2013; Wardle et al., 2008; Timpson et al., 2008; Tanofsky-Kraff et al., 2009; Mueller et al., 2012). In most studies, samples were from the general population and therefore of normal weight; two studies had overweight or obese samples (Dougkas et al., 2013; Ibba et al., 2013). Sample sizes ranged from 10 (Karra et al., 2013) to 3852 (Cornelis et al., 2013) participants and all studies were cross-sectional. Methods varied between studies, from self-reported or parent-reported food intake or eating behaviour to standardized laboratory test meal protocols.

1.4.2.2 *FTO and satiety sensitivity*

There is strong evidence that *FTO* influences satiety sensitivity. Wardle and colleagues (Wardle et al., 2008) genotyped 3337 children aged 8-11 years from the TEDS cohort for the *FTO* SNP rs9939609, and investigated associations of the higher risk A allele with the Child Eating Behaviour Questionnaire (CEBQ), a standardized, validated measure of appetite assessing satiety responsiveness and enjoyment of food (Wardle, Guthrie, Sanderson & Rapoport 2001). Weight and height were parent-reported and BMI SD scores were derived from the data. AA homozygotes had significantly reduced scores for satiety responsiveness, and this effect remained significant after adjusting for covariates including gender, family socioeconomic status (SES), and BMI SD score. However, reduced satiety sensitivity was not observed in children with the AT genotype; possibly owing to *FTO*'s small effect size. Mediation analysis indicated that

the association of *FTO* and BMI was in part mediated by satiety responsiveness, although this finding was only borderline significant (p = 0.05).

These findings were replicated in an experimental setting involving 103 adults (66 women and 41 men, mean age: 31 years, SD = 14 years) of predominantly borderline healthy weight (mean BMI 25.0, SD = 3.1; den Hoed et al., 2009). Participants were asked to rate hunger and satiety on visual analogue scales before and after consuming a fixed meal in the laboratory (providing macronutrients and calories according to individual needs) following an overnight fast. Individuals carrying at least one higher risk A allele were significantly more likely to be classified as 'high' in hunger and 'low' in satiety responsiveness after meal consumption, taking baseline values into account. The results remained unchanged after adjusting for age, gender and BMI.

Similarly, the randomised cross-over trial by Dougkas and colleagues (2013) described earlier also asked their sample of overweight men to rate hunger and satiety 90 min after consumption of preloads with varying energy density. Mean ratings in hunger were 23.9% higher (p =0.019) and satiety was reduced by 17.2% (p = 0.026) in participants who had at least one *FTO* A allele compared with those who had the TT genotype.

However, two studies failed to show and association of the higher risk A allele with reduced satiety responsiveness. Tanofsky-Kraff and colleagues (2009) did not detect any differences in satiety responsiveness by *FTO* genotype in a sample of 289 children and adolescents aged 6-19 years of predominantly normal weight (BMI_{TT}: 22.85, SD = 0.8; $BMI_{AT/AA}$ = 25.87, p = 0.002) after consuming an ad libitum lunch. Ibba and

colleagues (2013) used a sample of 412 obese (BMI SDS 2.7, SD = 1.43) Sardinian children and adolescents aged 4-20 years using the Satiety Responsiveness subscale of the CEBQ (Wardle et al., 2001). It is likely that the relatively homogenous sample (all were obese) did not show sufficient variation in satiety responsiveness to determine differences between genotypes. The wide age range that also included children going through puberty may have contributed to the findings, although stratifying the sample by age (0-6 n = 30, 7-11 n = 208, 12-15 n = 130, 16-19 n = 46) still did not show differences in satiety sensitivity between genotypes, but the sample sizes were small in each group.

In a very recent study, Lewellyn and colleagues (in press) created a polygenic risk score using 28 well-established obesity SNPs (including *FTO*), and investigated satiety responsiveness and adiposity in a sample of 2258 children (mean age: 9.9 years, SD = 0.84). A greater number of 'obesity genes' was significantly associated with lower satiety responsiveness and greater adiposity, further supporting the hypothesis that satiety responsiveness is a valid endophenotype for greater genetic susceptibility to obesity.

Recently, one research group provided evidence that secretion of hormones influencing hunger and satiety in response to a meal is altered in carriers with the AA genotype; providing a biological mechanism whereby *FTO* may decrease satiety sensitivity (Karra et al, 2013). The sample consisted of 359 males aged 18-35 of normal weight (BMI = 22.5, SD = 0.1). Ten AA and TT participants matched for age, BMI, fat mass, and visceral fat area (to avoid any confounding effects of these variables) were selected and received a standard test meal consisting of 1840 kcals

after an overnight fast and were given 20 min to consume it. Appetite was assessed using visual analogue scales before meal ingestion, 20 and 30 min post-meal and every 30 min thereafter until 180 min after meal termination; simultaneously, blood was drawn. AA homozygotes failed to suppress circulating levels of acetyl-ghrelin (the gut hormone responsible for sending 'hunger' signals to the brain) in response to the test meal, and levels remained elevated for the duration of the study period. Correspondingly, AA participants also reported significantly higher levels of hunger after meal termination and for the remainder of the study period than TT homozygotes. Furthermore, the authors showed that responses to food images differed between carriers of the lower-risk (TT) genotype vs. the higher-risk (AA) genotype using fMRI data from another group of 24 participants who were closely matched for age, gender and BMI. In contrast to TT carriers, AA carriers exhibited a reduced blood-oxygen-level dependent (BOLD) response to food images in the fasted state within brain areas related to food reward and goal-directed behaviour (hypothalamus, left ventral tegmental area/substanita nigra, left posterior insula, left globus pallidus, left thalamus, left hippocampus). Furthermore, the difference in BOLD response to high-calorie vs. low-calorie foods was reduced in AA carriers in the fed vs. fasted state; whereas TT carriers showed a greater BOLD response for low-calorie (vs. high-calorie) images in the fed (vs. fasted) state. These findings match emerging evidence from a series of in vivo studies by the authors which suggest that Fto regulates dopaminergic activity in the brain areas described above by altering Dopamine-2-Receptor (D2R) and Dopamine-3-Receptor (D3R) dependent signalling. However, it remains to be discovered how these findings link to its role of demethylation of N6-methyladenosine (m^6A) in RNA.

1.4.2.3 *FTO and eating disorders*

Evidence for the association of *FTO* with disordered eating is mixed. Tanoffsky-Kraff and colleagues (2009) discussed earlier also investigated self-reported loss of control over eating in their sample of 289 children and adolescents using the Eating Disorder Examination (EDE), a well-established self-report questionnaire (Luce & Crowther, 1999). A significantly higher number of children and adolescents with at least one higher risk *FTO* allele reported having had at least one loss of control eating episode in the month preceding assessment (34.7%, n = 66 vs. 18.2%, n = 18) compared with those with the lower risk genotype and this difference remained significant after adjusting for BMI z-score.

In a more recent study, Cornelis and colleagues (2013) reported on the association of *FTO* and 31 other obesity susceptibility loci with uncontrolled eating, emotional eating and eating restraint for each gene individually and for a combined genetic risk score. The sample consisted of 3852 individuals in their mid-sixties who were predominantly slightly overweight (mean BMI women: 25.9 kg/m^2, SD: 5.1; mean BMI men: 25.3 kg/m^2, SD = 3.1). Participants completed the Three Factor Eating Questionnaire (TEFQ), which is a self-report measure with excellent psychometric properties (Stunkard & Messick, 1985). *FTO* was significantly associated with all three aberrant eating behaviours, with each higher risk allele resulting in modestly increased scores (~0.12-0.33) on each TEFQ subscale. However, only the association with cognitive restraint remained significant after adjustment with BMI and none of the associations survived adjustments for multiple testing. This was also the case for associations of the genetic risk score with aberrant eating and for any of the other SNPs investigated.

Studies using clinical samples to determine the association of *FTO* and aberrant eating behaviours are also inconclusive. Jonassaint and colleagues (2011) did not find an association of *FTO* with anorexia nervosa (AN) comparing a sample of 1085 cases with 677controls, irrespective of subtype (AN with/without bingeing, AN with/without purging, AN with bingeing and purging); whereas Mueller and colleagues (2012) reported an association of *FTO* with bulimia nervosa (BN) in a case-control study including 477 participants with BN, 689 with AN, 984 non-population healthy controls and a population sample of 3951 control participants; although the association was only evident in comparison with the non-population-based sample of controls.

Taken together, it appears unlikely that *FTO* has a strong role in the onset of clinically significant disordered eating; although the transition from simple overeating to eating pathology may be fluid and *FTO* may make a minor contribution by influencing appetitive traits.

1.4.3 FTO and energy expenditure

Although there is no evidence for the association of *FTO* with energy expenditure in humans (e.g. Haupt et al., 2009; Berentzen et al., 2008; Speakman et al., 2008; Hakanen et al., 2009), evidence for the protective effects of physical activity (PA) in individuals carrying higher risk alleles is strong. A recent meta-analysis including 54 studies with a total sample of 218,166 adults and 19,268 children confirmed that the effect of *FTO* on BMI is attenuated by 27% in physically active individuals homozygous for the A allele (Kilpeläinen et al., 2010). The meta-analysis included 41 published and 13 unpublished studies. Included studies measured PA either using self-report or

pedometers. To account for these differences, PA was dichotomized into 'inactive' and 'active'. In studies using categorical outcomes, individuals reporting a sedentary occupation and less than one hour of light-to-moderate PA or commute per week were classified as 'inactive'; in studies reporting PA as continuous variable, participants in the bottom 20% of the sex-specific sample population were deemed 'inactive'. Pooled data analysis indicated that PA significantly attenuated the association of *FTO* with BMI, with the effect of the AA genotype being reduced by 30% in physically active adults. Samples were subsequently stratified by region, because of moderate study heterogeneity. Results indicated that the attenuating effect is stronger in North Americans than Europeans, with a 59% reduction of the association of *FTO* and BMI in North Americans, but only a 19% reduction in Europeans. Furthermore, waist circumference was significantly smaller and body fat was significantly reduced in physically active risk allele carriers (33% and 36%, respectively). However, differences between geographic regions were not significant for any of these variables. Level of physical activity also appeared to be irrelevant. In children, no significant associations with any of the outcome variables were observed.

In summary, studies conducted to date provide strong evidence that the higher risk alleles foster overconsumption in the current obesogenic environment by decreasing satiety sensitivity but are unlikely to be responsible for clinically relevant eating pathology. However, the effect can be attenuated by being physically active, perhaps because physical activity offsets excess energy consumed or because it improves satiety sensitivity. These findings are of clinical relevance because they provide scope for behavioural intervention. Furthermore, although *FTO* acts by affecting food intake,

results show that exercise is a vital component of any weight control program, particularly for individuals genetically predisposed to obesity.

1.5 Environmental influences in obesity development

Despite the strong evidence for genetic influences in obesity onset, sceptics often note that genes cannot be held accountable for the rapid rise in obesity levels, because the genome cannot have changed substantially in such a short time span. Furthermore, genes known to date can account only for a fraction of the estimated heritability in weight. Therefore, they conclude, causes for obesity must be rooted in the current environment (Gortmaker et al., 2011).

Undoubtedly, the profound technological progress over the past 30 years has created an environment that fosters overconsumption of food. Changes in farming practices and food production have reduced the 'time price for food consumption' and made highly palatable, energy-dense food widely and cheaply available. Unintentional, regular overconsumption ('passive overconsumption') is therefore easy and can add substantially to weight gain over time (Swinburn et al., 2011). Moreover, because lives have become increasingly sedentary, excess energy intake is less likely to be compensated for by physical exertion, tipping the balance further towards energy storage.

However, despite the pressures of this so-called obesogenic environment, not everybody exposed to it becomes overweight. In fact, the weight distribution curve is becoming increasingly skewed, indicating that overweight and obese individuals have

gained the most weight whereas numbers of lean individuals have not substantially changed (Foresight, 2007). This suggests that the obesogenic environment is detrimental predominantly for individuals who have a vulnerability to unhealthy weight gain. The *gene x environment interaction model* proposes that genes may predispose an individual to become overweight, but an environment that fosters their expression is needed, i.e. sufficient food availability *('Genes load the gun, environment pulls the trigger'* – Bray, 1998). Nature and nurture are thus not opponents in the obesity epidemic, but jointly drive obesity rates upward.

1.6 The importance of weight gain prevention

In their White Paper, 'Healthy Lives, Healthy People: Our Strategy of Public Health in England' (2010) the UK government made disease prevention *a priori*ty, because benefits on a population level are expected to be high: *'At a population level, it is not better treatment, but prevention – both primary and secondary, including tackling the wider social factors that influence health – which is likely to deliver greater overall increases in healthy life expectancy.'* (Department of Health, 2010).

Although obesity itself is not considered a disease in the UK and has only been recently classified as such in the US (which has been widely debated), the catalogue of associated chronic, and often severe, health conditions necessitates the reduction of its prevalence and is therefore included in the White Paper. However, although effective interventions for weight reduction exist (consisting of behavioural, pharmacological and surgical options), sustained weight loss even at the recommended level of 10% of body weight which has been associated with significant

health benefits, is difficult to achieve except with surgical methods (which have a very high success rate), and only a small proportion of individuals who initially lose weight succeed (Anderson, Konz, Frederich, & Wood, 2001). Physiological and metabolic changes in response to weight reduction persist long after weight loss and leave individuals vulnerable to weight regain and weight cycling (Sumithran et al., 2011; MacLean, Bergouignan, Cornier, & Jackman, 2011; Sumithran & Proietto, 2013; Reed, Chaput, Tremblay, & Doucet, 2013; Redman et al., 2009).

The high level of commitment required even among individuals who have achieved significant weight loss, to avoid weight regain is well documented in the National Weight Control Registry (NWCR). The NWCR consists of over 13,000 participants who have lost at least 13.6 kg (30 lb.) and kept it off for the minimum of one year; although the average time period since weight loss is 5.5 years. Comparison of successful and unsuccessful weight loss maintainers shows that successful weight maintainers are highly physically active (on average one hour of moderate to vigorous activity/day), consistently eat a low-calorie, low-fat diet (on average 1800 kcal/day with 24% of energy coming from fat), monitor their food intake closely, eat breakfast every day of the week, don't score high on dietary disinhibition (a measure of loss of control over eating), weigh themselves frequently (mostly daily), and correct small dietary 'slips' immediately using compensatory behaviours such as increased physical activity or further caloric restriction (Phelan, Wyatt, Hill, & Wing, 2006; Wing & Phelan, 2005). It can easily be seen why maintaining this level of behaviour change over the long-term just to prevent weight regain can be difficult.

Focusing attention on weight gain prevention appears to be the reasonable next step to stall obesity rates on a large scale for several reasons: First, obesity is commonly the result of a small, persistent energy imbalance in favour of excess energy of about 100kcal/day (Hill, 2003). Correcting this imbalance requires only small adjustments in energy intake or expenditure because the aim of weight gain prevention is to create equilibrium between energy intake and expenditure. Weight loss, in contrast, requires the creation of an energy deficit which can only be achieved through larger changes in energy intake and/or expenditure, which usually necessitate substantial behaviour change. Implementing and maintaining significant behaviour change is in itself a challenge, which requires considerable cognitive resources and skills in self-regulation such as self-monitoring and stimulus regulation (Mason & Butler, 2010). In contrast, implementing small changes to prevent weight gain should be less cognitively demanding and might thus be easier to sustain.

1.7 Risk of weight gain in young adults

Although it is sensible to assume that weight gain prevention efforts should begin as early as possible and continue throughout life, young adulthood constitutes a time where intervention might be particularly beneficial.

Whereas weight gain usually occurs gradually over a number of years (Hill, Wyatt, Reed, & Peters, 2003), some life stages have been associated with increased risk of rapid weight gain. One of these periods is the transition from late adolescence to adulthood. Evidence from epidemiological studies indicates that weight gain is most

pronounced between the ages of 18 and 35, with obesity onset usually occurring before the age of 30 (Gordon-Larsen, The, & Adair, 2010). Importantly, weight gained within this period is not lost over time, and thus leads to a significant increase in the proportion of young adults being classified as overweight or obese (Lewis, 2000). This is problematic because younger age of obesity onset is associated with more severe health outcomes for associated diseases, such as diabetes mellitus type 2 and cardiovascular disease, younger age of mortality, as well as less favourable social and economic status (Gortmaker, Must, Perrin, Sobol, & Dietz, 1993; Dietz, Gortmaker, Sobol, & Wehler, 1985; Ryan, 2009).

Moving out of home, going to university, starting work (which often leads to a more sedentary lifestyle), cohabitation, and pregnancy have all been identified as contributing to disproportionate weight gain during this period (Poobalan, Aucott, Precious, Crombie, & Smith, 2010). Perhaps the best studied phenomenon is the transition from school to university and the remainder of this review will focus on this contributor to weight gain because of the study population used for most of the studies in this PhD.

The transition from home to the university environment instigates a distinct life stage, associated with independence, yet without the major responsibilities of working adult life. Moving to a new environment and living independently allows for experimenting with different worldviews and lifestyles, developing and refining personality and self-identity (Nelson, Story, Larson, Neumark-Sztainer, & Lytle, 2008). The development of self-identity is crucial from a health promotion perspective, as self-efficacy and

identity have been important components in successful behaviour change and maintenance (Elfhag & Rossner, 2005).

Furthermore, as young adults are able to make the lifestyle choices they deem suitable, lasting lifestyle behaviours may be established within this period which may facilitate or hamper weight gain prevention. Therefore, the start of university offers a unique window of opportunity for weight gain prevention (Nelson et al., 2008).

Unfortunately, it appears that the college environment is not conducive to the formation and maintenance of health promoting behaviours. A substantial proportion of young adults gain disproportionate amounts of weight within the first three to four months of starting university (Mihalopoulos, Auinger, & Klein, 2008; Serlachius, Hamer, & Wardle, 2007). Anecdotally, it has been said that young people gain about 15lbs of weight after leaving for university (the so-called 'Freshman 15'), although this is probably an overestimate. The body of research has generally shown that actual weight gain is on average closer to 5 lbs (e.g. Holm-Denoma, Joiner, Vohs, & Heatherton, 2008; Anderson, Shapiro, & Lundgren, 2003).

Work carried out mainly in the United States (US) indicates that college life is marked by frequent consumption of fast-food (sometimes because no healthy options are available in the vicinity), late night eating, and heavy drinking. Furthermore, perceived work load limits the time for physical activity, which, alongside with stress, further contributes to weight gain (Lowry et al., 2000; Furia, Lee, Strother, & Huang, 2009; Nelson, Kocos, Lytle, & Perry, 2009). Environmental factors, such as lack of cooking

facilities and large distances to shops, lead students to keep considerable amounts of non-perishable food items in their dormitory rooms, which may lead to overeating.

Nelson & Story (2009) conducted an observational study and counted the food kept in dormitory rooms of 100 students at a large US university. Each existing item of food and beverage was classified into one of ten categories. Calorie and fat content was also recorded for each item that belonged to the student, as well as for shared foods and beverages. In addition, participants completed a survey about eating patterns. The authors found that 85% of students were on a campus meal plan. Nevertheless, number of food items and drinks kept in rooms ranged from zero to 208, with a mean of 47 items. This equalled an average calorie count of over 22,000 calories. As mentioned above, the specific setting of many US universities, which are campus universities, often in isolated areas, may contribute to students 'hoarding' food in their rooms. Therefore, these findings may not fully apply to Europe, where universities are commonly integrated within cities, and amenities are relatively easily accessible.

Studies examining weight gain in European students are rare. Serlachius and colleagues (2007) investigated the association of lifestyle changes and stress with weight change in 268 first-year university students at a British university. Health behaviours, weight, weight change and stress were self-reported. Over half of the sample (55%) reported weight gain, although 12% reported weight loss. Participants reporting weight change reported significantly more stress than those who remained at a stable weight. Students overall reported sleeping less, drinking more alcohol, exercising less, and eating fewer meals per day than in the last year of secondary school, although snacking frequency did not differ. This was consistent among all

groups. Mean reported weight gain was 1.53 kg, which is less than observed in the US. This difference may be because of differences in culture and university environment; alternatively it may be possible that selection bias contributed to the findings as the survey was voluntarily. However, these findings show that trends for weight gain in European university students may be in the same direction, even if not as pronounced.

1.7.1 Weight gain prevention interventions in young adults

In comparison with the literature on weight loss, weight gain prevention interventions occupy only a small niche in obesity research to date, with 858 entries in Pubmed as of August 2013 (compared with 6086 entries when searching for 'weight loss interventions').

Preventive interventions often use equivalent methods to those aimed at weight loss; namely improving dietary quality, increasing physical activity, and teaching behavioural skills such as self-regulation and goal setting to enable individuals to implement and maintain behavioural changes. Two recent reviews have assessed the efficacy of weight gain prevention interventions in young adults (Hebden, Chey, & Allman-Farinelli, 2012; Laska, Pelletier, Larson, & Story, 2012). Hebden and colleagues (2012) conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) for weight gain prevention. In addition to being RCTs, studies had to be published between 1980 and August 2011, and explicitly focus on young adults aged 18 to 35, who were free of chronic diseases (e.g. eating disorders, obesity-related diseases), studies should not be primarily concerned with weight loss or designed exclusively for the obese, and should focus on 'lifestyle' changes (rather than medication adherence) and should use mean weight change as outcome variable.

Databases searched included PubMed, MEDLINE, PsychINFO, ERIC, CINHAL, the Cochrane Library, Embase, Science Direct, Web of Science, Scopus and several others using a variety of keywords referring to the study population, intervention and outcomes. Of the nine studies identified, only eight were included in the meta-analysis, because one study (Matvienko, Lewis, & Schafer, 2001) did not report the precise mean change in body weight over the intervention period.

Laska and colleagues (2012) had identical exclusion criteria, but did not restrict their search to RCTs and also accepted studies who used measures other than weight/BMI change as primary outcome variables (although their paper discusses only studies in detail which included weight/BMI change). Their review was limited to studies conducted in the US or Canada that were published between 1985 and July 2011. Databases searched included PubMed, MEDLINE, PsychINFO, ERIC and CINHAL, using a variety of keywords referring to the study population, intervention and outcomes described above. In addition to the nine studies identified by Hebden et al (2012), Laska et al (2012) identified 28 further interventions which did not include weight/BMI change as outcome variables but focused on improvements in nutrition knowledge, physical activity and mastery of behavioural skills to prevent weight gain. The present review discusses findings from these 37 studies (43 publications) below.

Similar to interventions aimed at other age groups, studies with young adults focused on improving dietary quality, increasing physical activity and teaching skills to limit food intake above caloric need or a combination of those. With the exception of three studies which used convenience samples of young adults from the general population (Gokee LaRose, Tate, Gorin, & Wing, 2010; Klem, Viteri, & Wing, 2000; Kirk et al.,

2009) or from a group with one overweight parent (Eiben et al. 2006), all were conducted in a university/college setting and were designed for students.

1.7.1.1 *Dietary interventions*

Sixteen studies (discussed in 19 publications) attempted to exclusively improve dietary quality in young adults (Peterson, Duncan, Null, Roth, & Gill, 2010; Matvienko et al., 2001; Finckenor & Byrd-Bredbenner, 2000; Ha & Caine-Bish, 2009; Ha, Caine-Bish, Holloman, & Lowry-Gordon, 2009; Ha & Caine-Bish, 2011a; Chu, Frongillo, Jones, & Kaye, 2009a; Skinner, 1991; Shive & Morris, 2006; Brinberg, Axelson, & Price, 2000; Davis-Chervin, Rogers, & Clark, 1985; Freedman & Connors, 2011; Hekler, Gardner, & Robinson, 2010; Levy & Auld, 2004a; Clifford, Anderson, Auld, & Champ, 2009; Richards, Kattelmann, & Ren, 2006; Nitzke et al., 2007; Park et al., 2008; Poddar, Hosig, Anderson, Nickols-Richardson, & Duncan, 2010). Although only one study included weight change as outcome variable (Matvienko et al., 2001), and one assessed weight only at baseline but not follow-up (Ha et al., 2009), the framing of the papers often alluded to the assumption that better dietary quality would lead to avoidance of unhealthy weight gain and overweight in the long-term. Furthermore, studies targeted areas related to weight gain prevention such as knowledge about healthy food and eating, information about benefits of healthy eating and cooking skills.

Twelve interventions were designed to improve overall diet quality and seven sought to improve intake of one specific food group or dietary component. Of these interventions, most targeted fruit or vegetable intake (Ha & Caine-Bish, 2009; Richards et al., 2006; Nitzke et al., 2007; Park et al., 2008), two focused on dairy foods (Poddar

et al., 2010; Ha et al., 2009), one on fibre (Brinberg et al., 2000), one on whole grains (Ha & Caine-Bish, 2011b) and, one on fat (Finckenor & Byrd-Bredbenner, 2000).

Methods used varied, including distributing pamphlets and leaflets with information and tips about healthy eating around campus or sending them to students by email (Richards et al., 2006; Nitzke et al., 2007; Park et al., 2008), giving out free fruit and vegetables (Shive & Morris, 2006), providing cooking classes (Levy & Auld, 2004b), watching a cooking TV show (Clifford et al., 2009), providing calorie information for dishes sold at food outlets around campus (Chu et al., 2009a; Peterson et al., 2010; Davis-Chervin et al., 1985), and introducing a label that signified which foods were 'healthy'(Freedman & Connors, 2011). However, most interventions were nutrition courses, taught either face-to-face (Matvienko et al., 2001; Hekler et al., 2010; Finckenor & Byrd-Bredbenner, 2000; Skinner, 1991; Ha & Caine-Bish, 2009; Ha et al., 2009; Ha & Caine-Bish, 2011b) or online (Poddar et al., 2010)for which students received course credit.

Study duration ranged from four weeks (Park et al., 2008) to 16 months (Matvienko et al., 2001), with an average duration of 5 months (median: 4 months). Only two studies included one-year follow-up (Finckenor & Byrd-Bredbenner, 2000; Nitzke et al., 2007) and two further studies ran for more than one year (Matvienko et al., 2001; Evans & Sawyer-Morse, 2002)

The total combined sample size of all studies was 5505 participants. Sample sizes ranged from 65 (Levy & Auld, 2004a) to 2024 (Nitzke et al., 2007), with a mean sample size of 348 individuals; although four studies failed to report exact sample sizes

(Freedman & Connors, 2011; Brinberg et al., 2000; Davis-Chervin et al., 1985; Chu, Frongillo, Jones, & Kaye, 2009b). Attrition rates were often not reported; where they were reported, retention rate was over 80%. Only eight out of the 17 studies were trials, and of those, two did not use random group allocation (Finckenor & Byrd-Bredbenner, 2000; Hekler et al., 2010). Trials usually had two arms (intervention vs. control); only one study had three arms (Finckenor & Byrd-Bredbenner, 2000)

Results from these studies were mixed with some finding improvements in students' dietary intake and others being less successful. The one study including weight gain as outcome variable (Matvienko et al., 2001) found no change in BMI; although students with higher BMI in the intervention group made more beneficial changes than those with higher BMI in the control group and maintained these for at least one year. Because of the diversity in study designs and reliance on self-report for all outcomes, it is difficult to discern 'active' ingredients of interventions. Furthermore, the small number of studies that ran for more than one semester limits conclusions about efficacy regarding long-term dietary changes.

1.7.1.2 *Exercise interventions*

Twelve interventions (reported in 13 publications) focused exclusively on improving physical activity to achieve weight gain prevention (Cardinal, Jacques, & Levy, 2002; Sallis et al., 1999; Donnelly et al., 2003; DeVahl, King, & Williamson, 2005; Cholewa & Irwin, 2008; Boyle, Mattern, Lassiter, & Ritzler, 2011; Claxton & Wells, 2009; Jung & Heald, 2009; Parrott, Tennant, Olejnik, & Poudevigne, 2008; Ornes & Ransdell, 2007; Calfas et al., 2000; Jackson & Howton, 2008; Kirk et al., 2009); although only five assessed changes in weight, BMI or per cent body fat (Cholewa & Irwin, 2008; Kirk et

al., 2009; DeVahl et al., 2005; Donnelly et al., 2003; Boyle et al., 2011). Studies that did not report anthropometric changes most commonly assessed changes in levels of physical activity (8/13), either using self-report (4/8), pedometers (2/8) or using proxy measures such as resting energy expenditure (1/8); one study reported on changes in intentions to exercise as assessed by self-report (Jung & Heald, 2009).

Exercise was prescribed and carried out in the research setting in three studies and self-directed, with weekly goal recording in six studies. Type, frequency and intensity of physical activity were often not specified. In the four studies where it was reported, walking (no. of steps) or running were the most frequently mentioned activities, and one study specifically focused on resistance training.

Study duration varied across studies from two weeks (Parrott et al., 2008) to 18 months (Sallis et al., 1999), with only two studies running for more than 1 year (Donnelly et al., 2003; Sallis et al., 1999). Mean duration of interventions was 21 weeks (median: 12 weeks). Main outcomes were usually assessed at the end of the intervention period; although one study reported follow-up results at three weeks (Parrott et al., 2008), and another at 2 years (Calfas et al., 2000).

The combined total sample size of all studies was 2344. Individual sample sizes ranged from 39 (Kirk et al., 2009) to 540 participants (Cardinal et al., 2002), with a mean sample size of 195 participants. Studies usually randomly assigned participants to one of two arms (intervention or control); only one study had three arms and in this study participants could choose which group they wanted to be assigned to (Cholewa &

Irwin, 2008). Levels of non-attendance or attrition was frequently not reported (8/13 studies); and where it was mentioned, around 50% of participants were retained.

Overall, the efficacy of these interventions was mixed; eight studies were successful in increasing exercise intentions, or levels of physical activity. Anthropometric markers improved in four studies in at least some of the intervention participants. Limited information about the interventions in the majority of studies discussed here makes it difficult to assess whether any specific features may have contributed to the varied outcomes.

1.7.1.3 *Behavioural skills*

One publication reported on two studies which focused exclusively on self-monitoring in the form of daily weighing to prevent weight gain (Levitsky, Garay, Nausbaum, Neighbors, & DellaValle, 2006). In the first study, 32 female freshmen were randomly assigned to intervention or control groups after weights were recorded by the researchers. The intervention group emailed self-recorded weights (taken in the morning immediately after rising) daily to the research team. After the first seven days which were used to calculate a regression line of their weight change, they received daily reports about the slope of weight change for 10 weeks. In the second trial, intervention participants (n = 16) also reported self-recorded daily weights, but received feedback on caloric modification required to maintain weight after the first seven days which were used to calculate average weight for 10 weeks. Results from both studies were positive, showing no significant weight gain in intervention groups over the intervention period (0.1 kg ± 0.99 kg and -0.82 ± 0.56 kg) compared with controls who gained 3.1 kg ± 0.51 kg and 2.0 ± 0.65 kg, $p < 0.01$, respectively.

1.7.1.4 *Combined interventions*

Nine studies were designed to include a combination of dietary, exercise and behavioural components (Gokee-LaRose, Tate, Gorin, & Wing, 2010; Stice, Orjada, & Tristan, 2006; Gow, Trace, & Mazzeo, 2010; Klem, Viteri, & Wing, 2000; Eiben & Lissner, 2005; Hivert, Langlois, Berard, Cuerrier, & Carpentier, 2007; Boyle, Mattern, Lassiter, & Ritzler, 2011; Werch et al., 2008; Leermakers, Jakicic, Viteri, & Wing, 1998). All these interventions were delivered as structured programmes, comprised of lectures, seminars and small group discussions. One study (Gow et al, 2010) also included online materials that participants were asked to complete in their own time, sometimes for course credit (2/8 studies).

All studies used BMI/weight change as main outcome; self-reported in seven studies (Gokee-LaRose et al., 2010; Hivert et al., 2007; Eiben & Lissner, 2005; Gow et al., 2010; Hebden, Chey, & Allman-Farinelli, 2012; Leermakers et al., 1998) and measured by a researcher in two studies (Stice et al., 2006; Klem et al., 2000). Only one study (Gokee-LaRose et al., 2010) compared two different intervention approaches without a 'no-treatment' control group; all others included a 'wait-list control' group.

Course content was similar in all interventions; although the focus varied slightly: Gokee-LaRose et al (2010) included lessons on nutrition and dietary change. Gow et al(2010), Hivert et al (2007), Klem et al(2000) and Stice et al (2006) included information about causes and prevalence of obesity, the physiology of obesity, healthy eating and physical activity, and techniques required to maintain energy balance. Werch et al (2007) focused on the importance of goal setting in weight maintenance

(although this component was also covered in the other studies) and also included seminars on other behaviours (alcohol intake, smoking) into their programme. Eiben et al (2005) adjusted information based on individual needs, and Leermarkers et al (1998) included prescribed exercise sessions at the end of each weekly group meeting.

With the exception of three studies (Leermarkers et al., 1998; Klem et al., 2000; Gow, et al., 2010), in which one intervention arm was assigned to completing the programme entirely online after initial personal consultation, all interventions were delivered face-to-face.

Study duration varied considerably among studies from six weeks (Gow et al., 2010) to two years (Hivert et al., 2007) with a mean duration of 14 weeks (median: 12 weeks). Reported main outcomes were usually taken immediately after the end of the intervention period; although three studies also included follow-up data at six and 12 months.

Most commonly, studies had two or three intervention arms. In all interventions, sample sizes were small to medium, ranging from 40 to170 participants, with a mean of 91 participants. Levels of non-attendance and attrition varied, with most studies retaining 81% of initial participants. Study duration did not appear to influence attrition because the study with the two-year follow-up retained participants at a comparable level to studies with shorter duration (83% completed the two-year FU).

Efficacy of these studies was high. All studies reported small but significant weight loss or weight stability (~ - 0.83kg to -1.3 kg) in intervention groups in comparison with

control groups at the end of the intervention period. This difference was maintained in at six month follow-up in studies which included this time point. Although results have to be viewed with caution because of study heterogeneity and small effect sizes, if weight differences were maintained over the long-term, it would lower the risk of obesity and its associated conditions substantially. However, study durations were usually too short to make any predictions about long-term efficacy; the one study who included a two-year follow-up did not find any lasting effects of the intervention.

Taken together, the results from all studies included in the meta-analysis of RCTs by Hebden et al (2012) show comparable outcomes, with small positive effects for weight gain prevention or weight loss. Small sample sizes in some trials and short-follow-up periods limit the generalizability of the findings, especially with regard to long-term efficacy. However, these results demonstrate that complex interventions targeting multiple components are more successful at preventing weight gain than those focusing only on improving a single outcome.

1.7.1.5 *Evaluation of studies aimed at weight gain prevention in young adults*

The high level of intensity employed in the interventions discussed above, regardless of specific focus, is striking. Considering that most individuals in these studies are normal weight or only slightly overweight, one would expect that the processes required for energy balance should function reasonably well or that individuals already possess behavioural skills required to maintain energy balance. Efforts needed to maintain weight might therefore be expected to be modest. However, no study has investigated the efficacy of a low-impact intervention on the prevention of weight gain among students and therefore, evidence for this hypothesis is lacking. Although a

number of studies were successful in preventing weight gain, with the exception of the online studies, intervention format and delivery limit the applicability and cost-effectiveness on a large scale. Furthermore, these studies required a high level of commitment from students, which makes it likely that only highly motivated individuals participated which is evident in the high retention rates. However, students who are less concerned about weight gain may also be at risk, but those might be unlikely to take part in an intervention that requires high levels of commitment. Therefore, a low-intensity, low-cost intervention that could easily be applied to a large number of students might be a more feasible option to try to engage students with weight gain prevention.

1.8 Chapter Summary

In summary, this chapter discussed that genetic and environmental influences act in concert to drive obesity levels upwards. The physiological adaptations that are occurring in the overweight/obese state make long-term weight loss difficult to achieve. Therefore, weight gain prevention should be *a priori*ty. Young adults are especially vulnerable to unhealthy weight gain because many of the life stages associated with higher risk of disproportionate weight gain occur during young adulthood. Weight gain prevention interventions for this age group have focused predominantly on college students, with mixed success. Although the most intense interventions usually demonstrate efficacy, their labour intensity and high participation burden limits their applicability for the student population at large. Developing a personalized, low-intensity intervention to raise awareness about risk of unhealthy weight gain may be one way to engage less motivated students with weight gain prevention.

Chapter 2: Could genetic test feedback be a novel way to stimulate behaviour change?

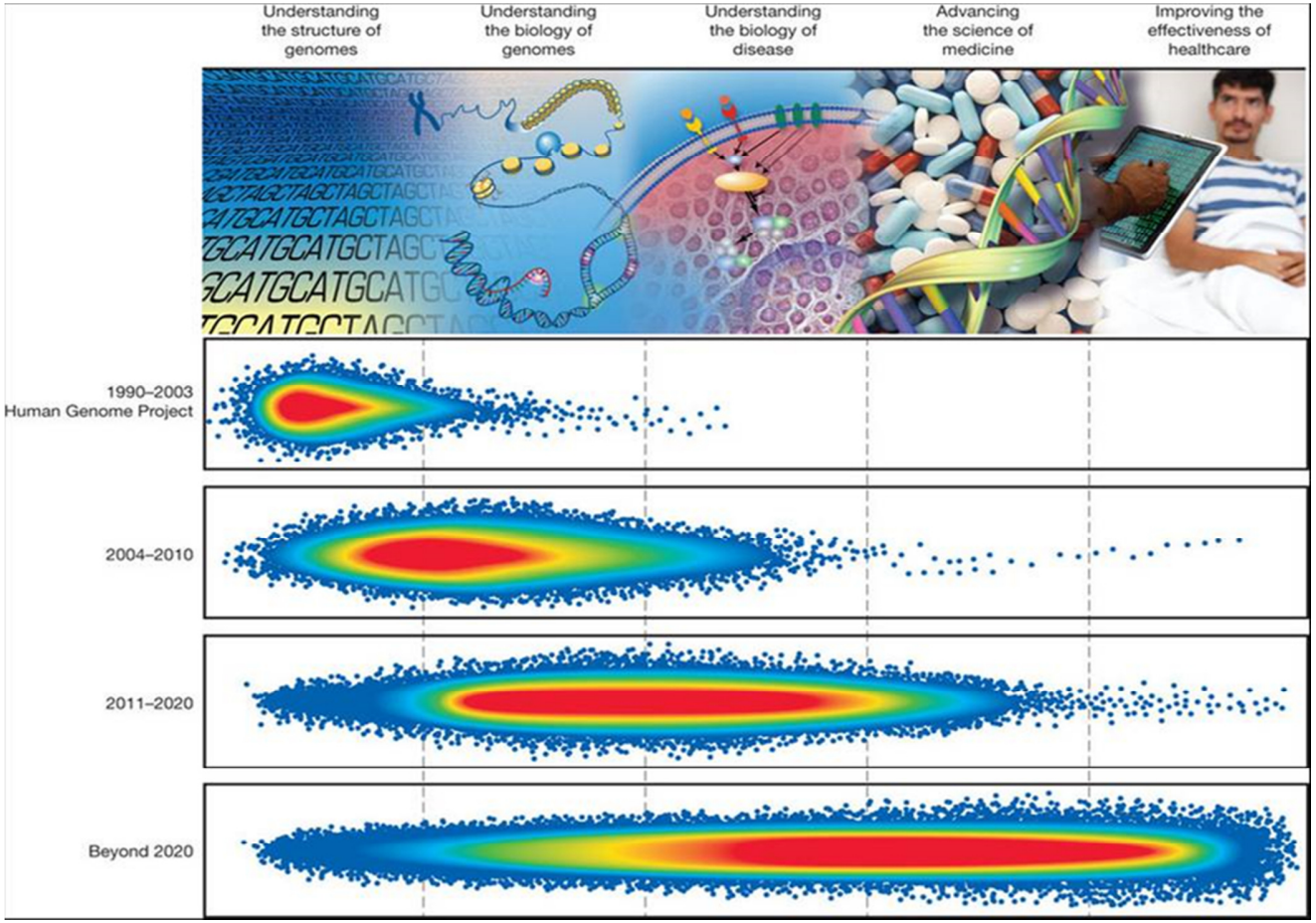
Completion of the sequencing of the Human Genome a decade ago constituted a major achievement in scientific discovery. Subsequent technological advances have led to increasingly reliable information about alleles implicated in disease development for a reasonable cost. Genetic discoveries made since have caused paradigm shifts in the understanding of health, pathogenesis, disease classification, and treatment approaches. To date, tests for nearly 2300 genetic conditions exist, 2028 of which are already available in clinical practice (NCBI, 2011).

However, despite the multitude of novel findings and enormously improved technology, it has become clear in recent years that the 'genomic hype' left many promises unfulfilled, at least in the short-term (Evans et al., 2011). This is partly because the emerging picture of the genetic basis of disease is far more complicated than expected. Only about 2% of diseases follow clear Mendelian inheritance patterns; the remainder are caused by a complex array of *gene x gene* and *gene x environment* interactions, as well as epigenetic changes in DNA (Fraser, 2009). Therefore, translation of research findings from genomic studies into the clinic is still in its infancy.

Even with the greatest efforts, translation of new discoveries from 'bench to bedside' usually takes several decades, with benefits and costs becoming visible only after a certain period of time. Figure 2.1 schematically displays past and expected achievements in genomic research, with different colours representing the density of discoveries in each area. Harnessing the full potential that genomic medicine has to offer is not expected to occur for at least another decade.

Nonetheless, the field is under enormous pressure because of the high expectations placed on it. The persistent media attention, presumably resulting from the 'sensed' potential that genomic medicine may hold for health, is evidence for this. Funding bodies are keen to see this perceived potential turning into reality, which places demands onto those working in the discipline to (perhaps sometimes prematurely) translate findings into clinical applications. This led to a situation where the 'genomic bubble' is perpetuated by the speed technology moves forward whereas the broader infrastructure as well as the evidence base for its effects lags behind (Evans, Meslin, Marteau, & Caulfield, 2011; Burke et al., 2010).

Figure 2.1. Schematic representation of accomplishments across five domains of genomic research



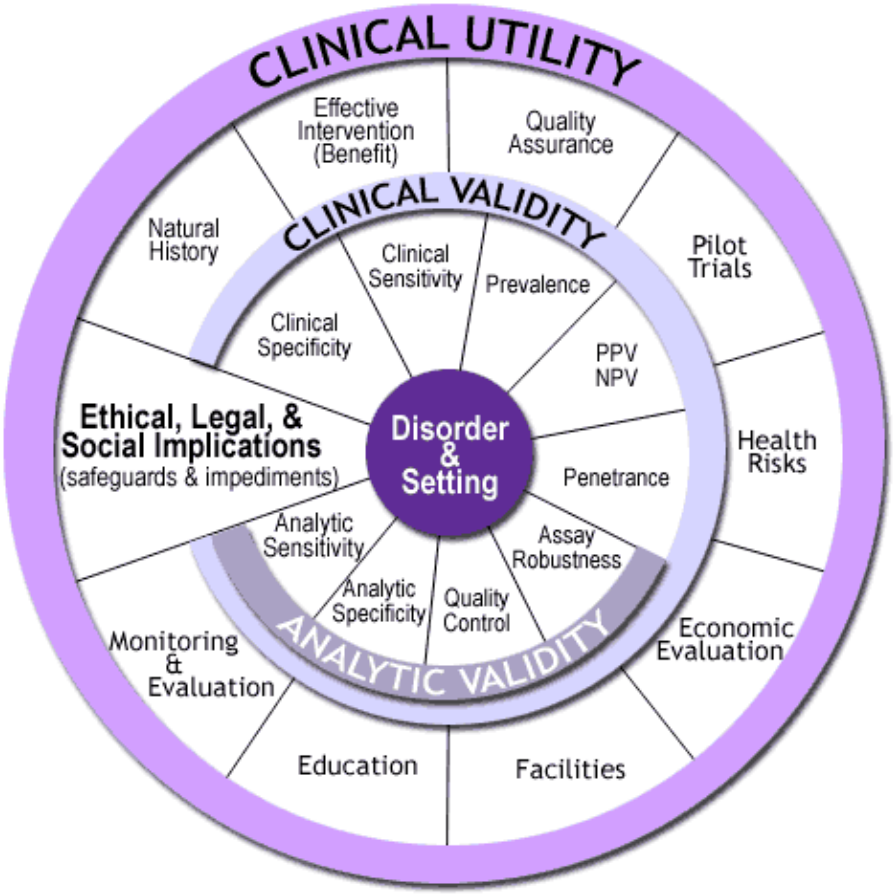
E D. Green *et al*. *Nature* **470**, 204-213 (2011) doi:10.1038/nature09764

2.1 Practical considerations and challenges

Before predictive genetic testing can be implemented on a large scale, multiple challenges need to be overcome. One important consideration is whether the quality of individual genetic tests[2] is sufficient to be used in clinical practice. The US Centre for Disease Control and Prevention developed a framework to address this question, called the ACCE model (Haddow & Palomaki, 2004). The acronym stands for analytic validity (including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)), clinical validity (incorporating scientific validity and clinical test performance), clinical utility (assessing whether the test improves health outcomes) and the ethical, legal and social implications (ELSI). Currently, genetic tests for complex conditions face challenges in all but the first of these domains. The model is shown in Figure 2.2.

[2] genetic test in this context refers to a test to detect (1) a particular genetic variant (or set of variants), (2) for a particular disease, (3) in a particular population and (4) for a particular purpose, Zimmern et al. 2007

Figure 2.2 ACCE framework for evaluation of genetic tests



Retrieved from: http://www.cdc.gov/genomics/gtesting/ACCE/

2.1.1 Challenge: Improving clinical validity

Probably the biggest challenge to date is improving clinical validity. Currently, the predictive value of genes implicated in common complex conditions is low because the effect sizes of most identified individual gene variants are small and penetrance[3] does not usually exceed 5% (Holtzman & Marteau, 2000). Furthermore, despite high

[3] Penetrance refers to the likelihood that the disease is expressed. If a disease has 5% penetrance it means that in 5% of the pop the gene will be active and thus the trait/disease will be expressed. In conditions with < 5% penetrance it is difficult to distinguish environmental and genetic effects.

heritability estimates, even in combination, genes known to date can only explain a fraction of common phenotypes such as weight or height. The gap between known heritability estimates and the contribution from known genetic variants to a trait is known as '*missing heritability*' (Manolio et al., 2009). It is likely that multiple genes of small effect, combined with *gene x gene* and *gene x environment* interactions as well as epigenetic effects account some of the discrepancy between heritability and variance explained by known genes.

The evolutionary advantage is self-evident: Having many genes of small effect for a certain trait results in less damage if errors in transcription and translation occur than if few genes were responsible for it because these genes would be more likely to be selected against in the course of evolution. Furthermore, existence of mechanisms to respond to environmental changes on a molecular level (epigenetic effects) yields greater flexibility and adaptive capacity of the organism (Manolio et al., 2009).

The importance of these additional factors for genetic risk prediction becomes clear when studying causes of mortality of monozygotic twins. Despite being identical genetic copies of one another, they usually do not die from the same disease; although they are far more likely to do so than two unrelated individuals (Roberts et al., 2012). This example highlights the fact that risk prediction based solely on underlying genetics is inherently limited. However, it has also been debated whether better understanding of genetic interactions could really improve risk prediction, or whether 'random' factors that cannot be accounted for, such as unique combinations of environmental exposure, would always constrain predictive value (Janssens & van

Duijn, 2008). Although there may be some conditions for which this may be the case, it is difficult to foresee outcomes for all complex conditions.

2.1.2 Challenge: Establishing clinical utility

The issue of uncertain clinical validity of genetic test feedback is entwined with that of clinical utility. Clinical utility, in this context, refers to the successful application of genetic test feedback in clinical practice to improve health outcomes. One problem is to define what this constitutes because 'health outcomes' may vary and can be difficult to quantify, especially with respect to psychological variables (Haga, Khoury, & Burke, 2003). Moreover, because clinical validity is suboptimal at present, it is unlikely that the test can meaningfully distinguish between those who require intervention and those who do not, as others who are cautious of using genetic test feedback for complex conditions to stimulate behaviour change have repeatedly pointed out: *'If all would benefit from a healthy diet, exercise, smoking cessation or prudent alcohol intake, regardless of genotype, the added value of the test is unclear unless it can be shown to motivate compliance in those who test positive without reducing compliance in those who test negative.' (Haga et al., 2003)*

Because the evidence base for the premise that predictive genetic testing for complex conditions would lead to health benefits is thin at present, research efforts need to focus on establishing clinical validity using a variety of measures and rigorous methodology to which this PhD aims to contribute.

2.1.3 Challenge: Ensuring privacy and management of incidental findings

The inherent individuality of genome sequences (except in the case of monozygotic twins) raises issues of anonymity in clinical and research contexts (Javitt, 2006). Concerns about discrimination based on genetic risk by insurance or employers led to the development of laws to protect individuals even before the genome was fully sequenced; although it was not fully implemented until 2008. Since then, the Genetic Information and Nondiscrimination Act (GINA) is in place in the US, which prohibits insurers to charge higher premiums and employers to discriminate against individuals based on genetic risk alone (http://www.govtrack.us/congress/bills/110/hr493/text)

However, genetic testing not only concerns the individual but also allows inferences about family members. This can pose problems when one family member seeks genetic testing and issues within the family influence sharing of their genetic test result (Corpas, 2012; Forrest, Delatycki, Curnow, Skene, & Aitken, 2010; Forrest et al., 2003). The question remains whether there is a 'duty to warn' family members of potential risks, possibly even at the expense of patient confidentiality, and, if there is, who should be informing them: Their General Practitioner (GP), family member, genetic specialist (Offit, 2004). Furthermore, relatives may not wish to know of their genetic risk status (exert the right not to know) which may cause conflict within the family and distress for relatives who sought testing because they may feel a responsibility to persuade others to seek testing (D'Agincourt-Canning, 2001; Foster, Eeles, Ardern-Jones, Moynihan, & Watson, 2004). However, because research to date has focused on families affected by severe conditions such as Huntington's disease and

hereditary cancer syndromes, effects on more common, complex conditions may be less pronounced.

A further difficulty is that genes rarely code only for a single trait and may be detrimental in combination with certain genes but protective when paired with others (Williams, 2001). Therefore, it is highly likely that genetic feedback for one condition will simultaneously reveal risk status for another (for example Apolipoprotein E (APOE) is implicated heart disease and Alzheimer's disease (Wilson, Schaefer, Larson, & Ordovas, 1996). This means that information about risk for conditions may become available for which the individual has not sought testing. Once again, the issue of duty of care to inform individuals about these 'incidental findings' must be resolved before genetic testing can become widely available in clinical practice, especially considering the prospective introduction of whole-genome sequencing where these issues will become commonplace (Berg, Khoury, & Evans, 2011; Tabor, Berkman, Hull, & Bamshad, 2011).

Recently, the American College of Medical Genetics (ACMG) released recommendations on how to best manage incidental findings for whole-genome sequencing (Table 2.1, Green et al., 2013), including conditions for which return of results should be mandatory. The European Society of Human Genetics followed up with similar, if slightly more conservative recommendations focusing on informed consent (Ayuso, Millan, Mancheno, & Dal-Re, 2013). However, it is difficult to predict at this point which issues will become most pressing once genetic testing is introduced on a large scale, so that these recommendations have to be viewed as flexible.

Table 2.1 ACMG recommendations on the return of incidental findings (Green et al, 2013)

1.	Constitutional mutations found in the genes on the minimum list should be reported by the laboratory to the ordering clinician, regardless of the indication for which the clinical sequencing was ordered.
•	Additional genes may be analyzed for incidental variants, as deemed appropriate by the laboratory.
•	Incidental variants should be reported regardless of the age of the patient.
•	Incidental variants should be reported for any clinical sequencing conducted on a constitutional (but not tumor) tissue. This includes the normal sample of a tumor-normal sequenced dyad and unaffected members of a family trio.
2.	The Working Group recommends that laboratories seek and report only the types of variants within these genes that we have delineated
•	For most genes, only variants that have been previously reported and are a recognized cause of the disorder or variants that are previously unreported but are of the type that is expected to cause the disorder, as defined by prior ACMG guidelines,[20] should be reported.
•	For some genes, predicted loss-of-function variants are not relevant (e.g., *COL3A1* and most hypertrophic cardiomyopathy genes).
•	For some genes (e.g., *APOB*), laboratories should only report variants for certain associated conditions.
3.	It is the responsibility of the ordering clinician/team to provide comprehensive pre- and posttest counseling to the patient.
•	Clinicians should be familiar with the basic attributes and limitations of clinical sequencing.
•	Clinicians should alert patients to the possibility that clinical sequencing may generate incidental findings that could require further evaluation.
•	Given the complexity of genomic information, the clinical geneticist should be consulted at the appropriate time, which may include ordering, interpreting, and communicating genomic testing.
4.	These recommendations reflect limitations of current technology and are therefore focused on disorders that are caused by point mutations and small insertions and deletions, not those primarily caused by structural variants, repeat expansions, or copy-number variations.
5.	The Working Group recommends that the ACMG, together with content experts and other professional organizations, refine and update this list at least annually.

2.2 The Promise

2.2.1 Health maintenance and early intervention

The vision of genomic medicine is not only to individualize medical treatment, but also to reduce risk and prevent illness by making personal recommendations for screening adherence, and lifestyle modifications based on the individual's genetic profile (Haga et al., 2006).

Genetic test feedback was hypothesised to motivate the initiation and maintenance behaviour change by providing the ultimate personalized message for several reasons. One was that assumptions about the beneficial impact of genetic testing are rooted in its historical use (mainly for reproductive decision making) in family groups afflicted by conditions with an underlying genetic contribution (Wright, 2011). In the case of chromosomal disorders with Mendelian inheritance patterns or genetic disorders with high penetrance, risk for illness can be predicted with high accuracy. Therefore, it has been assumed by many writers that knowledge of the full genomic sequence would reveal underlying genetic effects of similar magnitude in common conditions. Furthermore, it was thought that insights into genetic disease associations would be rapidly followed by translations into novel approaches to prevention and treatment (Khoury & Wegner, 1995, Collins, 1999).

Thirdly, individuals are usually optimistically biased with respect to their disease susceptibility and commonly perceive themselves to be less likely to fall ill than others; increasing risk of engaging in health-compromising behaviour (Weinstein, 1980).

Providing evidence for their 'true' susceptibility in the form of genetic test feedback was thought to serve as a 'wake-up call' to initiate health protecting actions before problems arise.

Lastly, there is also substantial evidence that 'tailoring' a message to the audience will improve outcomes, because it increases personal relevance and therefore salience (Petty & Cacioppo, 1981). Noar, Benac & Harris (2007) conducted a systematic review and meta-analysis of 57 studies on the effects of tailored print behaviour change interventions. Studies were included if they were randomised or non-randomised trials comparing effects of tailored print behaviour change interventions (as opposed to web-based or telephone interventions) with a 'non-tailored' or 'less tailored' condition. Health behaviour change was the main outcome variable. All included studies were published between 1989 and 2005. The total sample size in the meta-analysis was 58,454 participants (median N = 535 per study) of predominantly Caucasian origin and a mean age of 45 years. Behaviour change interventions focused on dietary change, improving physical activity, improving cancer screening behaviour, smoking cessation, vaccination behaviour and condom use, with durations from one week to 18 months. The results showed that tailored messages were modestly but significantly more successful in changing behaviour than non-tailored messages (Effect Size = 0.047); although there was considerable heterogeneity among studies. Further analysis revealed that interventions with the largest effect sizes were those that focused on preventive and screening behaviours (e.g. pap-smear), that generated newsletters, pamphlets or magazines, were theory-based, tailored on several concepts including demographics, included multiple time points, and had shorter-follow-up

periods. Findings from a meta-analysis of web-based interventions match those from print messages (Krebs, Proschaska & Rossi, 2010). Genetic testing could be regarded as the ultimately tailored/personalised information, although in the case of single gene testing, there are of course a limited number of possible outcomes. However, genetic test results from an individual biological sample have a personal salience and relevance that is not present when people are given general health behaviour advice.

In summary, the expected information value of genetic testing, reduction of optimistic bias, and personal nature of genetic test results have all contributed to expectations that personal genetic testing would be effective in engaging individuals with beneficial health behaviour change (Collins, 2006; Bowen, Battuello, & Raats, 2005; Gollust et al., 2012; Barns, Schibeci, Davison, & Shaw, 2000).

2.3 The Pitfalls

2.3.1 Fatalism and false reassurance

Enthusiasm for the beneficial prospects of genetic testing is not shared unanimously. Those cautioning against the use of predictive genetic testing argue that it has the potential to cause harm by inducing fatalism in the case of a higher risk result and false reassurance in the case of a result indicating no raised risk (Marteau & Croyle, 1998). This latter response would be particularly problematic for conditions such as obesity where prevention and treatment depend primarily on behaviour modification.

Much of this concern originates from the notion that, in contrast to other biomarkers, genes are unchangeable. In addition, early clinical genetic testing, which was almost exclusively performed for diagnostic and reproductive purposes, focused on monogenic or highly penetrant, severe diseases (Wright et al., 2011). Assumptions about the psychological impact have been extrapolated to genetic testing for low-risk common conditions; although it is currently unclear whether they hold true in the same way.

2.4 Predictions from Health Behaviour Models about psychological and behavioural outcomes of genetic test feedback for common, complex conditions

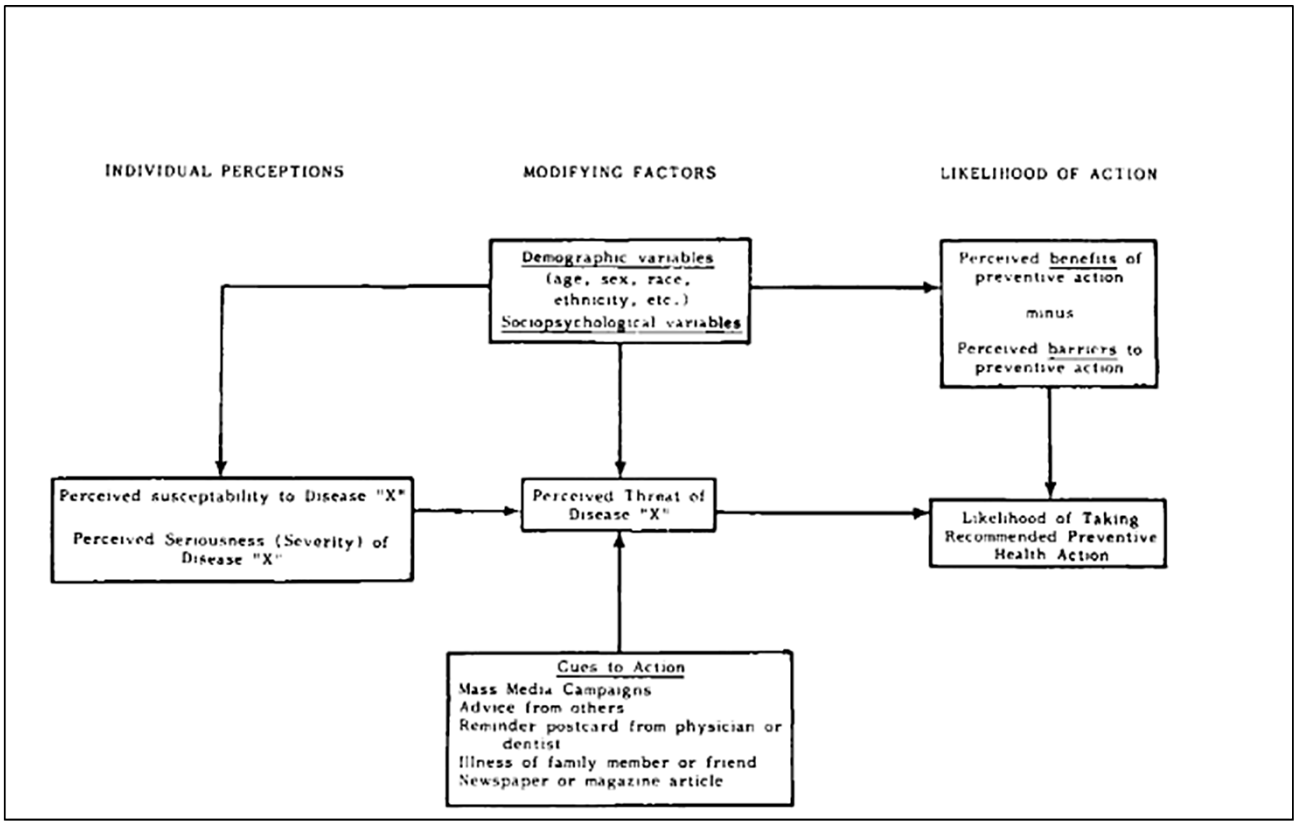
Theoretical models of health behaviour have attempted to capture the complex influences that lead to behaviour change, and have some application for assessing utility of genetic testing for behaviour change. Two of the most commonly cited models in the literature on genetic test feedback for common, complex conditions are the Health Belief Model (Rosenstock, 1974), and Leventhal's Illness Perception Model (Leventhal et al., 1997). Although there are alternative models of health behaviour that have been applied in studies of reactions to genetic test feedback (e.g. the extended parallel processing model by Witte and colleagues (1992), or protection motivation theory, Rogers, 1975), the study design in the current thesis was guided by the concepts and constructs discussed in the Health Belief Model and Leventhal's Illness Perception Model because they seemed most suited for the main outcomes investigated in this thesis (motivation to change behaviour, fatalism and false reassurance), and the type of genetic test feedback given (a single gene for a common, complex condition). Lastly, much work about fatalistic reactions to genetic test feedback has

been based on Leventhal's Illness Perception Model, and it seemed therefore sensible to use it in the current thesis.

2.4.1 Health Belief Model

Application of the Health Belief Model suggests that individuals may use predictive genetic test results indicative of personal risk to make beneficial behavioural changes to prevent adverse health outcomes. Perception of susceptibility to the specified condition and its perceived severity make up the 'perceived threat' from that condition (Figure 2.3). According to the model, these perceptions are modified by demographic factors and 'cues to action', for example through messages in the media. According to the HBM, high-risk results from predictive genetic testing for weight gain susceptibility should therefore increase perceived risk of gaining weight, which in turn would motivate lifestyle changes to minimise risk so long as they believed in the efficacy of that action (perceived benefits) and the perceived barriers were not too high.

Figure 2.3 Schematic representation of the Health Belief Model



Retrieved from http://nnlm.gov/evaluation/pub/witte/

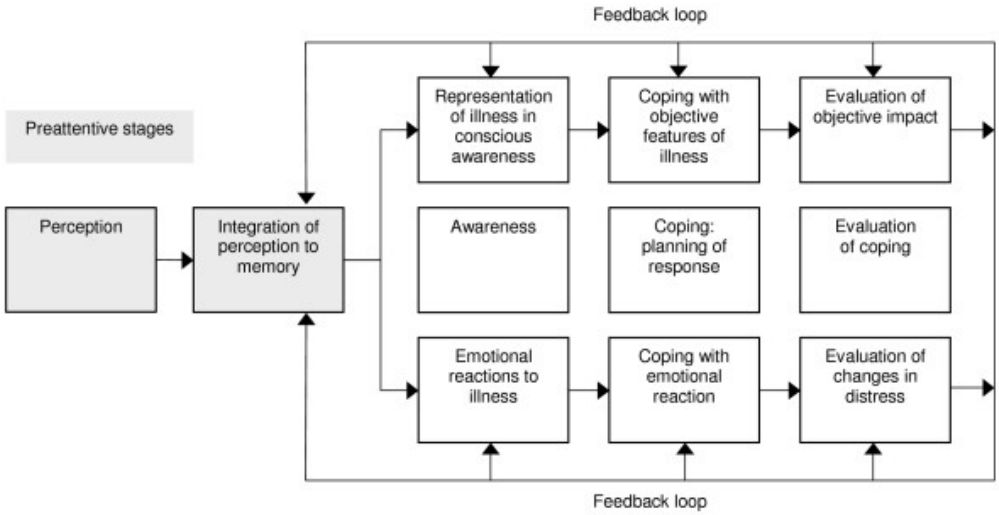
2.4.2 Self-regulation Model of Health and Illness

There are other theoretical perspectives. The Self-Regulation Model Leventhal, 1997,

Figure 2.4) proposes that risk-reducing actions are taken in accordance with perceived causes of illness. According to this model, individuals incorporate various aspects when thinking about an illness: symptoms (illness identity), causes, consequences, the extent to which it is controllable, and the duration and/or symptom change over time (timeline). So if someone

believes that weight gain is caused by modifiable factors, such as sedentary lifestyle or unhealthy diet, they will act accordingly and make the required behavioural changes. If however, causality is assumed to be non-modifiable (e.g. genes are assumed to be entirely determining), a high-risk genetic test result could lead to a fatalistic attitude. Likewise, assumed genetic causality could cause a false sense of immunity when the result indicates no raised genetic risk for the condition in question

Figure 2.4 Self-regulation Model of Health and Illness



Adapted from Leventhal, Nerenz & Steele, 1984

Retrieved from Munro, Lewin, Swart & Volmink (2007), http://www.biomedsearch.com/nih/review-health-behaviour-theories-how/17561997.html#fullText

2.5 The evidence to date

2.5.1 Psychological impact of genetic testing for common, complex conditions

A table of all studies reviewed in this section is included in Appendix 1.

2.5.1.1 *Fatalism*

The majority of studies investigating fatalism and false reassurance were conducted during the early applications of genetic testing. The body of literature that emerged is large, but studies are diverse in methodology and samples are often small and drawn from family groups afflicted with rare and severe genetic conditions. Therefore, it is very difficult to synthesize the information and draw more general meaningful conclusions, especially for predictive genetic testing for common, low-risk conditions.

One of the most frequently cited studies in support for potentially fatalistic response to testing is a qualitative study by Senior, Marteau & Peters (1999), cited 138 times on Google Scholar. The authors investigated parents' response to neonatal screening for familial hypercholesterolemia in semi-structured interviews with 24 parents of children aged between 15 and 30 months who had received positive screening results for their child and had been invited for re-testing. Interviews took place before a definite diagnosis of FH was made. Interview questions were based on Leventhal's Illness Perception Model (1997). Senior and colleagues found that parents felt the condition was more dangerous and less controllable when they thought of the result as genetic rather than related to the mother's diet during pregnancy. This is an important finding although the sample was small and from a very special population subgroup so it may not generate to the adult population. The qualitative design of the study excludes the generalizability of the findings *a priori*, and the authors themselves clearly caution against doing so, so it might be somewhat surprising that this study builds the foundation for the argument that genetic test feedback would result in fatalism.

Findings from this study also contrast with a RCT that was conducted by Marteau et al (2004). Individuals suffering with Familial Hypercholesterolemia (FH) (n = 341) and their relatives (n = 128) were randomly assigned to receive either a routine clinical diagnosis or the routine diagnosis and genetic test results. Affected participants were tested directly, and mutation searching was performed for unaffected relatives. Primary outcomes were perceptions of control over FH, cholesterol and heart disease, and fatalism about FH, which were assessed with the respective scales of the Illness Perception Questionnaire-Revised (Moss Morris, 2002), and scales devised especially for the study. In addition, risk-reducing behaviour, perceptions of diagnosis and emotional state were investigated. However, relatives for whom no mutation was found had lower perceived control over FH and heart disease one week after disclosure of results; this was no longer evident at the six-month follow-up. There was also no difference observed in risk-reducing behaviours. As this study was a RCT, which is the gold-standard for investigating causal relationships, results can be assumed to be relatively robust. This is also one of the few studies which were sufficiently powered, although the results are limited by the special population investigated who were aware of their potentially increased risk, and thus may have already taken action to minimise risk. The participants in this study may have sought confirmation of what has been a private assumption about FH risk. When the mutation search was unsuccessful, this may have resulted in disappointment and insecurity about causes of FH.

Families affected by Huntington's disease are another frequently studied population group for assessing outcomes of genetic testing. Huntington's disease is a severe neurological condition caused by a mutation in a single gene, for which to date no cure exists (Vonsattel, 1985). For example, a study by Wiggins et al (1992) investigated psychological impact of genetic testing in 135 members of the Canadian Collaborative Study. Eligible participants had to have at least a 50 % chance of having inherited the Huntington gene. About a quarter of participants (26%, 55 individuals) withdrew before testing or after learning that results could be uninformative. The remaining participants were split into 'increased-risk' group (those whose risk prediction increased from 50% after testing), 'decreased risk' group (those whose risk prediction decreased to 25 % or less after testing) and the 'no-change' group (those who declined the test or those for whom the test was uninformative but did not withdraw). Participants filled in several self-report questionnaires on anxiety, distress, depression and well-being, and were followed up one week, six months and one year after genetic result disclosure. The results showed a significant decline in distress in individuals with a test result indicating decreased risk, but no change in symptoms in those receiving an 'increased-risk' result. Both groups showed an increase in well-being compared with the 'no-change' group. Similar results were shown in a review investigating the impact of testing for Huntington's disease (Meiser & Dunn, 2001), with higher risk individuals being slightly negatively affected in the short-term which was, however, no longer evident after one year follow-up. Certainty about disease status and increased sense of control has been cited as the main reasons for the 'positive' effects (Gooding et al., 2006). Lack of increase in suicide rates after testing

became widely available is also a crude, but objective indicator of the absence of major detrimental effects after testing.

Evidence for lasting negative impact was also not found after testing for cancer, such as BRCA1/2 for breast cancer (Watson et al., 2004), or genes for hereditary colorectal cancer (Croyle & Lerman, 1993), or for Alzheimer's disease (Cassidy et al., 2008). A systematic review by Heshka et al. (2008) focusing on the psychological effects of genetic testing for nonpolyposis colorectal carcinoma, hereditary breast and ovarian cancer, and Alzheimer's disease included 30 studies discussed in 35 articles. The literature search was restricted to five databases (MEDLINE, EMBASE, Cochrane Central Register for controlled trials, CINHAL and PsychINFO) and encompassed articles related to genetics, genetic testing and psychological impact. Articles were included if they were published in English, were concerned with adults, focused on the psychological and/or behavioural impact of genetic testing and reported separate results for carriers and non-carriers. Studies were excluded if they only assessed screening intentions, assessed impact of single-gene disorders, or included samples with already affected individuals. The final set of studies spanned the following topics: affective outcomes (general distress, test-related distress, anxiety, depression, worry) behavioural outcomes (screening behaviour, prophylactic surgery, use of chemotherapeutics and other health-related behaviours) and perceived risk. The authors concluded that there was no difference in psychological distress, anxiety or depression after disclosure of the test result in those carrying a genetic mutation and those who do not. This was found to be the case regardless of method of assessment. Although there was a trend for distress immediately after individuals received their

result in some of the studies (Broadstock et al., 2000; Cassidy et al., 2008; Murakami et al., 2004; Tibben et al., 1993), this was modest in magnitude and disappeared with follow-up. Interestingly, risk perception was not related to risk status, although screening behaviour increased slightly in individuals with high-risk results.

However, distress over potential disease status in those samples may have occurred long before a decision for a genetic test was taken, as members of these rare population groups undoubtedly had a family history of illness. Testing may have simply acted to confirm what was already anticipated, acting as catalyst to relieve distress from uncertainty. It is also possible that individuals rationalized negative emotions towards the test result in retrospect, in an attempt to cope with the outcome. Moreover, the actual uptake of genetic testing has been found to be much lower than anticipated, which hints that there are factors which may hold individuals back from getting tested (Bernhardt et al., 2009).

It is uncertain whether findings from these studies are applicable to the population at large. Finding out about a genetic disease without family history may hold entirely different connotations and outcomes for affected individuals. Negative emotional impact would be expected to be much higher, and the potential for fatalism much greater, because of the life-changing impact such a result holds. Investigating how adopted individuals react to their genetic test result may potentially help gain an understanding of how individuals cope with adverse health-related information where no (known) family history exists.

2.5.1.2 *False reassurance*

Disengaging from health protective behaviours because of a false sense of immunity from a genetic test result showing decreased, risk of disease is the other reason commonly cited by those who favour test regulation. This concern is also based on the assumption that individuals adopt a deterministic attitude towards genetics, and will thus ignore other, non-genetic, determinants of illness development. Little empirical research has focused on this aspect; the majority of studies were concerned with fatalistic responses to genetic testing.

Sanderson & Wardle (2005) explored factors associated with a motivated or a complacent reaction to genetic testing for risk of heart disease or cancer in a survey including 186 smokers. The vignette included information about genetic testing and stated clearly that the test would only show a predisposition to illness, and not a definite outcome. Anticipated reactions were assessed with a single statement for each reaction of interest (motivation, complacency, and depression). In addition, the authors measured perceived family history, dispositional pessimism, desire to quit smoking, level of nicotine addiction, and understanding of genetic testing. The majority of smokers anticipated finding a high-risk result more motivating for smoking cessation than a result showing no increased risk. However, the predicted false reassurance was observed, with over one third of the sample (39%) thinking that it was safe to carry on smoking if they received a negative result. Out of those participants, a higher percentage had less formal education and less understanding of genetic testing, in addition to a lower desire to quit. However, in multivariate analyses, only the effect of age and level of education were maintained. Shortcomings

of the study were the small sample so that power issues may have impaired validity of the findings. Furthermore, as the authors noted, the potential misunderstanding of the test result in their study (it was framed as a 'positive' result if the susceptibility of lung cancer was increased and 'negative' if this was not the case) is a major shortcoming. Respondents may have reversed the meaning of the test results which may have rendered the current results inaccurate.

However, similar results were obtained by Frosch et al. (2005) in a vignette test scenario, for risk of obesity, which will discussed in detail below. The authors found that individuals who scored low on perceived behavioural control imagining not having the high-risk gene combination for obesity reported less intention to eat a healthy diet, although again, the sample was not powered to investigate interactions, and results should therefore be viewed with caution. Furthermore, both studies assessed only anticipated and not actual reactions to genetic testing. Individuals often overestimate their reaction in a hypothetical situation, and actual testing may have yielded less complacent responses. The number of studies conducted so far on the subject is by far not large enough to draw definite conclusions on complacency in reaction to a test result not indicating increased risk.

2.5.2 Impact on behaviour change

2.5.2.1 *Smoking cessation*

Decreased cost of genetic testing has made it possible to investigate potentially adverse psychological reactions after testing for common conditions. The paucity of research to date is noteworthy, considering that the commonly cited reason in favour

of predictive genetic testing is the subsequent adoption of a healthier lifestyle. Smoking cessation is the only area of behaviour change that has received reasonable attention over recent years with respect to utilizing genetic feedback. Early discovery of the link between genes coding for enzymes that reduce risk for lung cancer (GSTM1 and CYP2D6) may have led several groups to begin exploring the impact feedback may have.

Lerman and colleagues (1997) were one of the first groups to study the impact of genetic test feedback on smoking cessation in a sample of 427 individuals. Genetic test feedback for the CYP2D6 gene was incorporated into a minimal contact quit smoking counselling. Participants were assigned to receive counselling only, counselling and biomarker feedback or counselling, biomarker feedback and genetic test feedback. Feedback was successful in elevating perceived risk, perceived quitting benefits but also increased worry about lung cancer. There were no differences between groups in cessation rates and number of cigarettes smoked per day at the two-month follow-up. After one year, however, participants receiving genetic test feedback in addition to counselling had made more quit attempts and were more motivated to quit than those only receiving counselling, although no differences in actual quit rates emerged (Audrain et al., 1997).

Increases in actual quit rates were observed in another RCT (McBride et al., 2002), which used genetic feedback in addition to a smoking cessation intervention in a sample of 316 African-American smokers. In this study, quit rates nearly doubled at the six-month follow-up. (19% *versus* 10%), respectively; at 6 months but not at 12

months There were no increases in perceived risk or distress among participants. However, quit rates were high regardless of 'high-risk' or 'low-risk' genetic status for the GSTM1 gene. Considerably more support during the intervention was given to participants who also received genetic feedback. Therefore, increases in quit rates cannot be clearly attributed to test feedback, although it is possible that individuals used feedback as motivator for behaviour change, regardless of the actual test result.

More recently, Sanderson and colleagues (2008) conducted a RCT including 61 participants and found that smoking cessation rates increased significantly one week after providing individuals with feedback for the GSTM1 gene, compared with control participants (35 % vs. 0%). However, the effect was no longer evident after the two-month follow-up. In addition to smoking-related outcomes, perceived risk and self-efficacy were also assessed. There were no differences in those variables found at two-week follow-up, although perceived risk and worry about lung cancer was slightly, albeit not significantly, higher at the two-month follow-up in the control group. This may have been, as the authors suggest, because participants enrolling in the study may have participated to have certainty about their risk status (albeit the risk increase is very small), and not receiving a result may have led to disappointment and slight distress. However, this study was underpowered, which limits the reliability of the findings.

The overall effect of genetic testing for smoking cessation, and other risk-reducing behaviours, was recently investigated in a Cochrane review by Marteau et al (2010). Only studies qualifying as RCTs or quasi-RCTs were included. In addition, feedback had

to be given for conditions for which risk-reducing actions could be taken. The three studies discussed above were included in the analysis, in addition to two studies from Japan (Hishida, 2010; Ito, 2006).

Hishida and colleagues (2006) allocated 562 employees of a bank to either gene feedback group (n = 286, n = 257 agreed to genetic testing) or no intervention. At one-year follow-up fewer people in the intervention arm had quit than in the control group (15 vs. 22 participants). However, negative outcomes of gene feedback were also not reported.

Ito and colleagues used a sample of 617 smokers attending a local cancer centre and allocated them to receive either gene feedback or no intervention. Follow-up smoking status was collected at three and nine months. There were no significant differences in quit rates between the groups; neither at three-, nor at nine months; although there was a trend for quit rates to be higher in participants receiving gene feedback. Pooled data analysis from all clinical studies showed no statistically significant effect of incorporating genetic feedback results into smoking cessation programs, neither in the short term (two weeks), nor the longer term (six months). However, studies were very heterogeneous in sample size, assessment methods, and interventions used to aid smoking cessation. Confidence intervals for the pooled effect size estimates were wide, which indicates considerable variation in results. Furthermore, the past 10 years during which the studies were conducted were marked by rapid development and change in the genetic testing field; participants in the earlier studies may have viewed genetic testing differently from those who participated more recently. Although lack

of a positive effect is discouraging, there was also no evidence for a negative effect, which is encouraging as it suggests that it is safe to carry real genetic test feedback forward.

2.5.2.2 *Diet and exercise attitudes, intentions and behaviours*

Studies that looked at the utility of genetic testing for modifications in diet and exercise are fewer than those for smoking cessation. In fact, there are only two RCTs that gave actual genetic test feedback. One study gave feedback but did not include a control group, and three studies were based on hypothetical scenarios.

The first study to give real genetic test feedback specifically for obesity was conducted by Harvey-Berino (Harvey-Berino et al., 2001) who tested whether genetic testing would diminish self-efficacy and feelings of control over eating. This study gave feedback on the beta-3 adrenergic receptor gene (b3AR, thought to be implicated in obesity) to thirty postmenopausal obese women. Participants were informed that the gene increased risk for obesity, but no information was given on how the gene would act. Diet self-efficacy was measured with the Eating Self-Efficacy Scale (Poston, 1997), and four statements assessed potential responses and beliefs about the effect of having an 'obesity gene'. Diet and weight history were assessed via self-report. Feedback status had no impact on diet self-efficacy, confidence in the ability to lose weight, or attitudinal variables. Contrary to expectations, individuals who tested positive for the b3AR gene reported more confidence in the ability to overcome genetic predispositions with the right lifestyle choices. Individuals in this study were already obese and presumably had a history of struggling with their weight, so that the

findings cannot necessarily be translated for obesity prevention. Although the small sample size diminishes validity of the results, the findings indicate that individuals do not use genetic testing as an 'excuse' to disengage with weight loss efforts and become negatively affected or complacent. However, this study did not assess behaviour change, so inferences about potential benefits of testing cannot be made.

Hicken and Tucker (2002) addressed the question of whether a positive test result for the fictitious 'Asch syndrome' would affect individuals' dietary behaviour. The 115 participants read a pamphlet about the 'Asch syndrome' in which it was stated that it is an inherited condition and that the risk for its occurrence could be minimised by lowering the amount of fat in the diet and consuming soy products. Individuals gave information on family history for the symptoms of 'Asch syndrome' (fatigue, headache, and stomach pain), health behaviours, and perceived risk for falling ill with the disease. One experimenter 'reviewed' the individuals' family history. Participants whose pedigree supported the family history were retained, and divided into three groups: the experimenter informed one third that their risk was solely due to family history. The remaining participants were offered a 'gene test' for the disease. Half of the gene test group was misled to believe that the test was positive. After filling out the follow-up questionnaire, which included an assessment of intended fat reduction and soy consumption, participants were fully debriefed about the purpose of the study and the fictitious nature of the disease. Participants who received a high-risk result (either through family history or genetic test) perceived themselves to be at a higher risk for 'Asch syndrome'. However, no differences between the groups emerged in intended soy consumption or dietary fat reduction. Clearly, this study suffered from

major ethical shortcomings. Although participants did not display negative reactions after debriefing, letting someone believe they are at high-risk for a genetically transmitted disease, even if it is only for a short time, is highly questionable. Furthermore, the sample size was small which may have limited the validity of the findings.

The first study with a larger sample (n = 249) used a hypothetical scenario methodology (vignette) to assess the anticipated consequences of genetic test feedback for obesity risk (Frosch et al., 2005). It used a 2x2 factorial design, with two test conditions (hormone test vs. genetic test) and two levels of risk (higher-risk vs. lower-risk result). Participants were randomised to receive one of the four vignettes. Measures were chosen according to the Theory of Planned Behaviour (Ajzen, 1991) and included intentions to eat a healthy diet, attitudes, perceived behavioural control, perceived social norms, and expectations about benefits of eating a healthy diet. Higher-risk feedback led to increased intentions to eat a healthy diet, regardless of whether feedback was given for gene-or hormone-status; although dietary intentions were overall relatively low (mean = 2.0 (SD = 1.0) for higher-risk feedback vs. 1.7 (SD = 1.2) for lower-risk feedback on 4-point Likert scale). However, the interaction between feedback type (hormonal vs. genetic) and control beliefs was significant: individuals receiving higher-risk genetic test feedback felt less in control than those receiving lower-risk test result, whereas in the hormone group the opposite pattern emerged (individuals given higher-risk hormone test feedback felt more in control than individuals receiving lower-risk hormone test feedback). Intentions to eat a healthy diet were high when control was perceived to be high, independent of risk

status or feedback type. There was no significant interaction of BMI and feedback type on intentions to eat a healthy diet. These results contrast with those obtained by Harvey-Berino et al (2001) in terms of some evidence for a demotivated and fatalistic attitude in response to a genetic test result. Frosch et al interpret the lack of effect for feedback, and low dietary intentions for those who a higher BMI themselves, as a sign for fatalism. However, it may be that the lack of motivation for dietary change was due to a belief that a larger size was natural for them; which is subtly different from a fatalistic attitude. Furthermore, the study provided individuals with risk increase of 50% in the high-risk conditions. This is far higher than any real genetic effects known so far, and may have led individuals to (falsely) assume that overweight would be inevitable. As this study was only hypothetical, it is difficult to predict reactions to 'real' feedback. Lastly, the study did not employ a pre-post design, so conclusions about changes in attitudes cannot be made.

The meta-analysis by Marteau et al (2010) included the trial by her and her colleagues (2004) discussed in 2.3.1 and a study by (Chao, 2008) who looked at dietary change following disclosure of ApoE 4 status for risk of Alzheimer's disease in a sample of 162 individuals. Participants were asked three questions pertaining to behaviour change (changes in diet, exercise and changes in medication/supplements) in response to Apo-Lipoprotein E (a gene implicated in Alzheimer's disease, APOE) disclosure one year after learning about their results. In comparison with either control or lower risk participants, those receiving a higher risk result were significantly more likely to have made changes in one of the three healthy behaviours. Most commonly, participants

changed their medication/vitamin use, despite being explicitly informed that there was currently no effective prevention for AD.

Results from the meta-analysis of the clinical studies indicate that feedback is effective for dietary change. However, as only two studies were included in the analysis, one of which returned results for a highly debilitating disorder for which to date no cure exists, results have to be viewed with caution.

Two RCTs have been published since the meta-analysis became available, one aimed at encouraging smoking cessation and the other at diabetes prevention (Hollands et al, 2012; Grant et al, 2012).

Grant and colleagues investigated whether returning genetic feedback about diabetes risk to a sample of 102 overweight participants at high risk for diabetes would improve outcomes in a 12-week validated diabetes prevention programme. Assessed outcomes were weight loss (> 5%), programme attendance and motivation to lose weight. When either high-risk or low-risk participants were compared with control participants, there were no significant differences in programme attendance, weight loss or motivation between participants; suggesting that genetic feedback may have little impact in motivated individuals. These results also lend further evidence to the hypotheses that genetic test feedback is 'safe' to administer and would not decrease individuals' motivation to engage in behaviour change.

Null-findings were also reported in the RCT by Hollands and colleagues (2012). Here, 497 first-degree relatives of patients with Crohn's disease who were smokers received information on their personal risk of developing Crohn's disease based on either family history alone or in conjunction with genetic risk information. The main outcome was smoking cessation for at least 24 hours, assessed at 6 months and differences between groups were not significant, again suggesting that adverse outcomes of genetic test feedback are unlikely. However, there were several limitations to this study: First, risk recall was poor: Only 57% (124/219) remembered their DNA test results correctly, and this fell to 34% (137/209) at six months. Therefore it is likely that some participants misinterpreted their test result, or acted with the (incorrect) result in mind. Secondly, increases in absolute risk were small (5% or lower for Crohn's disease) and it is possible that this was not sufficient to change perceived risk, particularly given that the participants had a family history of Crohn's disease and may thus have had established risk perceptions. Lastly, the number of individuals who received higher risk results was relatively small (n = 50), and the study was under-powered to detect differences in quit rates by risk status.

2.5.3 Beyond 'objective' clinical utility: The potential for reduction of stigma

Despite the risks of fatalism and false reassurance, genetic testing specifically for obesity risk may yield positive effects, because obesity is still perceived by the wider society as resulting from a lack of self-control; it is a highly emotionally charged problem, stigmatizing and instilling guilt into individuals who suffer from it (Puhl, 2009). Guilt and self-blame may be significantly reduced by the notion that the condition is not solely in the control of the individual, leading to a more realistic

understanding of its origins, and thus to more effective strategies for weight management.

Conradt and colleagues (2009) included genetic information on obesity in a consultation with 147 obese individuals. Measurements included restraint eating, body acceptance, feelings of guilt, self-efficacy, and affect. Sessions were provided by consultants trained in genetics. The inclusion of genetic information led to a significant increase in genetic causal attributions of obesity in individuals, and those who also had a family history of obesity suffered from less negative affect after six months. Feelings of guilt were also reduced in the short-term, although this had disappeared at follow-up. This indicates that individuals who see their genetic test result reflected in their family history may be most likely to benefit from genetic testing.

However, findings from two recent randomized controlled trials by Lippa and Sanderson (2013) did not support the hypothesis that providing information about the genetic contribution to obesity would decrease internalized weight stigma in self-identified overweight/obese individuals (n = 655), or obesity stigma (in self-identified normal weight individuals, n = 396). Participants were randomized to receive information on obesity as being either caused by genes, environment, or gene x environment interactions in form of a short news article. In addition, they were randomized to receive behavioural advice about options to reduce obesity risk, or not. Subsequently, participants were asked to rate the information they just read (relevance, ease of understanding, perceived relevance), and to complete the Fat

Phobia Scale-Short form (FPS-S, Bacon, Scheltema & Robinson, 2001) if they self-identified as normal weight, or the Weight Bias Internalisation Scale (WBIS, Durso & Latner, 2008) alongside demographic information, eating attitudes, and a measure of self-esteem. Although significantly more participants in the genetic condition agreed that 'a person's genes' were a cause of obesity, there were no differences in obesity stigma, or internalized weight stigma, between the genetic and the non-genetic conditions. However, as this study did not assess obesity stigma or internalised weight stigma before the intervention, it is unclear whether the study was effective in changing causal beliefs about obesity. It is also possible that the brevity of the intervention (a short news article) was not powerful enough to change longstanding causal beliefs about obesity; which would explain the discrepancy between the current findings and those by Conradt et al (2009) who found that genetic information relieved stigma and self-blame in overweight individuals attending a weight loss programme.

However, it is noteworthy that none of the studies on obesity stigma to date have shown an increase in obesity stigma after providing genetic casual information which is reassuring in the light of concerns about possible adverse effects of genetic information.

2.5.4 Consumer-based genetic tests

Sometimes termed 'genetic horoscopes' or 'recreational genomics', direct-to-consumer (DTC) genetic tests have frequently been criticized, mainly for their low clinical utility and lack of oversight (Hogarth, 2008; Grosse et al., 2009; Annes, 2010). The FDA has recently responded to these concerns and placed restrictions on

advertising (FDA, 2010). However, there is still little distinction in internet advertising between tests without much scientific credibility such as intelligence, tests about physical characteristics such as the texture of a person's earwax or eye colour (which are already apparent to the individual), and tests for severe genetic diseases with firmly established evidence base and life changing consequences such as Huntington's disease. Carrier status for recessive diseases, pharmagenomic profiles (genetic differences in the ability to metabolise medications), and ancestral lineage determination, is also part of the DTC landscape. In fact, results from all the above categories are commonly returned online together with those for severe illnesses, without the presence of a genetic counsellor.

2.5.4.1 *Psychological and behavioural reactions to DTC testing*

How individuals take in and process multiple genetic risk information and its consequences is only beginning to be understood. One of the first studies to assess effects of DTC test results was published by Bloss and colleagues in 2011. They investigated psychological (anxiety and distress after testing) as well as behavioural changes (dietary fat intake, exercise levels, intended or real use of screening tests) after testing. Discussion of the results with a physician or genetic counsellor was also examined. Participants in the Scripps Genomics Health Initiative obtained the Navigenics Health Compass at a reduced rate in return for being followed up longitudinally. The Navigenics Health Compass is a DTC genetic test, assessing risks for a wide range of traits and medical conditions as well as providing pharmacogenomic profiles. Test-related anxiety, distress, fat intake and exercise behaviour were measured with standardized questionnaires at baseline and after 3-6 months.

Initially, 3639 participants took part, but only 2037 completed the three to six months follow-up (mean = 5.6 months, SD = 2.4). The sample was demographically no different from regular Navigenics costumers. The majority of the non-completers (44% in total) accessed their results but did not respond to the survey. Among the responders, genetic test results had no effect on anxiety, dietary fat intake, exercise levels, or any of the test-related distress variables at follow-up, regardless of whether they indicated increased or decreased risk for disease. No significant difference between baseline and follow-up was found in the number of screening tests completed since genetic testing; although intended use of screening tests was significantly increased. Just over a quarter (26.5 %) of participants shared their result with a physician, but only 10.4 % made use of the free genetic counselling service offered by Navigenics.

These results are the first to demonstrate that genetic testing for multiple conditions is relatively unlikely to result in harmful effects. Although the possibility remains that non-completers of the questionnaire had more pronounced negative effects, it is unlikely as they did not differ in any of the variables at baseline and distress might have been expected to moderate study participation. The lack of effect on behaviour may be discouraging at first sight; however, it is likely that 'early adopters' of genetic testing are already health conscious, and engage in as many of the recommended behaviours as they can which could have caused a ceiling effect for the follow-up results. Unfortunately, 'health consciousness' was not assessed at baseline, so this explanation remains speculative.

Potentially, the time frame of investigation may have been to narrow, and beneficial effects may become apparent only in the longer term. Intentions to undergo more screening was mainly due to a small number of individuals planning to utilize a large number of screening tests, which may have artificially skewed the results. These individuals may differ from the overall sample in their personality or in health-anxiety related traits; at this stage it is too early to draw conclusions about actual screening uptake.

It is also difficult to extrapolate findings from this study to a group that undergoes genetic testing specifically because they feel at an increased risk for disease, as perceived relevance may influence the results. DTC tests provide individuals with a large amount of risk information for a wide range of conditions. Inevitably, risk will be raised for some conditions, and will be lower for others. It is unknown how this affects the overall health risk perception of individuals, and whether this differs from receiving feedback for several risk markers for a single condition, or a single risk marker for a single condition. More research is needed to understand the ways in which individuals take in and process genetic information.

Motivation to change is a central factor to achieve behaviour change, and if the majority of the sample underwent testing for reasons other than utilizing feedback to motivate behaviour change, results may not have enough impact to tip people towards change. Nonetheless, they may bring change of lifestyle more to the forefront of consciousness, with potential for future impact.

Concern about potential harm caused by receiving medical test results appears to be widespread and is not restricted to genetic testing. Results from any blood or screening test always have to be returned by a healthcare provider. So the call for regulation of returning genetic test results is not surprising. At the same time however, there is a push towards achieving a better informed, more autonomous patient population and a need for minimization for use of healthcare services to reduce healthcare costs. It is not clear at this stage that the evidence base of adverse effects for testing justifies the request for stringent regulation.

Although results from clinical studies have shown no lasting negative effects (e.g. Dougall, 2009;Watson, 2004 ;Broadstock, 2000), the assumption of potential for harm from genetic tests remains. Fatalism on the one hand, and false reassurance on the other, in response to the test result are of special concern for obesity prevention, because certain coping strategies, such as overeating in response to negative events, or passive reactions to problems, have been associated with poorer weight management (Elfhag & Rossner, 2005). Behavioural means such as exercise or sensible eating are crucial for successful weight control. At the same time, potential positive effects of genetic testing may outweigh the risks, particularly in the area of obesity prevention. As McBride and colleagues (2010) note, it is important that research into potentially positive outcomes of testing is not hampered by fear of potential harm.

2.6 Chapter summary and discussion

This chapter reviewed the latest developments in the area of genetics and discussed the challenges that would need to be overcome if genetic test feedback was to be introduced on a large scale. Demonstrating any 'added value' from genetic test feedback to already established methods of disease prevention without causing harm by creating false beliefs about inevitability of, or immunity to, disease are of particular importance; as is the careful consideration of ethical implications. Impact appears to differ among different domains of health behaviour change ; although the evidence base for the likely impact of genetic test feedback is slim at present, and conducting studies focusing on genetic test feedback for common, complex conditions are needed. Returning genetic test feedback for susceptibility to unhealthy weight gain serves as a good model for this endeavour because of its well-defined genetic and behavioural influences.

Chapter 3: Thesis Aims

3.1 Aims of the current thesis

As discussed in the previous chapters, genes interact with obesogenic environments, leaving some individuals more vulnerable to weight gain than others; testing for these genetic risk variants has recently become affordable. However, studies investigating the psychological and behavioural effects of genetic testing for common conditions, where effect sizes are very small, are only beginning to emerge. Particularly with respect to obesity genetic testing, the literature is scarce.

As genetic testing becomes more popular, there is a need to increase our understanding of how individuals 'make sense' of genetic risk and how it might affect behaviour. To date, studies into psychological and behavioural effects of genetic test feedback have mainly focused on ascertaining that there are no harmful effects. This is in line with recommendations for complex interventions by Campbell et al. (2000) which outline the exclusion of harm as the first stage when implementing complex interventions to improve health. The next step is now to build on the early literature to discover whether providing genetic risk feedback could be used to motivate healthy individuals to engage with disease prevention. *FTO* genetic feedback for risk of weight gain serves as a good model because of the scope for effective weight gain prevention through behaviour modification.

The overall aim of the PhD was to investigate the motivational, affective and behavioural responses to *FTO* genetic test feedback in young, healthy individuals, as well as in already affected individuals of varying ages to discover whether i) genetic feedback is 'safe,' and ii) it could be an aide in initiating behaviour change; although it is important to note that in clinical practice, feedback would never be given for only one gene, but a whole gene panel, or possibly even the whole-genome, so that findings from this PhD should be regarded as proof-of-principle only.

3.2 Research Questions

This thesis aimed to answer the following questions:

1. *'What is the psychological impact of anticipated and 'real' genetic test feedback for risk of weight gain? Will genetic test feedback cause fatalism (with a higher-risk result) or false reassurance (with a lower-risk result)? Will responses differ by weight status?'*

I explored these questions in a vignette study to gauge anticipated responses by avoiding the potential for harm to participants (Study 1), in two small and selected samples of predominantly normal weight and overweight participants, receiving 'real' feedback (Studies 2a and 2b), and quantitatively in a larger sample in participants immediately after they received 'real' genetic test feedback (Study 4b).

2. *'What is the impact of genetic test feedback for weight gain susceptibility on motivation to avoid weight gain or to lose weight? Does it enhance or decrease motivation to control weight? Does the effect depend on genetic risk status? Does the effect depend on current body weight?'*

I attempted to answer these questions in the vignette study (Study 1) and a RCT by giving weight control advice with or without genetic test feedback to a sample of young adults with low motivation to control weight (Study 4a).

3. *Is FTO status associated with weight gain at university? Will returning genetic test feedback alongside weight control advice be effective at diminishing weight gain during this time period?*

I explored these questions in an association study (Study 3) and the RCT (Study 4).

4. *Will awareness of genetic risk status result in behaviour change?*

I explored this question in the RCT (Study 4).

Chapter 4: Study 1 – Psychological Responses to Genetic Testing for Weight Gain: A Vignette Study [4]

4.1 Background

Chapter 2 reviewed the most recent developments in the field of genetic testing which make it important to establish the evidence base for its effects on the general population. The current obesity epidemic calls for novel ways to engage individuals in weight gain prevention. Supporters of the genetic testing movement claim that the personalized nature of the result will constitute one of those ways. For example, in his recent book on personalized medicine, the head of the National Institutes of Health describes how finding out about his raised risk of diabetes from such a genetic test motivated him to make changes in his lifestyle: "*The DNA test result has forced me to face up to this part of my unhealthy lifestyle. […] I've embarked on a more disciplined exercise program, I'm paying more attention to what I eat, and I have shed about 15 pounds"* (Collins, 2010*).*

As discussed in Chapter 2, the debate about potentially harmful vs. beneficial effects of genetic test feedback held in other areas of behaviour change equally applies to weight gain prevention and weight loss. Following the Health Belief Model (Rosenstock, 1974), genetic feedback should be effective in the prevention of overweight because of its ability to raise perceived risk; however, following Illness Perception Models (e.g. Leventhal, 1993), the

[4] A version of this chapter has been published in *Obesity*[4]*: Meisel, S. F., Walker, C., & Wardle, J. (2011). Psychological responses to genetic testing for weight gain: a vignette study. Obesity, 20(3), 540-546.*

unchangeable nature of genes may lead individuals to assume genetic determinism in the case of a high-risk result, or complacency when faced with a low-risk result.

4.2 Study aims and contribution to the literature

The aim of Study 1 was to explore anticipated psychological and behavioural reactions to higher risk and lower risk *FTO* gene results in two populations: i) a general student sample, and ii) overweight/obese individuals. Investigating the effects of genetic testing in overweight and obese individuals may have implications for treatment, whereas investigating the effects of testing in a predominantly 'normal' weight sample may have implications for prevention of weight gain.

Outcomes included anticipated motivation to make healthy lifestyle choices, fatalism, negative affect, and the perceived value of genetic information in 'explaining' current weight status. I also asked questions about interest in taking a real genetic test. Based on predictions from the Health Belief Model (Rosenstock, 1974) and findings from Frosch et al (2005) and Conradt et al (2009), I hypothesised that higher risk feedback compared with lower risk feedback, would increase motivation for behaviour change, but would also increase negative affect among 'normal weight' individuals. I also expected that women would show more negative affect than men in response to a higher risk test result because of higher societal pressure placed onto women to be slim. More fatalistic responses among those who were already obese were expected, based on predictions from Illness Perception models (Leventhal, 1997), but I also expected this group to place more value on having an explanation for their body weight.

Several shortcomings of the literature discussed in Chapter 2 are addressed. The study begins to fill the void in the literature investigating the use of genetic test feedback specifically for the prevention of weight gain and as aid for weight loss, it uses two large samples which provide sufficient power to draw meaningful conclusions, assumptions are based on theoretical models of health behaviour, and the vignette was designed in accordance with recommendations by Persky and colleagues (2008) to increase validity of the results.

4.3 Methods and Procedure

4.3.1 Participants

Student sample

A convenience sample of students from a university in London, UK, was recruited through a mass mailing to all students.

The obese 'Panel' sample

Members of a nationwide online 'user panel', set up and supported by the charity Weight Concern, consisting of adults who are or have been overweight/obese, were invited to participate.

Sample size estimations were based on evidence from Conradt et al. (2009) which showed that a sample of 300 people would have sufficient power to detect a small effect size difference in motivational responses to different genetic test results in a within-subjects design.

4.3.2 Procedure

The study design was cross-sectional. The email invitation to participate, which included a link to the online survey, was sent out to all students and panel members. Potential participants were informed that consent would be presumed from filling out the questionnaire and clicking the 'submit' button. The introduction to the survey included brief information about the *FTO* gene, and before proceeding further, participants had to confirm that they had understood the information. The information given was piloted before inclusion in the questionnaire. Several details were dropped from the original piece of information for the sake of conciseness, clarity and to reduce complexity. For example, references to allelic variation in individuals were not included in the final version because participants in the pilot appeared to have difficulties with the concept without further explanation. Also, references to workings of the gene were not included as research in this area is still emerging. The final version included the following four statements about the *FTO* gene: '*1.One of the first genes linked with weight (called the FTO gene) was discovered in 2007. 2. About 1 in 6 people have the two high-risk variants of FTO. 3. Having the high-risk variants of FTO makes a person more likely to put on weight. 4. Having the high-risk variants of FTO increases your chance of becoming obese at some point in life by 20 %.'* The final version was perceived as very clear, unambiguous and easy to understand by participants in the pilot. Participants responded to both vignettes with order of presentation randomised.

4.3.2.1 *The vignettes*

Vignettes were developed according to the five criteria outlined by Persky et al (2008) which are as follows:

1. Dichotomous scales should not be used as response scales, as these do not provide opportunities to assess an individual's true opinion.
2. Mention should be made of the test occurring in the immediate future.
3. Length of text can be variable, and depends on the specific group studied.
4. Hypothetical scenarios should be pilot tested and build on appropriate theoretical foundations.
5. Rigorous study design should be employed in order to avoid methodological and statistical problems. It is sensible to develop overarching criteria for using vignette designs as this will increase reliability and validity considerably and make it easier to compare vignette studies across populations. This will allow for drawing more general conclusions regarding potential reactions to genetic test uptake.

Several versions of the vignette were piloted before arriving at the final version. Mentioning that the saliva would be analysed at a special laboratory was dropped after the pilot, as participants felt that it was unimportant. The final version read the following: '*Imagine you have taken a gene test for FTO. It was done by getting saliva (spit). Imagine receiving your genetic test result in a letter from your doctor.'* In one scenario, participants were asked to imagine that their result showed increased susceptibility to overweight (higher risk condition) and in the other they were asked to imagine that they received a result not indicating increased risk (lower risk condition). Individuals on whom the vignette was piloted (n = 35; members of the general population) perceived the vignette as clear, sufficient to explain the scenario, and easy to understand.

Participants were asked to think how the result would affect them by indicating their level of agreement to 16 statements broadly relating to the following constructs: motivation to counteract weight gain, fatalism, negative affect and having an explanation for their current body weight Each statement was preceded with: *'If I received a genetic test result which [did not] put me at a higher risk for gaining weight I would …'* and responses were on a 5-point Likert scale, from 'strongly disagree' to 'strongly agree'. Mean scores for responses in each category were calculated to obtain a composite score on a 5-point scale ('strongly disagree' to 'strongly agree') that was comparable across groups and risk conditions.

4.3.3 Measures

Because no published questionnaire covered all domains of interest, statements used to assess the anticipated psychological and behavioural impact of genetic testing were in part based on previous research as well as self-developed.

4.3.3.1 *Participant characteristics*

Participants were asked to provide basic information (age, course and year of study for students, employment status and educational attainment for Panel members) and to report height and weight for BMI calculation. For all analyses, BMI was dichotomized into underweight/normal weight(BMI ≤ 25.0 kg/m^2) and overweight/obese.(BMI > 25.0 kg/m^2), according to WHO criteria (WHO, 2000).

4.3.3.2 *Principal component analysis*

Principal component analysis (PCA) was carried out on data from both samples and in both conditions to explore whether the individual statements could be categorized according to

overarching themes. Grouping several statements according to underlying constructs was thought to improve reliability of the results. Another option would have been to use exploratory factor analysis, but PCA has been shown to be as psychometrically sound, but be less mathematically complex than factor analysis (Field, 2005).

PCA using Oblimin rotation with Kaiser Normalization confirmed that 16 of the 23 statements fell into five domains: Motivation to control weight, Negative Affect, Fatalism (which remained assessed through a single item), Information Seeking and the 'Explanatory Value' of the genetic test result. Table 4.1 displays the statements used and their respective factor loadings. Scale scores were derived by adding scores for the individual items loading on that factor, and then deriving the average. This made scores fall onto a five-point scale allowing for comparison across groups. Crohnbach's alphas were as follows: Motivation (six items) = 0.89; Fatalism (one item) = 0.46; Negative affect (four items) = 0.70; Explanation (two items) = 0.69; Information Seeking (three items) = 0.58.

Table 4.1 Statements used to assess the anticipated psychological and behavioural reactions to *FTO* feedback and their factor loadings

If I received a genetic test result which [did not] put me at higher risk for weight gain…	Motivation	Fatalism	Negative Affect	Explanation	Information Seeking
I would be more conscious about the amount of physical activity I do	0.80				
I would take steps to prevent myself from gaining weight	0.87				
I would try to change my lifestyle to prevent weight gain	0.87				
I would want to take some action to prevent weight gain (Sanderson et al. 2008)	0.83				
I would be more conscious of my diet	0.77				
I would take up exercise	0.80				
I would feel that there is nothing I can do to prevent weight gain		0.64			
I would regret having taken the test			0.83		
I would be glad that I knew about the genetic test result (reversed)			- 0.71		
I would feel angry about the test result			0.73		
I would feel depressed			0.57		
I would be glad that I have an explanation for my body weight				0.72	
I would feel that this confirms what I have always thought of as the reason for my weight				0.75	
I would want to discuss my result with a health professional					0.54
I would go to the Internet to find out what the result means					0.86
I would like to know more about how the gene acts					0.72

4.3.3.3 *Interest in and predicted uptake of genetic test feedback*

After completing the vignette component, participants were asked how interested they would be to in obtaining a free genetic test within the next six months to test their susceptibility to overweight (response options: 'not interested at all', 'slightly interested' and 'very interested'). They were then asked whether they would take up an offer of the test ('no, definitely not'; 'no, probably not'; 'yes, probably'; 'yes, definitely').

4.4 Statistical Analyses

Analyses were carried out using the Statistical Package for Social Sciences (SPSS) version 14.0. Descriptive information was based on frequency tables and cross-tabulation. T-tests were used to assess the influence of condition order on the results, and they were non-significant. Categorical variables were investigated with chi-square tests. The influence of BMI and gender as predictors of test interest and anticipated uptake was examined with one-way analysis of variance (ANOVA). Repeated-measures analysis of variance (ANOVA) was used to determine whether there were significant differences in responses across conditions. Where significant interactions were found, I tested effects of each BMI/gender group individually with one-way ANOVA. Age was included as a covariate in all analyses. I did not include education as covariate as there was very little variation in both samples, so that no meaningful differences would emerge. Sidak correction was applied to control for potential alpha inflation of multiple testing without losing power to detect significant effects, and the level of significance was set at $\alpha = 0.05$.

4.5 Results

4.5.1 Participant characteristics

A summary of the characteristics of the two samples is displayed in Table 4.2.

Table 4.2 Participant characteristics

Participant characteristic	Students (n = 395)	Panel (n = 306)
Age (years; mean ± sd)	24.7 ± 6.1	44.4 ± 11.5
Gender % (n)		
Male	29.4 (116)	10.0 (32)
Female	70.6 (279)	90.0 (274)
BMI % (n)		
Underweight/Normal weight (BMI≤ 25 kg/m^2)	80.0 (316)	9.2 (27)
Overweight (BMI 25.01-30.0 kg/m^2)	15.2 (60)	20.7 (66)
Obese (BMI ≥ 30.01 kg/m^2)	4.8 (19)	70.1 (213)

Student participants

Out of 28,000 students registered on the email system, 395 undergraduate and postgraduate students took part in the study (1.4 % response rate). Of the students who took part in the survey, the age range was from 18-61 years (mean = 24.7 years, SD = 6.1). Over two thirds (71%) of respondents were female, and they were studying a variety of subjects, ranging from arts and humanities to medical and biological sciences. For the majority (69%), self-reported height and weight placed them in the 'normal weight' category, with a mean BMI of 23 kg/m^2; 15% were classified as overweight and 8% as obese.

Panel participants

Out of 1119 panel members, 306 individuals took part, yielding a response rate of 27%. Participants' ages ranged from 21 to 82 years (mean = 44.4, SD = 11.2). The majority were female (90%) and employed (70%). Over two thirds of the sample held at least A-level education (64%) with half having completed university level education (52%). Self-reported heights and weights resulted in BMIs from 20 kg/m^2 to 75 kg/m^2, with a mean of 35 kg/m^2. Relatively few respondents were 'normal weight' (9%) or overweight (20%), and 71 % were obese. Most (93%) perceived themselves to be overweight or very overweight, and 87% were either 'very' or 'fairly' dissatisfied with their current body weight.

4.5.2 Interest in and predicted uptake of the genetic test

Almost half the student sample (46%) indicated that they were 'very interested' in a genetic test for prediction of weight gain, and 78% said they would probably or definitely take up the offer of a free test. Interest in testing was significantly higher in the Panel sample than in the student sample (difference: χ^2 (1) = 56.45 p<0.001), with 75% of the Panel reporting that they were 'very interested' in obtaining a genetic test. Almost all Panel respondents who were interested (93%), indicated that they would 'probably' or 'definitely' take up an offer for a free test, which was significantly different from the students (χ^2 (1) = 29.67, p < 0.001). There were no gender differences in interest in testing in either sample.

Respondents who were overweight or obese were significantly more interested in a genetic test for obesity susceptibility than those who were 'normal weight' in both samples: ($F_{Students}$ (1, 390) = 7.42, p = .007, η^2 = 0.019; F_{Panel} (1, 300) = 5.72, p = 0.017, η^2= 0.019). In the student sample, those who were overweight or obese were more likely to intend to have the test (F (1,

390) = 12.21, p =0 .001, η^2 = 0.030). There was also a significant interaction between gender and weight status in the student sample; with overweight females being more likely to take up a test offer than overweight males (F (1, 390) = 4.12, p = .043, η^2 = 0.010).

4.5.3 Vignette results in the student sample

The complete results of the repeated-measures ANOVA for the student sample, including mean scores of the outcome measures, are shown in Table 4.3. All analyses included gender and BMI as covariates.

Motivation There was a significant difference in motivation to make behaviour changes between average risk and higher risk conditions. As displayed in Figure 4.1, mean scores were 2.57 in the average risk condition and 4.02 (η^2 = 0.153) in the higher risk condition. The interaction with gender was not significant.

Fatalism scores were slightly higher in the higher risk condition (2.01) than the average risk condition (1.74), but both means indicated disagreement with the fatalism statement. 10% of students agreed or strongly agreed with this statement in the higher risk condition, versus 1% in the lower risk condition, χ^2 (1) =12.69, p < 0.001. There were no significant interactions with gender or BMI.

Negative Affect scores were higher (mean score: 2.28) after a higher risk than after an average risk result (mean score 1.88). However, the effect size of η^2 = 0.025 indicates that this increase was modest. Interactions between condition and either BMI or gender were not significant.

Having an explanation for body weight did not differ significantly by feedback condition (p = 0.413). However, the interaction of risk condition and gender was significant. Women reported significantly more relief about having an explanation for their body weight in the higher risk than in the lower risk condition, F (1, 300) = 6.26, p = 0.013, η^2 = 0.016.

Information seeking A higher risk result led to more anticipated information seeking, as shown in Figure 4.2. Gender and BMI did not predict the extent to which individuals would seek information about the *FTO* gene.

Table 4.3 Results of the repeated-measures ANOVA for the Student and the Panel sample

Outcome (range 1-5)	Risk condition: lower risk mean ± sd	Risk condition: higher risk mean ± sd	Partial eta squared	F(df, error)	p-value
Students (n = 395)					
Motivation	2.99 ± 0.57	3.97 ± 0.55	0.13	62.99 (1, 300)	< 0.001
Fatalism	2.16 ± 0.90	2.54 ± 1.00	0.02	9.97 (1, 300)	0.002
Negative Affect	2.18 ± 0.72	2.24 ± 0.66	0.03	13.56 (1, 300)	< 0.001
Information Seeking	3.49 ± 0.80	4.19 ± 0.58	0.02	10.37 (1, 300)	< 0.001
Explanation	3.09 ± 0.86	3.79 ± 0.78	0.01	0.67 (1, 300)	0.413
Panel (n = 306)					
Motivation	2.57 ± 0.67	4.02 ± 0.65	0.16	60.99 (1,390)	< 0.001
Fatalism	1.74 ± 0.04	2.01 ± 0.06	0.01	1.18 (1,390)	0.279
Negative Affect	1.88 ± 0.55	2.29 ± 0.72	0.01	0.37 (1,390)	0.545
Information Seeking	3.29 ± 0.79	4.08 ± 0.68	0.07	23.09 (1,390)	< 0.001
Explanation	2.70 ± 0.82	3.00 ± 0.97	0.02	6.19 (1,390)	0.013

4.5.4 Vignette results for Panel respondents

Mean scores of the composite scales for both conditions and complete results of the repeated-measures ANOVA are shown in Table 4.3.

Motivation to change behaviour was high in the Panel sample regardless of test feedback, but was even higher when anticipating a higher risk result, displayed in Figure 4.1 (mean scores: 2.99 lower risk vs. 3.97 higher risk). This effect was independent of BMI or gender.

Fatalism did not differ between the different risk conditions for Panel members, as shown in Figure 4.1. As indicated by the relatively low mean scores (2.16, SD = 0.90 lower risk and 2.54, SD =1.00 higher risk), few respondents believed that there was nothing they can do about further weight gain. BMI or gender did not significantly affect the results.

Negative Affect likewise was not affected by risk condition. The mean score of 2.18 (lower risk) and 2.24 (higher risk) out of 5 for both conditions shows that respondents did not expect to be depressed or upset by a result placing them either at average or higher risk for weight gain. There was also no significant interaction with BMI or gender.

Having an explanation for body weight was endorsed more strongly following a higher risk test result, regardless of BMI or gender.

Information seeking: Panel members anticipated informing themselves more about genetics and *FTO* following a high than a lower risk result. This effect was secondary to the significant

interaction of risk condition and gender, with men being slightly more interested than women in the higher risk condition F (1, 300) = 5.26, p = 0.022, η^2 =0.017. BMI did not predict information seeking.

Figure 4.1 Motivation, Negative Affect and Fatalism in both samples

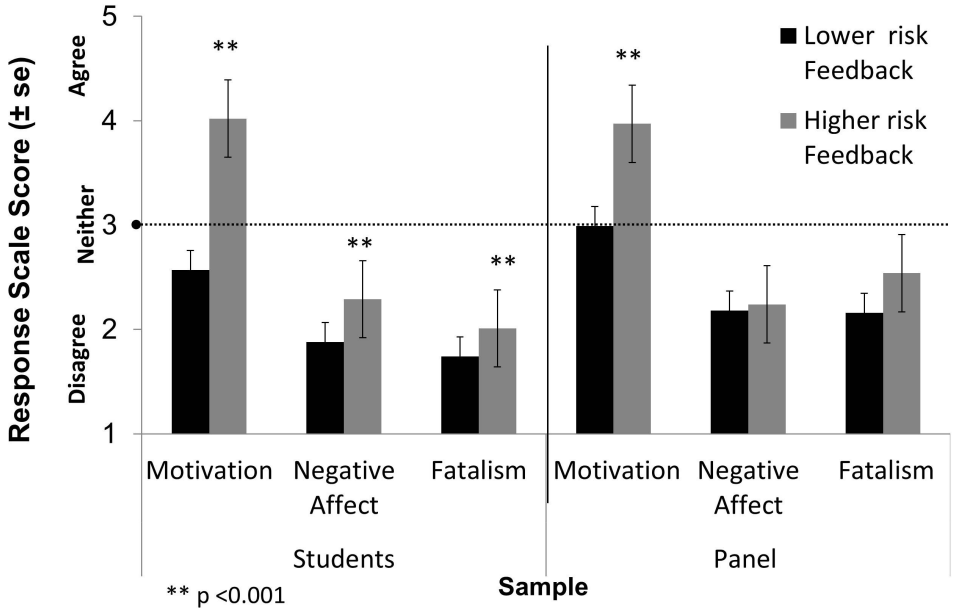
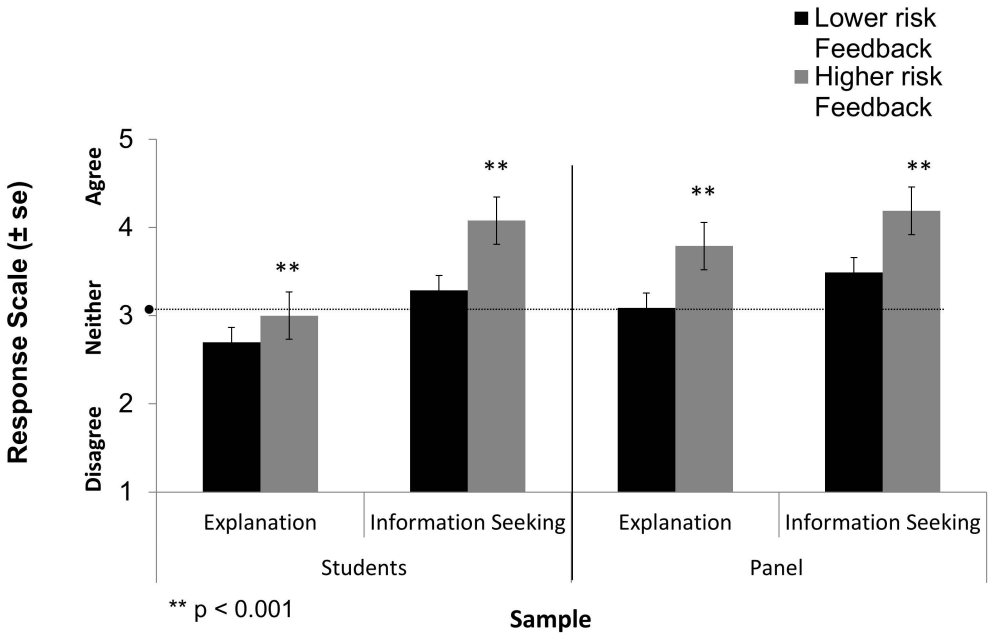


Figure 4.2 Value of Explanation and Information Seeking in both samples



4.6 Discussion

The present study investigated anticipated psychological and behavioural responses to genetic test feedback for susceptibility to weight gain in a panel sample of overweight/obese individuals and a general student sample. In both groups, higher risk test feedback elicited increases in anticipated motivation to adopt a healthier lifestyle or lose weight. This is consistent with social cognition models such as the Health Belief Model (Rosenstock, 1974) which identify perceived risk as a determinant of motivation. However, higher-risk feedback also resulted in increased negative affect for some participants; although these effects were mild. Overweight and obese individuals anticipated to derive a greater explanatory value from a higher risk genetic test result than normal weight individuals.

4.6.1 Study limitations

The study had several limitations. First, the hypothetical scenario precludes inferences regarding actual behaviour, because intentions do usually not translate fully into actions (Sheeran, 2005). Secondly, although all individual items used to assess anticipated reactions to genetic test feedback were based on the literature and their factor structure was confirmed by Principal Component Analysis, they were not taken from a validated questionnaire. Therefore, they may have not been sensitive enough to capture the nuances in psychological affect, particularly if reactions were mild. However, findings allow for gauging any potential reactions, while avoiding at the same time the potential for harm. A further limitation is that samples are not representative of the population from which they were drawn. Spam filters and non-use of the university email address may have contributed to the low response rate in the student sample. Furthermore, individuals with more positive attitudes towards genetic testing and who anticipated reacting more positively to genetic feedback, would have been more likely to choose to take part in the study (Sanderson & Wardle, 2008), which could lead to an underestimation of potential adverse reactions if test feedback was given to individuals who were not in a position to choose whether or not to receive it. However, in the real world, genetic testing for disease susceptibility is voluntary and so the same situation would hold. Nonetheless, to forestall adverse emotional reactions in individuals who might be more affected than they anticipate, offering the option of professional advice alongside the test result might be sensible. Thirdly, the *FTO* information provided was referring to risk of future weight gain, and not to losing weight. This may have had a different impact for those individuals who are already overweight or obese. Negative outcomes may have been more severe if the risk information was framed to include the difficulty in losing weight. Lastly, the current study gave information on only one gene with modest effect size to assess obesity risk.

In clinical practice, this scenario would be highly unlikely as returning feedback for gene panels is now feasible and cost-effective, and whole-genome sequencing is expected to follow in the foreseeable future. Therefore, reactions to results from panel-or whole-genome sequencing may differ because participants may assign more meaning to these results.

4.7 Conclusion

Results from this vignette study indicate that anticipated personalized feedback about raised genetic risk for weight gain increased motivation for change with only modest adverse emotional effects in both a student sample and a clinical group. These results provide some confidence in taking forward research using real *FTO* feedback as part of a package of personalized risk information and behaviour change advice.

Chapter 5: Study 2 – Reactions to *FTO* genetic test feedback for weight gain – a qualitative exploratory investigation[5]

5.1 Background

The findings of Study 1 indicate that genetic test feedback for weight gain susceptibility may be motivating, and is unlikely to result in pronounced harmful effects. However, hypothetical responses can provide only an impression of likely outcomes in the real situation; although, the lack of anticipated major adverse effects gave confidence in setting up a study to examine effects of giving real genetic test feedback to individuals.

5.2 Study aim and contributions to the literature

The aim of the current study was to explore reactions to real *FTO* feedback in a small number of interested individuals to establish potential benefits and harms associated with this technology. The study addressed the following shortcomings of the existing literature: Reactions to genetic test feedback could be studied instead of relying on assumptions made on the basis of hypothetical studies by returning 'real' genetic test feedback to individuals. Furthermore, it provided in-depth qualitative data in this area of research, which was used for hypothesis development for further quantitative research.

[5] A version of this chapter has been published in the *Journal of Genetic Counseling Meisel, S. F., & Wardle, J. (2013). 'Battling my Biology': Psychological Effects of Genetic Testing for Risk of Weight Gain. Journal of genetic counseling, 1-8.*

5.3 Methods

5.3.1 Development of the FTO information leaflet

A short information leaflet was developed for participants. The leaflet gave a brief overview about the *FTO* gene, its mode of inheritance, and magnitude of influence on body weight (Appendix 1). Readability was assessed with the Flesch Reading Ease formula and the Flesch-Kincaid Grade Level formula, and received a score of 70.0, which translates to the reading level expected in grade 6 (age 12). The leaflet was piloted in a number of individuals not familiar with genetics and wording and design were adjusted according to their feedback.

5.3.2 Participants

The sample consisted predominantly of interested individuals who responded to advertisements for Study 3 (p. 146), but whom we had to exclude because they did not match the inclusion criteria. They were offered to have their details added into a database so that they could be contacted at a later stage. The sample was therefore doubly self-selected by participants first opting to participate in the association study (Study 3, p. 146), and then agreeing to participate in the interview. Participation was voluntary, and participants did not receive remuneration for their time. Although the sample is not representative of the population at large, this is not a requirement for qualitative studies (Ritchie et al., 2003). At this stage it was unknown whether actual reactions would differ from anticipated reactions to test feedback for weight gain; therefore, we thought it as important to choose individuals who were comfortable with the idea of genetic testing for weight gain, and who would be able to talk openly about their experience. We included the first 18 volunteers because saturation of themes was reached after 15 interviews and further interviews felt unjustified. Ethical

approval was granted by the UCL Ethics Committee for non-NHS research (ID Number 2471/001). The approval letter is included in Appendix 2.

5.3.3 Procedure

Participants were sent an email with the invitation to receive a free genetic test for their obesity risk status in exchange for being interviewed about the experience. The invitation email stated clearly that pseudonyms would be used and that all personal information would remain confidential and included the *FTO* information leaflet. After replying to the initial invitation, participants received an information sheet with further details about the study, were invited to provide saliva for genotyping. Before saliva collection, the procedure was explained in detail and participants were given a consent form to sign. Saliva flow was stimulated with a small amount of sugar placed onto the participant's tongue and 1.5-2 ml of saliva was collected by drooling into the collection tube. Participants were asked to refrain from eating, drinking (other than water), smoking or brushing their teeth in the hour beforehand. Samples were coded with a unique identifier number so that they were anonymous but could be linked back to the interviews.

5.3.3.1 *Genotyping*

Saliva samples were collected for genotyping and anonymised before further analysis. DNA was isolated and extracted from saliva as described in Chapter 7: . Genotyping of rs9939609 was done using TaqMan as previously published (Wardle et al., 2008). Participants were contacted by email to accept or decline receiving the result, and to arrange an interview appointment. Results were sent by email one day before the interview to give participants time to think about the test result before the interview while ensuring that responses were

still vivid. The *FTO* information leaflet was included again in the email to refresh participants' memories.

5.3.3.2 *Interviews*

I conducted semi-structured, face-to-face exploratory interviews at University College London. Prior to the interview, permission was sought to record it to avoid the need to write. The interview guide consisted of a small number of open-ended questions (see Table 5.1), which were principally to keep the conversation flowing and not necessarily rigidly followed. Questions were chosen on the basis that they would lead to sharing of thoughts and feelings experienced before and after testing, and reveal the narratives that participants had constructed about weight and genetics. Participants' answers largely established the direction of the conversation and I only moved on to the next topic when it was felt that no new answers were acquired.

Participants were told that pseudonyms would be used and all personal information would be confidential. They were invited to a meeting where the procedure was explained in detail and they were given the opportunity to consent.

Table 5.1 Core questions of the interview guide

Interview question
What made you interested in the study?
Can you remember your test result? Can you explain what it meant?
Were you concerned in any way before you decided to take part?
Can you take me through your thoughts from when you heard about the study to when you received your result?
How did you feel when I told you your test result was ready and when you received your result?
Did you tell anyone that you took the test?
Is there anything else that you would like to tell me that we have not covered?

5.4 Data analysis

Interviews were transcribed verbatim and analysed with Framework Analysis, which allows analysis by case and by theme (Ritchie, 2003). This method was appropriate, because areas of investigation were chosen a priori, based on predictions of health behaviour models. For example, interviews were searched for evidence of perceived susceptibility, perceived severity, benefits, barriers, and cues to action that make up the Health Belief Model (Rosenstock, 1974), and illness identity, cause, consequences control beliefs, and timeline that comprise the Illness Perception Model (Leventhal, 1997).

Interviews were coded by me, Jane Wardle and an independent researcher (Katriina Whitaker). Triangulating data in this manner ensured high reliability and validity of the current results. At first, statements were loosely coded until common themes emerged that were extracted to develop overarching categories. These categories were refined and subdivided by coding and recoding the interviews. As new themes arose, previously coded interviews were re-analysed. Quotes were organized to represent the same themes: for example, 'reactions

to *FTO* feedback' at first included all reported emotions or behaviours after receiving the genetic test result; this was then further subdivided into positive and negative reactions, with immediate and future implications. Data coding followed an iterative process, revisiting the interviews until no new themes emerged, as described. Constructs from the Health Belief Model and Illness Perception Model discussed in Chapter 2 were kept in mind when interviews were coded. For example, I After coding was complete, the research team met to discuss results. Agreement of the researchers for extracted themes was very high; where minor discrepancies arose they were discussed until agreement was reached.

5.5 Results

5.5.1 Participant Characteristics

Of the 18 participants who took part in the study, two thirds were women (*n* = 12), and the average age was 27 years (SD = 8.40; Median: 25 years). Eight participants worked or studied in fields allied to health or genetics. Self-reported heights and weights resulted in a mean BMI (kg/m^2) of 23.1 (SD = 3.9), with one person classified as underweight, three as overweight, one obese, and the remainder as healthy weight. Eight participants had at least one overweight or obese parent.

5.5.2 FTO status and recall of the test result

All participants chose to know their result and receive it by email, and all came to the interview. All but one remembered their test result correctly, and all were able to give a correct explanation of the meaning of the result. All said that they would remember their test

result in the future. Four participants had the TT genotype (22%), 10 AT (56%) and four AA (22%); approximating to the population distribution in larger studies.

5.5.3 Interviews

Interviews lasted on average 27 min (range: 20-38 min). Every effort was made to create a relaxed atmosphere for participants by establishing rapport and offering refreshments on arrival. All participants seemed in a positive mood and keen to share their thoughts on their experience.

5.5.4 Themes

Eleven themes were extracted from the data which are described in detail below. Quotes were included where appropriate to illustrate findings. Participant number and weight status are included in brackets to add some context. Themes are presented in descending order of prevalence.

Theme 1: Curiosity as driver for participation

Without exception, participants cited *'curiosity*' as the main reason for participation. The prospect of '*uncovering something about myself that I don't already know'* (P4, TT, normal weight) that would otherwise be *'completely hidden'* was seen as intriguing and exciting. There was a perception that '*most people probably go through their life and will never know anything about their genetic make-up.'* (P16, AT, underweight), and as such, learning about one's *FTO* genotype was perceived as a unique opportunity.

Theme 2: Weight is a salient issue

Weight regulation was seen as an important personal issue for most participants. For some, this was because they felt they only maintained weight by *'being fairly controlled about what we eat' (*P4, TT, normal weight); for others, because of on-going difficulties with weight control: 'I have *struggled so much with my weight probably since about the age of eight […]'* (P11, AA, overweight). Regardless of current weight status, the desire to know whether maintaining body weight was a result of '*self-control or because of genes'* (P4, TT, normal weight) was a strong motivator for participation.

Theme 3: No consideration of potential negative outcomes before taking the test

Despite the reported importance of body weight regulation for most participants, none considered the potential implications of their genetic test result beforehand. For example, one participant reported that *'it was only when you sent me the email invitation for the interview to talk about the implications then I started to think: oh wow, are there implications?'* (P16, AT, underweight). Similarly, another said 'I *kind of just did it, I didn't think too much about the outcome of it, or how it would affect me really'* (P12, AT, normal weight).

Participants frequently explained their lack of concern about negative effects retrospectively by 'ranking' the severity of obesity relative to other conditions. The ultimate decision to get tested appeared to be a function of perceived susceptibility to and severity of obesity. For example, one participant explained that '*if you'd tell me you'd test me for an Alzheimer's gene then I would say no, but for weight gain […]'* (P3, AT, normal weight), whereas another would have been more enthusiastic about genetic testing for a gene for a more 'severe' condition: *'[...] Alzheimer's or Huntington's Disease or something, then I would probably be more jumping at the chance because it would feel like more applicable to me'* (P5, TT, normal weight).

However, both appeared to use a more severe disease and perceived relevance as 'anchors' onto which to base their decision to participate.

Theme 4: Weight gain is perceived as interplay of genes and environment

Weight gain and obesity were consistently understood as due to a complex interplay of genetic and environmental factors by all participants, and not seen as caused by a single agent. Recognition of family differences in the propensity to gain weight were frequently cited as a reason for reaching the conclusion that weight gain must be governed by factors other than willpower: *'I think as someone who can eat whatever I want – at least I thought that – and didn't put any weight on, with a sister that is the complete opposite – she eats and she puts on weight – I have always been very intrigued by why that is [...]'* (P16, AT, underweight). Another woman observed that similar eating traits were displayed within the family which left her wondering about heritability of appetite *'[…] I just also see with my niece and nephew, 5 and 3, that they have these similar kinds of eating traits that we all, me, my sister and my mother have […] they are just obsessed by food […] so I have always wondered whether it was genetic or not'* (P6, AT, overweight).

Theme 5: Personal responsibility for control over food intake

Although participants acknowledged genetic differences in the propensity to gain weight, personal responsibility was perceived to be more important: *'I don't think the gene actually contributes 100% to weight gain, because it happens with food differences and normal lifestyle, you know, so that's not an excuse [...]*' (P2, TT, normal weight). The notion of controllability of weight surfaced repeatedly across all weight groups and regardless of genotype; expressed by one woman as *'whatever I am made up of, if I eat a lot and don't*

exercise then I'm gonna get fat' (P4, TT, normal weight). Weight gain and overweight appeared intertwined with beliefs about behavioural efforts and personal control, extending even to the biological forces: *'[…] I think* [having a genetic tendency to gain weight] *is not applicable to me; it is maybe there but I can override it'* (P7, AT, normal weight). Beliefs were formed by personal experience: *'[...] my experience with weight throughout my life and it's definitely, I don't blame it all on that* [genetic factors]*, a lot of it is what I did and didn't for a number of different reasons'* (P11, AA, overweight), leading to the conviction that weight management is ultimately a matter of personal control.

Theme 6: Feedback affirms private constructs of weight gain

Regardless of actual risk status, receiving genetic test feedback often affirmed private constructs of causal agents of weight gain, which was apparent in the reactions to the test result. Those who felt that they were struggling with weight, either by exerting too much or too little control, felt relieved and reassured by their test result: *'[…] although it wasn't, like AA, the strongest, I still had one risk allele and that was kind of reassuring to me in a sense because I always suspected that my kind of appetite [pause] I mean, I have always struggled to control my appetite and if I kind of had been like TT and it was completely behavioural, that would have been [pause] I would have found that quite hard to deal with in a way because you know I feel like, ok it's a combination of both, but it is in part biology and I am in a sense battling against my biology[…]'* (P6, AT, overweight). A similar view was evident in the following quote: *'[…] I still feel that I gain weight more quickly than other people do and its very reassuring to have that knowledge that I don't necessarily have that condition, that I do naturally put on weight while eating just normally, so for me that's a big reassurance to just know that I can be a healthy person if I adjust my diet to a normal standard'* (P14, AT, normal

weight). The former quote was from an overweight woman who was actively trying to lose weight and the latter from a woman with a history of anorexia nervosa (now recovered); nonetheless, the quotes were strikingly similar. Both reflected the perception of differing from the 'norm', and the desire to understand the reasons for their struggles. Receiving an AT personal result was concordant with their private constructs of weight gain, which appeared sufficient to resolve internal conflict.

Theme 7: Evidence for relief of guilt and self-blame by the test result

The relief that overweight participants felt from having a partly biological explanation for their problem was evident again when asked about the personal meaning of the result: *'[…] it would just help understand yourself really. Kind of [pause] it makes me feel better that I have AT, if I had TT I think I'd be a bit upset, because it would be like, oh my gosh I've got [pause] it's all me, it's me [pause] but as it's AT, at least it's got something to do with my genes and it's not just me being a pig'* (P17, AT, obese). In addition to the stigma stemming from perceived loss of control as the cause for overweight, this participant clearly expressed how much self-blame and guilt is attached to this perception. Similar to the previous comment by P6, this suggested that a result indicating no increased genetic risk (TT) could have led her to be negatively affected by affirming her perceived personal shortcomings.

Theme 8: No evidence for adverse or fatalistic responses

Confirmation of private assumptions was also evident in those receiving an 'AA' (higher risk) result. However, no-one expressed fatalistic reactions. Most participants responded by asserting that the contribution to weight gain is only small: *'I thought bad luck, but then I was like, oh well, it doesn't mean much'*. Another woman focused on how she was motivated by

her test result to take on the battle against her biology: '*If I'm thinking I want to go to the gym or thinking about oh yeah I'll just eat what I want this weekend and not bother, it will give me a bit of a push in the right direction to just think no actually, you know you need to be a bit careful.' (*P11, AA, overweight). Test feedback appeared thus to act as motivator and catalyst to shift attention to modifiable aspects of weight gain.

Similarly, TT (lower risk) participants were not surprised by their result because they already attributed their body composition to factors other than solely their eating behaviour. However, as one woman (P4, TT, normal weight) explained with a smile: '*This has deprived me of the chance to say, well look at me, I have it* [the gene] *and I still managed to stay lean for most of my life'*. In none of the narratives was there any sign that TT participants thought of themselves as protected from becoming overweight. This may be because they were aware that the contribution of *FTO* to weight gain is only small, or because it did not 'fit' with their preconceived beliefs about weight gain; either way, there was no evidence for complacency.

Theme 9: Evidence for a motivational effect of the result

Many participants thought that knowledge of the result would help them to maintain weight control activities in the future by alerting them to their genetic predisposition, and to *'be more careful in the future, especially when you get older and you get fatter more easily'* (P1, AA, normal weight). Participants who thought that their result would not change their behaviour in the near future justified this by explaining how they were already taking action against weight gain by eating '*already reasonably healthy and go[ing] to the gym, and I don't think it is a huge problem for me. If I was overweight, it would have a sort of bigger, you know, significance'* (P3, AT, normal weight). The themes of taking personal responsibility and being

in control of weight gain were again central to the conversation, as participants seemed compelled to justify why they felt they could disregard potential implications of the test result.

Theme 10: Inducing an overly restrictive attitude – a concern for genetic test feedback

Several participants raised a concern about inducing an 'overly restrictive' attitude to food or fuelling anorectic tendencies: *'yeah, I don't know, if someone got AT or AA they might be like, oh god, I really shouldn't eat this, or they might go a bit, a bit too far, but then you probably need to have these kinds of tendencies anyway'* (P9, AT, normal weight). However, the young woman with a history of anorexia nervosa did not confirm this fear. She explained why, in her opinion, receiving genetic test feedback would be beneficial: '[…] *because when it's kind of scientifically objective you are able to see whether that's just your genetic condition and it helps to deal with it the best way possible […] to be able to address these things and not to make it into some sort of taboo that can't be talked about'* (P14, AT, normal weight). Once again, the theme of a 'scientifically objective' result alleviating guilt, stigma and shame attached to disordered eating emerged. Confirmation of a partly biological explanation for weight problems appeared to increase, not decrease, perceptions of control by shifting the focus away from it being a personal shortcoming towards being a 'condition'. The test result was sought to remove the 'taboo' that surrounds disordered eating by permitting dialogue about it. The other participants who raised the issue of potential adverse effects noted that the risk would be minimal if accurate information about the genetics of weight gain was given alongside the genetic feedback.

Theme 11: Sharing genetic test results

There were no concerns about sharing their genetic test results with friends or family, and in many instances participants had already done so. However, opinions were split on the subject of genetic testing being part of routine healthcare, or test results being on the medical record. Concerns centred predominantly on potential discrimination by employers or insurance: *'[…] if you have to produce a medical record for insurance purposes or for a job or a high stress environment […] you might not get that job, but you might have been managing your condition your whole life and be healthier than someone who has got no disposition but is eating donuts every day'* (P16, AT, underweight). Interestingly, this participant not only acknowledged potentially negative future implications of genetic testing, but at the same time implicitly supported the assumption that awareness of genetic risk would positively influence health behaviours.

5.6 Discussion

Results from 18 interviews, carried out after respondents had received feedback on genetic susceptibility to weight gain, indicated that feedback is likely to have beneficial motivational and psychological effects with little risk of negative affect; supporting findings from Study 1 and the hypothetical study by Frosch and colleagues (2005). This suggests that, at least in this instance, hypothetical studies served as a good model to gauge outcomes of giving 'real' genetic feedback. The reported reasons for positive responses to the test result varied depending on current weight status and test result. Normal weight participants with an AT or AA result described the result as *'little warning bell'* that would help them to be more conscious of their weight and monitor weight gain in the future. Participants struggling with weight control described reassurance and relief of stigma, guilt or self-blame as benefits of

receiving the test result, which has so far received limited attention in the literature. Constructs discussed in the Health Belief Model (Rosenstock, 1974) were all evident in the interviews. There was less support for the Illness Perception Model (Leventhal, 1997) with respect to fatalistic responses or false reassurance; however none of the participants appeared to have had representations of obesity that relied exclusively on genetics, and therefore the Illness Perception Model would not strictly speaking have anticipated either fatalism or false reassurance in response to the test result.

5.6.1 Study limitations

However, this study had many limitations. As in all qualitative studies, reliability and validity of the current results have to be viewed with caution. The sample was highly selected because participants were drawn from a pool of educated individuals who had previously expressed interest in genetics and weight control and therefore, findings may not generalise beyond the sample studied here. However, the aim of the study was to explore potential benefits and problems of testing for risk of weight gain, and not to draw general conclusions. Furthermore, we tried to increase reliability by constantly comparing cases with one another, following suggestions by Glaser & Strauss, 1967. Social desirability bias cannot be excluded; although the interview questions were open-ended, some answers may have been intended to make a good impression on the interviewer. Obesity is stigmatized, and a 'moral imperative' to fight against it is prevalent (Townend, 2009; Saguy, 2005). Participants may therefore have felt compelled to exaggerate the beneficial effects of their test result. However, because they were participating out of personal interest and did not think deeply about the implications of their result beforehand, this seems likely to be a modest effect. In addition, we had no 'mismatches' between genotype and phenotype in the sample (i.e. no slim AAs or overweight

TTs), and responses may differ in these individuals which should be explored in further research. Finally, the present study focused only on responses the day after receiving the result, and the long-term effects of receiving genetic feedback need to be investigated in future research.

5.7 Conclusion

This qualitative study indicated that real genetic test feedback did not engender fatalistic or complacent responses, and most respondents reported increased motivation towards healthy lifestyles and relief of stigma and self-blame. The findings provide a strong foundation for further research to investigate the clinical utility of *FTO* feedback as part of weight control advice.

Chapter 6: Study 2b – Affective responses to genetic test feedback for obesity in a sample of overweight individuals: An Interpretative Phenomenological Analysis [6]

6.1 Background

Findings from the previous study indicate that *FTO* feedback may have positive psychological effects, especially for individuals struggling with weight control. However, there was also some indication that overweight and obese participants had been disappointed if they had received a lower risk genetic test result; but because there were no 'mismatches' between genotype and weight status (no very slim AAs or overweight/obese TTs), this emerging theme could not be further investigated. The literature on genetic test feedback has almost exclusively focused on the impact of receiving higher risk results. However, it is important to understand the impact of a 'mismatch' between the manifestation of a condition in the absence of tested genetic markers, particularly because the low predictive ability of most genetic markers for common conditions will make this scenario a common occurrence.

[6] A version of this chapter has been published in *Genes & Nutrition: Meisel, S. F., and J. Wardle. "Responses to FTO genetic test feedback for obesity in a sample of overweight adults: a qualitative analysis." Genes & nutrition 9.1 (2014): 1-4.*

6.2 Study aims and contribution to the literature

Therefore, this study explored the impact of receiving *FTO* feedback in a small sample of overweight/obese individuals to explore the process by which individuals make sense of their genetic test result. Using a sample where some individuals would be expected to have the lower risk genotype (TT) despite being overweight (being 'discordant' for gene status and condition) also allowed me to explore how this discrepancy is resolved cognitively. This study will contribute to the understanding of how affected individuals 'make sense' of genetic risk and offer insights into coping strategies used to come to terms with an unanticipated genetic test result.

6.3 Methods and Procedure

6.3.1 Participants

Participants were seven volunteers drawn from the 'Big Panel', which was also used in the vignette study (Study 1, p. 99). An invitation email was sent to the 306 panel members who had taken part in the vignette study and had expressed interest in participating in other studies. Sixty-eight individuals (22%) were interested in the current study and we selected the first seven female respondents because the analysis method used (Interpretative Phenomenological Analysis, IPA) requires the sample to be small and homogenous.

6.3.2 Procedure

The invitation email included the information materials used in Study 2 and 3 (Appendix 3). Briefly, the information sheet explained that feedback would be given only for *FTO*, that associations with weight gain are small and that DNA samples would be destroyed on

completion of the study. Participants were mailed a saliva collection kit, the *FTO* information leaflet (Appendix 1), a consent form, instructions on how to collect saliva, a pre-paid return envelope, and a telephone contact number. Ethical approval for the study was granted by the UCL Research Ethics Committee for non-NHS research (ID Number 2471/001).

6.3.3 DNA analysis and genetic test feedback

DNA was extracted from saliva as previously described (Wardle et al., 2008) and *FTO rs9939609* was genotyped using TaqMan at the Institute of Metabolic Sciences, Cambridge, UK. Participants were notified by email once their result was available, and could choose to receive it by providing a date and time for a telephone interview or decline to receive it. We included this step to ensure that participants still wanted to receive their genetic information (which they all did). Result letters were attached to an email, so participants could choose when to access them and were sent one day before the interview to allow some time for reflection but to be recent enough to be memorable.

6.3.4 Interviews

I conducted semi-structured telephone interviews which were recorded with the participant's permission. We chose telephone over face-to-face interviews because we wanted to avoid participants feeling self-conscious about their weight, or the researcher's appearance influencing their responses; although we recognised that some contextual information was lost by being unable to see facial expressions and body language (Holt, 2010). The interview guide included open-ended questions adapted from Study 2a (Table 5.1, p. 122), broadly covering thoughts and feelings before, during and after genetic testing, causal attributions of weight gain, and feelings of being 'at risk'. Care was taken to let participants tell their 'story'

while still steering the conversation towards the main points of interest using prompts and follow-up questions. The interview was concluded when the conversation reached a natural end and further probing did not reveal new insights.

6.4 Data analysis

Interviews were analysed using Interpretative Phenomenological Analysis (IPA). IPA focuses on exploring in detail the 'lived experience' of individuals in all its complexity and is therefore particularly suited for the use in studies of novel aspects of the human experience (Smith, 2009; Chapman & Smith, 2002). For this study, we felt that IPA's emphasis on the *process* by which individuals understand their experience of genetic testing fitted well with the aims of the study.

Transcripts were read and reread to extract broader topics, which were then further refined into themes following an iterative process. Frequent discussions among the research team ensured high agreement on extracted themes and avoided researcher bias. All transcripts were coded by a researcher not involved in the study to ensure reliability. Inter-rater agreement was high, and any minor discrepancies were discussed until agreement was reached.

6.5 Results

6.5.1 Participant characteristics

Table 6.1 shows demographic characteristics for each participant. Participants were white British or European women, all of whom were currently overweight or obese. The age ranged

from 34 to 54 years (mean age = 45, median age = 44), and BMIs from 25-39 (mean BMI = 32.6 kg/m^2, median BMI = 34.6 kg/m^2).

Table 6.1Participant characteristics

Participant	*FTO* status	Age (years)	BMI	Weight Satisfaction	Education	Self-rated understanding of genetics
P1	AT	54	34.6	Very dissatisfied	Postgraduate	Higher than other people
P2	AT	53	26.7	Very dissatisfied	Postgraduate	About the same as other people
P3	TT	37	28.7	Very dissatisfied	Postgraduate	Much higher than other people
P4	AA	34	25.4	Very dissatisfied	Degree	Higher than other people
P5	AT	46	38.6	Very dissatisfied	Degree	Higher than other people
P6	TT	43	36.7	Very dissatisfied	A-level	About the same as other people
P7	TT	45	37.4	Very dissatisfied	Degree	About the same as other people

6.5.2 FTO status and recall of the test result

One participant was homozygous for the higher risk A variant (AA), three were heterozygous (AT), and three were homozygous for the lower risk variant (TT). All participants correctly recalled their test result and could explain its meaning in their own words.

6.5.3 Interview characteristics

Interviews lasted on average 33 min (Range: 26-42 min). Efforts were made to establish rapport, so that participants felt comfortable enough to talk openly. All of them seemed keen to share their experience and gave elaborate answers without much prompting.

6.5.4 Themes

Five overarching themes were extracted from the data and are described in detail below. Illustrative quotes are used throughout the text where appropriate and genotype is provided in brackets to add context. Themes described were common to all interviews.

Theme 1: In search of an explanation

All participants took part to help understand their condition; as one participant put it*'[…] to find another piece in the jigsaw*'. The quest to find out *'whether there are genetic reasons why I find it extremely difficult to lose weight or why I am larger than other people, is there a reason why, other than the fact that I do love food?' (P7, TT)* was described as a *'life-long curiosity*'. Feeling different from people who did not struggle with their weight despite apparent similarities in behaviour, and finding explanations for the difference was the main driver of participation. One woman explained that she was interested *'[...] from a selfish point of view. I do understand that having these genes, that's not the whole picture, there's a lot of other stuff going on, but I am still interested to find out whether that might be, you know, a contributing factor to why I was struggling.' (P3, TT).*

Theme 2: Early origins of weight control problems

The descriptions participants used to for their experiences with body weight regulation revealed the difficult emotions that underlie this issue. For all participants, weight control had

been a *'continuous battle'* since childhood, many recalling that '[...] *even from being quite young I've always been on some diet or another' (P2, AT).* Weight gain was gradual yet continuous. The trajectory described by this woman is not unusual: '*I was slim up to the age of about 10 and then I was a chubby kid until I was about 14 and then I slimmed down a bit. Well, I've never been skinny and then weight started to come on again after I got married, which is 21 years ago, and even more so with childbirth.' (P7, TT).* All had tried to lose weight many times in the past with varying success. However, because they could not prevent weight regain, they were left *'defeated*'. *'I just think, what's the point now, you have done everything under the sun [...]' (P6, TT).* Alternatively, they tried to *'make peace'* with their bodies by adjusting their body image, which proved to be a struggle in itself, *'because it's something that can be difficult to accept' (P7, TT).*

Theme 3: Guilt and stigma

Regardless of their test result, many participants were quick to note that they never intended to use it an as '*excuse'* for their weight status; perhaps reflecting acceptance of broader societal attitudes towards obesity as a personal shortcoming for which the individual is to blame. Instead, having a genetic *'explanation'* helped confirm the perception that forces beyond personal responsibility contributed to their difficulties with healthy body weight maintenance: '*I understand that genetics and the things that we are likely to choose as a result of our genes or how we are likely to feel means that we can't always help the fact that we eat what we eat, if that makes sense' (P4, AA).*

Knowledge of the underlying genetics was seen as able to alleviate some of the guilt and stigma associated with overweight. In this context, some participants also mentioned that

there might be value in popularizing the message that genetics is a contributor to overweight, because *'it could make some people more understanding, it would perhaps make the medical profession more understanding*' (P7, *TT*). Considering these expectations, surprisingly little thought was given to the possibility of not having the higher risk variant of *FTO* before testing and no participant had considered the potential impact of this possibility.

Theme 4: Emotional reactions

Participants described feeling brief, but intense, emotions upon learning their *FTO* gene status. All of them assumed they would be a carrier of the higher risk variant. Those with one or two higher risk alleles (*AA* or *AT)* often felt *'pleased with the result'*, although it came as *'no surprise, because it just confirmed what I felt anyway'* (*P4, AA*). One participants described her *AT* result as *'normal'* genotype and explained that she was *'living that result' (P1, AT)*; perhaps reflecting the understanding that overweight is caused by a combination of genes and environment.

A 'lower risk' status was unexpected in all cases and resulted in disappointment. However, participants described rallying quickly, as in this example: *'I felt disappointed. I suppose deep down you hope there is a reason for being overweight but for me there isn't apart from I must be eating too much and not exercising enough. So I suppose in that respect it was a bit of a disappointment because [pause] I don't know [pause] maybe if there was a reason you are more likely to say, oh well, it's not totally all my fault. But, I'm glad I know. Yeah. You know it's not that, so, okay, what is it? (P7, TT)*. Once again, the desire for an explanation that absolves individuals from some of the responsibility for their weight status became apparent. However, those getting a TT result were not left hopeless, but reported that initial emotional reactions

were short-lived, as this participant explained: *'I just thought, 'Oh well, I haven't got the fat gene, and I guess carried on with life' (P6, TT).*

For participants getting a lower risk result cognitive defence mechanisms appeared to be activated which reduced dissonance between the test result (which threatened the belief in genes as a source of external influence) and the prior expectation. All TT participants spontaneously offered alternative explanations for causes of weight gain, diminishing the importance of genes, and drawing instead on environmental and psychological explanations: *'It's not all down to genetics because it's down to the environment, the way you have been brought up and all that that has an influence, I think, on you, the choices that you make and stuff like that, you know' (P6, TT).* Similarly this participant said: '*I think until obesity is tackled from the mind, I'm not sure that it will ever change' (P3, TT).*

One pointed out that the contribution of *FTO* is only small and that there may be other genes that are the cause of their weight gain: '*And it doesn't make a lot of difference having it. Because if you have got it you are 3 kilos, 7.3 pound, yeah, no, it's a very small amount […]. I still think that there's something in the genes, but not in these particular ones, which are simply related to body build […]' (P7, TT).*

One participant also considered potential advantages from not having the 'higher risk' variant, demonstrating evidence for positive active coping: *'[…] in a way I should be pleased because then, you know, there's less things that stop you from losing weight because if I did have the gene, maybe it's harder to lose weight.' (P6, TT)*.

Although AA and AT participants also held multifaceted beliefs about the causes of obesity, they were only shared once prompted. Furthermore, TT participants showed tendencies to draw distinctions between themselves 'as a person' and their genes, as if to distance themselves, for example: *'I felt, you know, this is my issue. It's not my genes; it's to do with what's going on in my head' (P3, TT).* These observations suggest that reflexive assertion of alternative explanations for obesity helped TT individuals to accept their test result without having to adjust their core beliefs, thereby resolving cognitive dissonance and maintaining a coherent, integrated sense of self.

Theme 5: Anticipated behavioural reactions

Awareness of *FTO* status was considered beneficial for behaviour by most participants. For example, one woman thought it would help maintain control over eating: '*I know that I am likely to want more food, whether or not I really need more. So I suppose it's helped, it's definitely helped in the way I will decide what to do when I make food choices so it will definitely make a difference.' (P4, AA)*. Another explained how it would help motivate healthier lifestyle choices: *'you know what - I think I have already. Because I am thinking about it more now, I am consciously making an effort to make better choices' (P2, AT)*. It appeared that participants intended to use their result as a reminder to make an effort to make healthy choices, either because their biology was different (AA and AT participants), or, because it '*it is really just down to me*' (TT participants); again demonstrating that participants make their result 'fit' with their beliefs about weight control.

6.6 Discussion

This qualitative study allowed for an in-depth exploration of emotional reactions to genetic test feedback for obesity risk in a sample of overweight and obese individuals. In line with findings from Studies 1 and 2a, and other hypothetical and clinical studies (Conradt et al., 2009, Harvey-Berino et al., 2003), the results suggested that genetic test feedback for obesity risk may have beneficial psychological effects for overweight and obese individuals beyond 'objective' clinical utility.

6.6.1 Study limitations

However, the current study has many limitations. Consistent with the methodology and aims of qualitative research, the sample was small and highly selected. Findings cannot therefore be generalised to the wider population; yielding findings low in validity and reliability. All participants in this study had high levels of weight dissatisfaction, which may have influenced their responses. However, weight dissatisfaction is very high in the general population, particularly among women (Rodin, Silberstein, & Striegel-Moore, 1984) and therefore, may merely be a reflection of societal attitudes towards bodies that do not confirm to the 'thin ideal'. Reactions may thus be less pronounced in men, but because the current sample only included women, this could not be investigated further. Like in Study 2a, social desirability bias cannot be excluded and participants may have overstated the benefits of their respective results. However, these effects would have been mild, because participants still expressed their disappointment with unexpected *FTO* results. Furthermore, using telephone interviews was likely to diminish social desirability bias because they commonly make the participant more comfortable (interviews are carried out in the participant's familiar environment)

(Oppendakker, 2006). Lastly, qualitative methods always carry the risk of the researchers' personal background shading the research findings (Brocki & Wearden, 2006). We tried to minimise this by meeting frequently to discuss the interviews, having a third researcher code the interviews, and by choosing an analysis method that acknowledges the researchers' role in the analysis process.

6.7 Conclusion

In this sample, genetic test feedback for obesity risk had personal value beyond 'objective' clinical utility by potentially providing an 'explanation' for their weight control problems and relieving some stigma and self-blame. However, the consequence was that a lower risk result is disappointing, although defensive cognitive processes appeared to be activated that limited any lasting adverse psychological effects. This is the first study to describe that accepting a negative rather than a positive genetic test result was a personal challenge, which is a reversal of common findings. Adverse effects on weight control intentions or self-control were not reported. These findings offer interesting hypotheses for further research and may be considered in clinical practice.

Chapter 7: Study 3 – The association of *FTO* SNP rs9939609 with weight gain in the first year of university

7.1 Background

As discussed in Chapter 1, the genetic susceptibility model proposes that genetic differences in appetitive traits leave some individuals more prone to weight gain than others in the current environment. *FTO* is one gene which has unambiguously been shown to be associated with obesity susceptibility. Chapter 2 gave evidence that the start of university can be considered as a 'high-risk' period for unhealthy weight gain, because of high environmental pressures to engage in obesity-promoting behaviours and low motivation to resist these forces.

If the genetic susceptibility model is valid, moving into this environment would be expected to have differential effects on individuals depending on their genotype. The established effects of *FTO* make it a good model for testing this hypothesis further. However, no study to date has investigated the effect of *FTO* status on weight gain in the first year of university.

7.2 Study aims and contribution to the literature

The aim of the present study was to investigate the association between *FTO* and weight gain over a one-year period in a large sample of young adults starting university. I hypothesised that individuals carrying at least one higher risk allele (AT, AA) would gain more weight during

the study period than TT individuals because of their higher genetic vulnerability to weight gain when environmental pressures are high.

Because some weight fluctuation within individuals is common, small changes in weight might not be meaningful. The weight loss literature considers a 5% weight loss as sufficient to mitigate some of the health problems associated with obesity (Blackburn, 1995;Goldstein, 1992). Conversely, a 5% weight gain should raise the risk of many conditions related to obesity. Therefore, I supplemented analyses investigating mean weight change with an analysis that explored the association of *FTO* status with weight gain of 5% or more over the course of the year.

The study contributes to the literature by being the first to focus on the effects of *FTO* young adults exposed to a high-risk environment for weight gain. Identifying individuals at high risk for weight gain early might ultimately support the development of targeted strategies for obesity prevention and treatment; particularly for those at the highest risk.

7.3 Methods and Procedure

7.3.1 Participants

In total, 1518 first-year students from UCL participated in the study. They were recruited at the beginning of three consecutive academic years (2010-2012); follow-up anthropometric data was collected in the last week of May of each respective academic year. Figure 7.1 includes a flowchart of participants through the study. Analyses included participants from all three study waves.

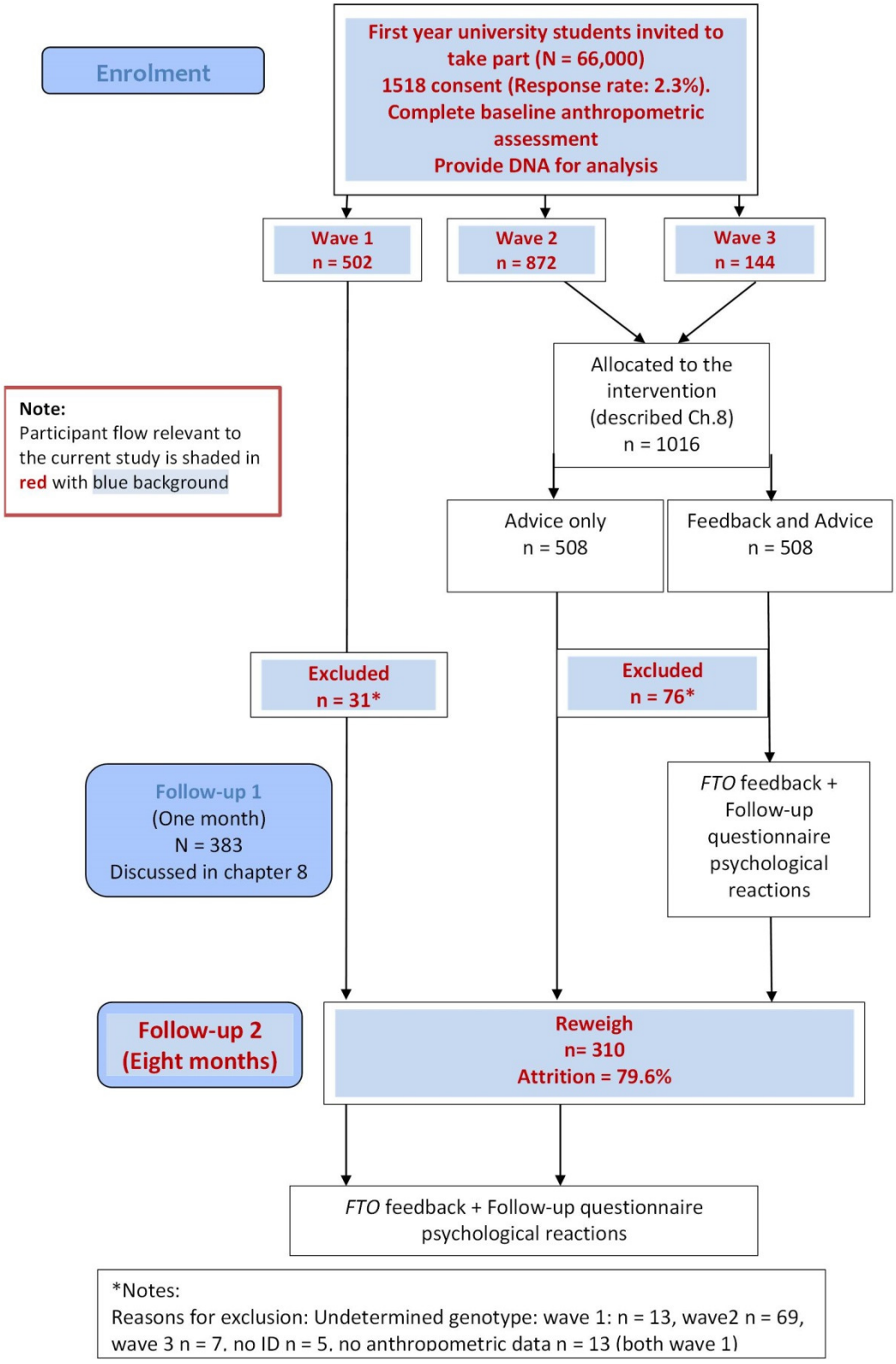
Inclusion and exclusion criteria

We included all interested individuals within the university aged between 18 and 30 years who were able to give informed consent. Although it would have been preferable to restrict the age range to age 25 because older students are unlikely to only have just started university, in practice it was too difficult to distinguish between participants aged 18 to 25 and those older. Instead, we opted to dichotomize age into participants aged 18-20 and those older, as the younger age group should consist predominantly of first-year students.

7.3.1.1 *Recruitment and Consent*

Potential participants were invited by email, poster advertisements and by setting up a stall with a 'collection-station' on campus, in halls of residence and at the 'Welcome Fayre', inviting students to take part in a study on genetic influences on weight gain. Recruitment materials are included in Appendix 5. Interested participants were invited to come to the 'collection station' during the second week of term. When they arrived at the station, a researcher explained the project in more detail. An information sheet was given out and participants had the opportunity to ask questions. Written consent was obtained once all questions were answered. Ethical approval for the study was granted by the UCL ethics committee for non-NHS research (study no. 2471/002). A copy of the approval letter is included in Appendix 3.

Figure 7.1 Flowchart of study procedures



7.3.2 Measures

7.3.2.1 *Demographics*

Demographic information collected included age and gender.

7.3.2.2 *Anthropometric data*

Anthropometric data were collected upon study enrolment and at 8-month follow-up. Follow-up measures were taken in the same location as at baseline to minimise the risk of measurement error. Participants were asked to remove shoes, socks and heavy items, but stay otherwise fully clothed. Height was measured using the Leicester Height Measure (Marsden Group, UK). They were then invited to step on the TANITA scale which measured weight and body fat using electrical impedance. Electrical impedance usually compares well to other measures of body composition such as whole body magnetic resonance imaging and dual X-ray absorptiometry (Beeson et al., 2010). Antibacterial gel was applied to the footplate area to minimise risk of infection and facilitate contact. BMI was calculated from weight and height data obtained. Participants could opt to receive a printout of the results together with an explanation of the body composition results from the research team or not. All participants opted to receive their printout and explanation of the body composition results.

7.3.2.3 *DNA Collection*

Participants were asked to give a saliva sample for DNA collection by placing some sugar on their tongue to stimulate saliva flow and then spitting into a plastic tube to generate 1.5 -2 ml of saliva. Although it would have been preferable if participants had refrained from eating,

drinking (other than water), smoking or brushing their teeth in the hour beforehand, the practicalities of data collection (at a busy welcome fayre and in student halls around dinner time) made it impossible to adhere to this restriction. However, staff from the Institute of Metabolic Sciences, Cambridge, where the data was analysed, assured that analysis would still be possible (if slightly unpleasant), so we decided to drop them. Samples were coded with a unique identifier number immediately after collection so that they were anonymous but could be linked to the anthropometric data.

7.4 Analyses

7.4.1 DNA analysis

DNA was isolated from saliva and analysed at The Institute of Metabolic Science, Cambridge UK, under leadership of Professor Sir Steve O'Rahilly (I had no role in it). DNA was analysed using TaqMan and an automatized extraction system. The Taq Man is an assay for identifying single nucleotide polymorphisms (SNPs) after DNA is amplified with a polymerase chain reaction (PCR). TaqMan molecules are usually fluorophore and bind to the site of interest to make it visible. The polymorphism of interest was a base substitution from A to T at SNP rs9939609. For PCR, the DNA double-helix was denatured (split open) with heat, and enzymatic complementary DNA fragments (primers) were attached to the target regions to replicate DNA. The newly generated DNA constituted a template for further replication, causing a chain reaction, thereby causing the DNA to replicate exponentially. Protocols for saliva isolation and extraction are shown in Appendix 7.

7.4.2 Statistical analyses

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) version 20.0. Significance levels for all analyses were set at $\alpha = 0.05$.

A power calculation was carried out *a priori* using *GPower* (version 3.1) which showed that a sample size of 1302 participants would be required to detect a small effect (d = 0.10) of *FTO* on weight gain with 95.0% power.

Descriptive information was based on frequency tables and cross-tabulation. Differences between participants in each wave were assessed with one-way ANOVAs for continuous variables and chi-square tests for categorical outcomes. All data were tested for assumptions of normality (Skewness, Kurtosis, Levene's Test) and results are only reported if these were violated. For Skewness and Kurtosis, values between -1 and + 1 were acceptable.

FTO risk status was dichotomized into higher (AT/AA) and lower risk (TT) for the current analyses. Inspection of baseline means showed that mean BMI and weight were more similar in AT and AA individuals and thus grouping higher risk variants together was appropriate.

Differences between participants who did and did not return for follow-up weighing were assessed with chi-square tests for categorical variables and t-tests for continuous variables.

Associations of *FTO* genotype status with baseline BMI, baseline weight, follow-up BMI and follow-up weight, respectively, were determined in identical manner: For all models, analyses were run at first only including *FTO* status. Thereafter, the models were run including age and gender as covariates. Analyses with weight as the outcome variable included height as

covariate in all analyses. Thereafter, analyses were repeated, including interactions between respective covariate and *FTO* status. For the purpose of all analyses, age was dichotomized into 'younger' (aged 18-20) and 'older' (aged 21 and over). Analyses using follow-up data also adjusted for trial participation because some participants were later enrolled in a trial (details of which are discussed in Chapter 8).

The association of *FTO* genotype with body weight change over the year was assessed using linear regression models, adjusting for baseline values. As before, the first model included only *FTO* status and baseline weight and height. Analyses were repeated with age, gender and trial participation as covariates, investigating only main effects. This was followed by an analysis including the *FTO**age, interaction because the strength of the association of FTO and BMI has been shown to vary by age (Hardy et al., 2010) . As at baseline, age was dichotomized into 'younger' (aged 18-20 years) and 'older' (aged 21-30 years).

Weight change (absolute, in kg, and relative, in per cent) was calculated for each participant. Participants who gained 5% of their starting weight or more were classified as 'gainers'; those who lost weight, stayed the same or gained below the 5% threshold were classified as 'non-gainers'. Predictors of a 5% weight gain over the course of the year were investigated using binary logistic regression analyses. At first, only *FTO* status was included in the model. Analyses were repeated adjusting for age (dichotomized), gender and trial participation. Thereafter, the model was re-run, including the *FTO**age interaction.

Although several methods exist to account for missing data, all analyses were conducted using completers only; accepting a significant loss of power for analyses using follow-up data.

Replacing missing values with mean scores (either overall mean or *FTO* group mean) or by using regression substitution would have resulted in imputing nearly 80% of the outcome data, which would almost certainly have yielded inaccurate results. Similarly, using intention-to-treat design or last-observation-carried-forward would have been problematic because we had only baseline values available; as weight change was the main outcome of interest, this would have distorted the data.

I conducted a sensitivity analysis, including only wave 1 participants who did not receive any weight-related information to exclude potential effects of trial participation on BMI change, weight change and 5% weight gain. Analyses were identical to those described above.

7.5 Results

7.5.1 Participant characteristics

Table 7.1 displays participant characteristics of the final sample by wave. In total, 1518 participants took part in the study. 107 participants (7.0%) had to be excluded for the following reasons: Genotype could not be determined (5.8%, n = 89), missing anthropometric data (1.4%, n = 16) and no assigned ID so genotype data could not be matched to anthropometric data (0.03%, n = 5). The final sample consisted of 1411 participants at baseline. However, only 21.9% of participants (n = 310) provided follow-up anthropometric data.

There were significantly fewer males in wave 1 and wave 3 than in wave 2 (χ^2 (2) = 24.99, p < 0.001). Consequently, height differed modestly, but significantly between all three waves at baseline, with participants in wave 3 being shortest, followed by participants in wave 1 and

those in wave 2 being tallest (F (2, 1408) = 19.15, p <0.001). Although baseline weight differed between waves 2 and 3, with participants in wave 3 being lighter (F (2, 1408) = 8.61, p <0.001) than those in waves 1 and 2, there were no significant differences in BMI at baseline (BL) or follow-up (FU) between waves (F_{BMIBL} (2, 1408) = 0.47, 0.621; F_{BMIFU} (2, 305) = 2.87, p = 0.058). There was also no significant difference between waves in the proportion of individuals who gained 5% of body weight or more (χ^2 (2) = 1.70, p = 0.427). There were no significant differences in either mean age (F (2, 1408) = 0.96, p = 0.496) or proportion of participants aged 18-20 and those older (χ^2 (2) = 2.53, p = 0.282). Differences in *FTO* genotype distribution between waves was also not significant (χ^2 (2) = 8.11, p = 0.088) and *FTO* was in Hardy-Weinberg equilibrium, (χ^2 (2) = 0.54, p = 0.462.

Table 7.1 Participant characteristics

	Wave 1		Wave 2		Wave 3		χ^2/F	Sig
N baseline = 1411 % (n)	33.9	(479)	56.5	(797)	9.6	(135)		
N follow-up = 310 % (n)	21.1	(101)	22.5	(179)	22.2	(30)	0.33	0.846
Height at baseline (m), mean (SD)	1.69[a]	(0.09)	1.71[b]	(0.09)	1.66[c]	(0.09)	19.15	<0.001
Height at follow-up (m), mean (SD)	1.70	(0.09)	1.71	(0.09)	1.68	(0.09)	1.10	0.334
Weight at baseline (kg), mean (SD)	63.9[a]	(11.9)	65.0[a, b]	(12.0)	60.4[c]	(10.9)	8.61	<0.001
Weight at follow-up (kg), mean (SD)	64.6	(12.9)	63.3	(11.0)	63.4	(10.1)	0.44	0.644
BMI at baseline, mean (SD)	22.0	(3.0)	21.9	(2.8)	21.7	(3.1)	0.47	0.621
Normal % (n)	84.6	(405)	87.1	(694)	87.4	(118)	1.77	0.411
Overweight/obese % (n)	15.4	(74)	12.9	(103)	12.6	(17)		
BMI at follow-up mean (SD)	22.2	(3.4)	21.4	(2.5)	22.2	(2.7)	2.87	0.058
Normal % (n)	85.1	(86)	93.8	(166)	80.0	(24)	8.45	0.015
Overweight/obese % (n)	14.9	(15)	7.3	(13)	20.0	(6)		
Gender male, % (n)	44.7	(214)	54.3	(433)	34.1	(46)	24.99	<0.001
Age in years, mean (SD)	20.3	(2.3)	20.4	(2.5)	20.6	(2.6)	0.70	0.496
Age 18-20 % (n)	63.5	(304)	63.1	(503)	56.3	(76)	2.53	0.282
Age 21-30 % (n)	36.5	(175)	36.9	(294)	43.7	(59)		
***FTO* status % (n)**								
TT	38.4	(184)	43.4	(346)	51.1	(69)	8.11	0.088
AT	47.2	(226)	44.2	(352)	39.3	(53)		
AA	14.4	(69)	12.4	(99)	9.6	(13)		
5 % Weight gain % (n)	21.8	(22)	16.4	(29)	13.3	(4)	1.70	0.427

Note: Means that do not share superscripts differ by p <0.05.

7.5.2 Baseline associations of FTO status with BMI and body weight

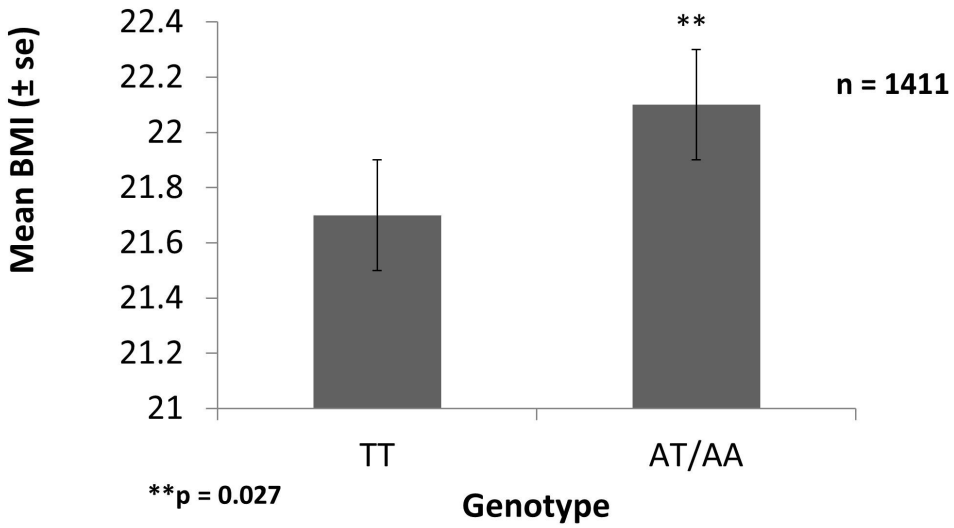
The majority of participants (87.3%) had a BMI in the 'normal' range, with a mean of 21.96 kg/m^2 (SD = 2.95); only 13.7% (n = 194) of participants were classified as overweight/obese. Table 7.2 shows mean BMIs by *FTO* genotype and results from the ANCOVAs, including age and gender as covariates. Although the effect was modest, as shown in Figure 7.2, the association of *FTO* genotype status with baseline BMI was significant, with AT/AA participants having a higher BMI than TT participants (F (1, 1409) = 4.89, p = 0.027). This association remained significant when age and gender were added as covariates, p = 0.017. Main effects of age and gender were also significant, with BMIs of older participants and those of men being higher than those of younger ones (F (1, 1406) = 30.37, p < 0.001) and those of women (F (1, 1406) = 100.12, p < 0.001). However, the interaction between *FTO* and age revealed no significant effect; suggesting that the effect of *FTO* was similar for both age groups (F (1, 1405) = 0.071, p = 0.789).

Table 7.2 ANCOVA results for associations of *FTO* status with baseline BMI and body weight

Outcome	***FTO* status**				
	mean ±sd TT	mean ±sd AT/AA	F (df, error)	Sig	Cohen's d
Baseline BMI	21.7 (2.8)	22.1 (2.9)	5.72 (1, 1405)	0.017	-0.14
Baseline weight	63.2 (11.6)	65.0 (12.1)	6.55 (1, 1405)	0.011	-0.15

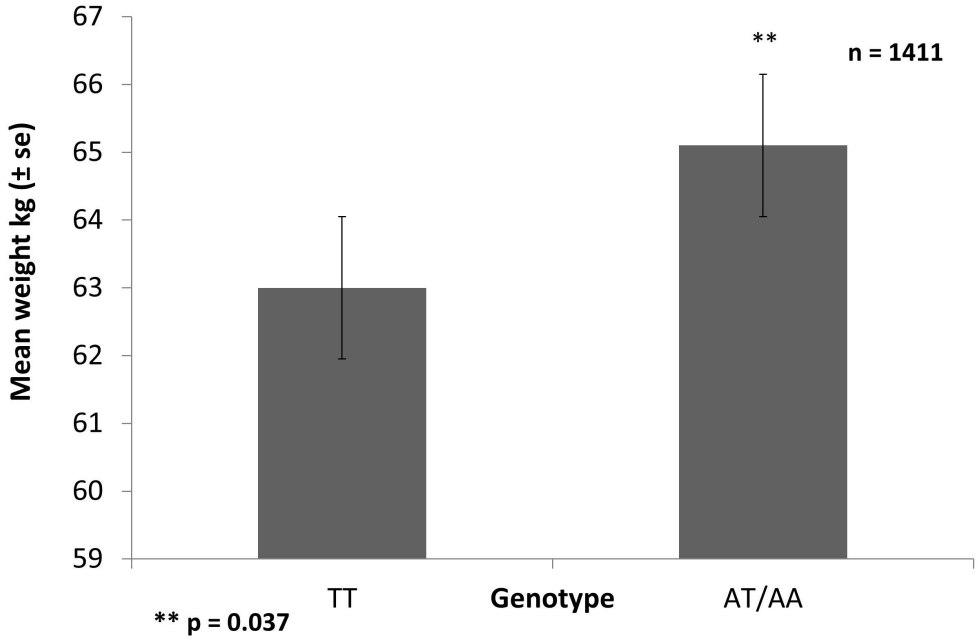
Note: Results are adjusted for age and gender

Figure 7.2 Mean differences in baseline BMI by *FTO* genotype



Mean weight of participants was 64.22 kg (SD = 11.98) and height was 1.70 m (SD = 0.09). Table 7.2 shows mean weights by genotype and results from the ANCOVAs, adjusted for age, gender and height. Consistent with *FTO* and BMI association, the association of *FTO* status and body weight was also significant, with AT/AA participants being heavier than TT participants (F (1, 1408) = 4.26, p = 0.039) in the model adjusting only for height (Figure 7.3). This difference remained significant once age and gender were added (p = 0.011). However, as before, the *FTO*age* interaction were not significant (F (1, 1404) = 0.115, p = 0.734).

Figure 7.3 Mean differences in baseline body weight by *FTO* genotype



7.5.3 Follow-up differences in body weight and BMI by genotype

Attrition was very high, with nearly 80% of the sample not returning for follow-up weighing. In total, only 310 participants provided follow-up anthropometric data. The poor follow-up may have been in part due to delays in DNA analysis which caused subsequent delays in return of genetic test results, and in part due to the overall timing of follow-up being scheduled at the end of the academic year where students also have exams, or have already returned home.

Table 7.3 shows differences between participants who did and did not return for follow-up weighing. Notably, participants who returned had a significantly lower BMI at baseline ($t(1409) = 2.33$, $p = 0.020$) and were less likely to be overweight or obese (χ^2 (1) = 5.55, p = 0.018) than those who did not return, but there were no significant differences in other variables. Although the range of weight change varied widely, mean body weight changes over the year were modest, Δ weight = 0.54 kg, SD = 3.36, range: -12.60 kg to 14.40 kg). Body weight remained stable in only a small number of participants (2.9%, n = 9); over half of the participants returning for follow-up gained weight (51.3%, n = 159) and slightly fewer lost weight (45.8%, n = 142).

FTO was not associated with follow-up BMI in cross-sectional analyses ($F(1, 308) = 0.33$, $p = 0.566$), and this remained unchanged in multivariate analyses ($F(1, 306) = 0.61$, $p = 0.435$). Similarly, *FTO* was not associated with body weight at follow-up ($F(1, 307) = 0.24$, $p = 0.618$), and adding covariates had no effect ($F(1, 305) = 0.91$, $p = 0.339$). Younger age and male gender were significantly associated with follow-up BMI ($F_{age}(1, 306) = 6.64$, $p = 0.010$; $F_{gender}(1, 306) = 21.66$, $p < 0.001$) and body weight ($F_{age}(1, 305) = 7.24$, $p = 0.008$; $F_{gender}(1, 305) = 20.75$, $p < 0.001$). The interaction between *FTO* and age was not significant.

Table 7.3 Baseline differences between participants who returned and did not return for follow-up weighing

	Follow-up Weighing n = 310	No follow-up Weighing n = 1101	χ^2/t	Sig
Height at baseline (m), mean (SD)	1.70 (0.09)	1.70 (0.09)	- 0.21	0.813
Height at follow-up (m,) mean (SD)	1.70 (0.09)	--- ---		
Weight at baseline (kg), mean (SD)	63.2 (11.3)	64.4 (12.1)	1.62	0.105
Weight at follow-up (kg), mean (SD)	63.7 (11.6)	-- --		
BMI at baseline, mean (SD)	21.6 (2.8)	22.0 (3.0)	2.33	0.020
Normal % (n)	90.3 (280)	85.1 (937)	5.55	0.019
Overweight/obese % (n)	9.7 (30)	14.9 (164)		
BMI at follow-up, mean (SD)	21.9 (2.9)	-- --		
Normal % (n)	89.0 (276)	-- --		
Overweight/obese % (n)	11.0 (34)	-- --		
Gender male % (n)	47.7 (148)	49.5 (545)	0.29	0.584
Age in years, mean (SD)	20.3 (2.6)	20.4 (2.5)	0.71	0.475
Age 18-20 % (n)	63.9 (198)	62.2 (685)	0.28	0.595
Age 21-30 % (n)	36.1 (112)	37.8 (416)		
***FTO* status % (n)**				
TT	42.9 (133)	42.3 (466)	0.04	0.978
AT	44.2 (137)	44.9 (494)		
AA	12.9 (40)	12.8 (141)		

Table **7.4** shows the complete results for predictors of weight change over the year. Baseline weight was highly predictive of follow-up weight (OR = 2.50, 95%CI = 2.39-2.62, $p < 0.001$), and this first linear regression model, including baseline weight, height and *FTO* status, accounted for 95.8% of the variance in weight change ($R^2 = 0.919$, $F(3, 306) = 1151.72$, $p < 0.001$). However, *FTO* status was not a significant predictor of weight change; neither in the model including only *FTO*, baseline weight and height (OR = 1.01, 95%CI = 0.48-2.14, p = 0.557), nor

once age, gender and trial status were added (OR = 1.01, 95% CI = 0.47-2.16, p = 0.577) Adding these variables improved the predictive value of the model marginally; now explaining 95.9% of the variance in weight (R^2 = 0.919, F (6, 303) = 547.00, p < 0.001). Main effects of age, gender and trial status were also not significant (OR $_{age}$ = 0.96, 95%CI = 0.20-4.70, p = 0.183; OR $_{gender}$ = 1.02, 95% CI = 0.11-9.13, p = 0.722; OR $_{Trial}$ = -0.99, 95% CI = 0.44-2.21, p = 0.599), and neither was the *FTO**age interaction (p =0.595).

Table 7.4 Linear regression predictors of weight and BMI change

Model	**Predictors only**			**Interaction *FTO**age**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Baseline weight	2.51	2.42-2.61	< 0.001	2.51	2.42-2.61	0.001
Baseline height	1.05	0.00-579.52	0.050	1.05	0.00-580.10	0.048
***FTO* status**	1.01	0.48-2.13	0.577	0.98	0.10-9.53	0.707
Age	0.97	0.44-2.17	0.119	0.94	0.07-12.54	0.294
Gender	1.00	0.35-2.88	0.990	1.00	0.34-2.94	0.976
Trial status	0.99	0.44-2.21	0.599	0.99	0.44-2.21	0.556
***FTO**age**	---	----	----	1.04	0.22-5.01	0.595

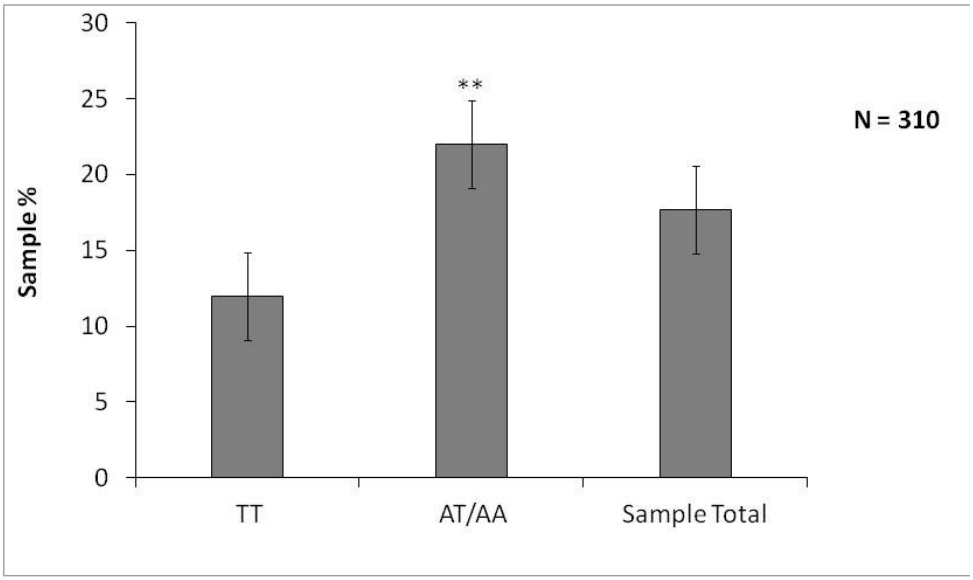
7.5.4 FTO status and 5% weight gain

Results from the logistic regression analysis are shown in Table 7.5. Of the 310 participants that provided follow-up weight data, 17.8% (n = 55) gained at least 5% of their initial body weight (Mean gain: 8.86%, SD = 4.08, range: 5.8% - 26.8% of initial body weight). The first model including only *FTO* status revealed that participants with AT/AA genotypes were about twice as likely to have gained at least 5% of their body weight over the year than those with the TT genotype (OR = 2.06, 95% CI = 1.10-3.89, p = 0.024). As shown in Figure 7.4, when age, gender and trial status were added to the model, *FTO* status remained a significant predictor of 5% weight gain (OR = 2.05, 95% CI = 1.08-3.90, p = 0.029). Furthermore, age was a significant predictor of weight gain, with those who were aged between 18 and 20 being three times more likely to have gained at least 5% of their starting weight than older participants (OR = 3.11, 95% CI = 1.47-6.56, p =0.003); gender was not a significant predictor of weight gain (OR = 0.79, 95% CI = 0.43-1.45). The *FTO**age interaction was also not significant (OR = 1.81, 95% CI = 0.40-8.31, p = 0.447).

Table 7.5 Predictors of 5% weight gain

Model	**Predictors only**			**Interaction *FTO**age**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
***FTO* status**						
TT	1			1		
AT/AA	2.05	1.08-3.90	0.029	1.30	0.41-4.14	0.704
Age						
21-30	1			1		
18-20	3.11	1.47-6.56	0.003	2.11	0.66-6.75	0.225
Gender						
Male	1			1		
Female	0.79	0.43-1.45	0.113	0.80	0.25-2.57	0.477
Trial status						
No	1			1		
Yes	0.60	0.32-1.13	0.113	0.66	0.19-1.96	0.129
***FTO* TT*age 18-20**				1		
***FTO* AT/AA*age 18-20**	----	------	-----	1.81	0.40-8.31	0.447

Figure 7.4 Weight gain by genotype status over the year



7.5.5 Sensitivity analysis: Weight change and 5% weight gain

The sensitivity analysis included 101 participants from wave 1 who provided follow-up weight data. Characteristics of wave 1 participants are shown in Table 7.1.

Baseline BMI in wave 1 participants was comparable to BMI in waves 2 and 3 combined (mean BMI wave 1= 22.03 kg/m^2 vs. mean BMI waves 2/3 = 21.93 kg/m^2, t (1409) = 0.65, p = 0.513).

FTO status, BMI and body weight at baseline FTO status was not associated with baseline BMI in the subsample; neither when *FTO* status was the only predictor, F (1, 477) = 2.53, p = 0.112, nor when age and gender were added to the model, F (1, 475) = 2.43, p = 0.120. However, age and gender were significantly associated with baseline BMI in the subsample, with women and younger participants having lower BMIs than men or older participants (F_{age} (1, 475) = 4.12, p = 0.043; F_{gender} (1, 475) = 28.82, p <0.001). *FTO**age or *FTO**gender interactions were not

significant (p = 0.736; p = 0.661). Likewise, *FTO* status was not significantly associated with body weight; neither in analysis including only *FTO* status and height (F (1, 431) = 2.08. p = 0.149; nor once age and gender were added as covariates (F (1, 429) = 2.36, p = 0.125). As before, age and gender were significantly associated with body weight, with women and younger participants being lighter than men or older participants (F_{age} (1,429) = 4.94, p = 0.027; F_{gender} (1, 429) = 13.57, p 0.001). However, interactions between *FTO* status with either age or gender were not significant (p= 0.511; p = 0.439).

FTO status, BMI and body weight at follow-up Differences between wave 1 and wave 2/3 participants in BMI at follow-up were not significant (mean BMI follow-up wave 1 = 22.20 kg/m^2 vs. mean BMI = 21.59 kg/m^2 follow-up waves 2/3, t (308) = 1.72, p = 0.086). *FTO* status was not significantly associated with BMI at follow-up in cross-sectional analyses when it was the only predictor (F (1, 99) = 0.17, p = 0.673; nor when age and gender were added to the model (F (1, 97) = 0.81, p = 0.368). Gender was now the only variable significantly associated with BMI (F (1, 97) = 4.86, p = 0.030; F_{age} (1, 97) = 1.91, p = 0.170). Interactions between *FTO* status and age were not significant (p = 0.189 and p = 0.867). *FTO* status was also not significantly associated with body weight at follow-up; neither in analyses including only height as the other covariate (F (1, 65) = 0.23, p = 0.631); nor once age and gender were added (F (1, 65) = 0.71, p = 0.412). Gender was associated with body weight at follow-up (F (1, 63) = 5.21, p = 0.26); whereas age was not (F (1, 63) = 0.82, p = 0.367). The *FTO**age interaction was also not significant (p = 0.742).

FTO status and body weight changes Weight change was of similar magnitude as in wave 2 and 3 participants, Δ weight= 0.56 kg, SD = 3.90, range: -12.50 kg -14.40 kg, t (308) = 0.097, p =

0.923). Only 3% of participants (n = 3) stayed the same weight; 45% lost weight (n = 45) and 52% (n = 53) gained weight. Results of the linear regression analysis are shown in Table 7.6. The first linear regression model including only baseline weight, height and *FTO* status explained 95.6% of the variance in weight change, R^2= 0.914, F (3, 97) = 341.62, p < 0.001. As before, *FTO* status was a significant predictor of weight change, OR = 1.07, 95%CI = 0.33-3.41, p = 0.032, as was baseline weight, OR = 2.58, 95%CI = 0.81-8.26, p < 0.001. However, when covariates were added to the model, *FTO* status was no longer a significant predictor of weight change; although a trend still existed which indicated that that higher risk status was predictive of greater weight change (OR = 1.06, 95% CI = 0.33-3.38, p =0.067). The *FTO**age interaction was not significant ($OR_{FTO*age}$ = 0.94, 95% CI = 0.30-3.02, p = 0.644).

Table 7.6. Linear regression analysis for weight change in the sensitivity analysis

Model	**Predictors only**			**Interaction *FTO**age**		
	OR	95% CI	p-value	OR	95% CI	p-value
Baseline weight	2.62	2.43-2.84	<0.001	2.63	2.43-2.85	<0.001
Baseline height	1.01	0.00-580.10	0.853	1.01	0.00-580.1	0.911
***FTO* status**	1.06	0.22-5.08	0.067	1.10	0.01-173.43	0.351
Age	0.96	0.20-4.70	0.183	1.10	0.001-177.22	0.178
Gender	1.02	0.12-8.78	0.722	1.02	0.11-9.13	0.714
***FTO**age**	---	----	---			

FTO and 5% weight gain About five per cent of participants (n = 22) in the subsample gained 5% or more of their initial body weight (mean: 9.29%, SD = 5.34, range: 5.08% -26.86%). Results from the logistic regression analyses are shown in Table 7.7. The first model including only *FTO* status as predictor variable showed that *FTO* status was a significant predictor of a 5% weight change. Participants with higher risk status were about four times more likely to gain 5% or more of their initial body weight than lower risk participants (95% CI = 1.29-13.43, p = 0.017). When covariates were added to the model, *FTO* status remained a significant predictor of 5% weight gain (OR = 3.80, 95% CI = 1.15-12.53, p = 0.028). Age and gender were not significant predictors of 5% weight gain (OR_{age} = 2.12, 95% CI = 0.76-2.6.42, p =0.145; OR_{gender} = 0.90, 95%CI = 033-2.44, p = 0.844). The interactions of *FTO**age was also not significant (OR = 6.51 95% CI = 0.61.14, p = 0.101).

Table 7.7 Logistic regression for 5% weight gain sensitivity analysis

Model	**Predictors only**			**Interaction *FTO**age**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
***FTO* status**						
TT	1			1		
AT/AA	3.08	1.15-12.53	0.028	6.61	0.69-62.90	0.100
Age						
21-30	1			1		
18-20	2.12	0.76-6.42	0.145	4.26	0.40-45.45	0.229
Gender						
Male	1			1		
Female	0.90	0.33-2.44	0.844	0.94	0.34-2.59	0.915
***FTO* TT*age 18-20**						
***FTO* AT/AA*age 18-20**	----	------	-----	1 0.45	0.03-6.37	0.553

7.6 Discussion

This study investigated associations of the *FTO* gene with weight gain at the start of university to explore the validity of the genetic susceptibility model. As hypothesised, participants who had at least one higher risk *FTO* A allele were twice more likely to gain a clinically significant amount of weight over one year than *FTO* lower risk homozygotes; although weight change was modest overall (about 2 Pounds), and far less than the anecdotally described 'freshmen 15' or the 5kg commonly observed in American samples.

7.6.1 Study limitations

The study had many limitations. First, participant retention proved a true challenge. Despite several personalized email reminders and small incentives to return for follow-up weighing, nearly 80% of the sample was lost to follow-up. One reason for poor follow-up may have been major unanticipated problems in the time frame of DNA analysis in wave 1 which delayed return of the test results and therefore follow-up. Problems with the automation of DNA extraction caused a delay of three months, meaning that results could not be returned until late June. However, because of exams and summer holidays, timing was crucial for participant retention, especially because the incentive for returning for follow-up was to receive test results at the same time. The delay meant that the majority of students were not reachable any more, as the email address provided was commonly the UCL email, which students might not access outside term times. A further problem associated with the delay was that I had to spend considerable time managing participants who were understandably displeased with not receiving their result on time. It is also possible that students might have been less cooperative than at the beginning, which was further augmented by the delays in DNA

processing. One way to improve retention rates (apart from collecting follow-up data earlier) would perhaps been incentivizing participants more if they completed all measures. However, this practice is not without ethical concerns and therefore, we refrained from offering incentives beyond a small compensation for participants' time and effort.

The small sample size at follow-up meant that it was necessary to dichotomize *FTO* genotype into higher risk (AT/AA) and lower risk (TT) participants to increase power, instead of investigating the effects of each individual genotype on weight gain; and even then; the follow-up sample was significantly underpowered to detect *FTO*'s small effects on weight gain. Therefore, it was even more surprising to observe the described effects of *FTO* on clinically meaningful weight gain, which makes it likely that the 'true' effect of *FTO* on weight gain is larger than observed here.

A further limitation is that participants in the current study may differ from the general student population in their interest in genetic testing and/or weight control which may have caused them to participate. However, as students often participated as a group together with their friends, it is unlikely that these effects were very pronounced. However, only few overweight and obese individuals took part in the study, and even fewer returned for follow-up weighing, which may be the reason why we failed to observe an effect of *FTO* genotype on mean weight change. This suggests that the 'true' mean weight gain in students at the start of university is likely to be significantly higher than we observed. However, unless a programme is introduced that would make weighing of every student at the beginning and the end of their first academic year compulsory, accurately estimating the rate of weight change in this population will remain difficult. It would have also been useful to assess body fat alongside

weight and BMI, and we attempted to include this measure, but because of measurement errors the data had to be disregarded.

Lastly, it is important to note that two thirds of the baseline sample were later enrolled in a trial designed to motivate individuals to engage with weight gain prevention (discussed in Chapter 8) which may have diminished the effects of *FTO* on weight gain. It would have been preferable to use only participants in this study who did not participate in the trial, but the time and staffing constraints of the PhD did not allow for mustering another sample size large enough to be sufficiently powered. However, we controlled for trial participation in the current analyses, and I conducted a sensitivity analysis with the subsample that was not involved in the intervention to assess whether trial participation would unduly influence results. Results were unchanged which suggests that trial enrolment was not a confounding variable for the observed effects of *FTO* on weight change.

7.7 Conclusion

Despite high attrition rates and low rates of enrolment of participants with higher BMI, this study demonstrated that carriers of at least one *FTO* higher-risk allele were more likely to gain weight when starting university than participants with the lower risk TT genotype. Developing an intervention that informs individuals about their *FTO* status alongside tangible weight control advice may provide a novel avenue of forestalling these effects.

Chapter 8: Study 4 – Adding genetic test feedback for weight gain susceptibility to weight control advice: A randomised controlled trial[7]

8.1 Background

The previous chapter demonstrated that genetically susceptible individuals are at risk of gaining significant amounts of weight, when exposed to the obesity-promoting university environment. Although weight gain prevention interventions targeting this time period have shown some positive effects, these are limited to the most time- and resource intensive interventions (courses/small groups); running over an extended time period and incorporating different aspects of weight control.

Considering the low motivation to prevent unhealthy weight gain of young adults discussed in Chapter 1, these interventions are unlikely to reach the majority of students, especially if they are of normal weight upon entering university and perceive themselves to be at low risk of weight gain. Returning FTO genetic test feedback may be a novel, cost-effective way (FTO genetic testing currently costs about £5) to increase awareness of weight gain susceptibility, especially in individuals previously unaware of their risk, which in turn may motivate engagement in weight control behaviours, as predicted by the Health Belief Model

[7] The trial protocol has been published as part of this work in *Trials Meisel, S. F., Beeken, R. J., van Jaarsveld, C. H., & Wardle, J. (2012). Genetic test feedback with weight control advice: study protocol for a randomized controlled trial. Trials, 13(1), 235.*

(Rosenstock, 1974). With further research into effective interventions, linking genetic test feedback to simple weight control advice that can be delivered in a cost-effective manner may provide a feasible option for increasing weight gain prevention in higher risk contexts.

8.2 Study Aims and contribution to the literature

Although several RCTs were concerned with effects of genetic test feedback on other health behaviours such as smoking cessation (Audrain et al., 1997; Hollands et al., 2012), only two studies have explored the effect of genetic test feedback for weight loss in clinical samples and no study to date has explored the effects on motivation to prevent weight gain in young, healthy individuals. Results from these earlier studies cannot be assumed to equally apply to weight gain prevention because their purpose is somewhat different: Whereas weight loss and smoking cessation studies aim to initiate treatment and improve maintenance (weight loss and abstinence), the current study was designed to motivate engagement with disease prevention (avoidance of unhealthy weight gain) in a young, healthy population.

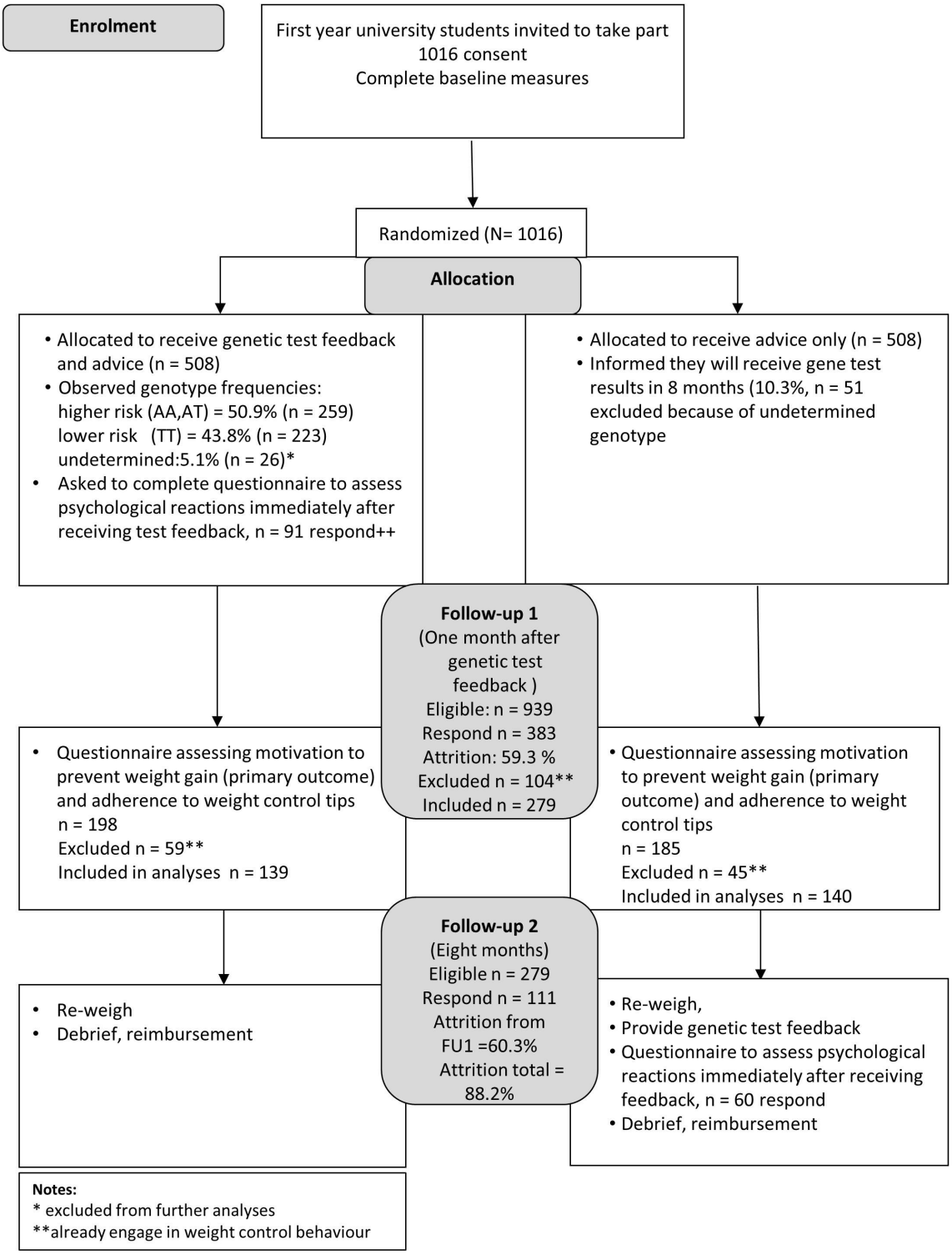
The aim of the current study was therefore to discover whether genetic feedback provides an impetus for individuals to prevent unhealthy weight gain in young adults entering a life stage where weight gain is relatively common; contributing to the on-going debate about clinical utility of genetic test feedback for common, complex conditions.

8.3 Methods and procedure

8.3.1 Study design

The design was a single-centre, open, two-arm, parallel group, individually-randomised controlled trial comparing the effects of genetic test feedback for risk of weight gain combined with weight control advice (FA) with a control condition of giving weight control advice only (AO) on motivation to prevent weight gain. The control group received their genetic test result at the end of the study. A summary of the study procedures is shown in Figure8.1.

Figure8.1 Flowchart study procedures



The study was designed according to the Consolidated Standards of Reporting Trials CONSORT 2010 (Kenneth, Douglas, & David, 2010). CONSORT guidelines were developed to counteract the widespread, inadequate reporting of clinical trials and the associated risk of biased results. The original guidelines were revised in 2001 and 2010 to encapsulate new evidence and provide minimum criteria for reporting clinical trials. The completed checklist of information to be included when reporting a randomised trial is shown in Appendix 12. The Trial was registered (Registration no. ISRCTN91178663), an analysis plan was designed and the study protocol was published before data collection was complete. A copy of the published protocol is included in Appendix 13.

8.3.2 Participants

A volunteer sample of 1016 students took part in the study.

Inclusion and exclusion criteria

All interested students between 18 and 30 years who were able to give informed consent were included. We chose this age range because the association between *FTO* and BMI peaks in early adulthood, with less effect thereafter (Hardy et al., 2010).

Although it is specified in the original protocol that we would exclude students over 25, in practice, it was very difficult to distinguish between those aged 18-25 and those aged over because of the method of data collection and the large number of people required to achieve the target sample of 1000 participants. Although the group aged over 25 were unlikely to be first-year students, this group was small (5.6%, n = 76) and there is no reason why the intervention would not be applicable to older students. Therefore, we decided after

discussion not to exclude them but to dichotomize age into 'younger' (aged 18-20) and 'older' (aged 21 and over) and to include the dichotomized variable in all analyses. As *FTO* has effects in all major ethnic groups, participants were not excluded based on ethnicity.

We anticipated that a small number of individuals suffering from eating disorders would express interest in taking part, because eating disorders are relatively common in this age group. However, because eating disorders are difficult to screen for, and findings from Study 2 indicated that genetic test feedback might be helpful for affected individuals, we decided not to exclude participants based on suspected eating disorders.

Recruitment and Consent

Ethical approval was granted by the University College London Research Ethics Committee for non-NHS research in September 2010 (Application no: 2471/003). A copy of the approval letter is included in Appendix 3. A copy of the information sheet and consent form is included in Appendix 4. To ensure that participants were aware of the details of the study, especially about DNA handling and privacy, information contained in the information sheet was verbally reiterated by me or one of my colleagues before saliva was collected. Participants were told that the DNA analysis would be only for one gene (*FTO*) which is related to a small increase in weight gain susceptibility and that they would be randomly allocated to receive their results either during term 2 (FA, intervention group) or at the end of the academic year (AO, control group). Participants were informed that their samples would be destroyed on completion of the study and not stored for further analyses. Written consent was obtained before participants gave saliva for DNA analysis. The right to withdraw from the study without giving

reason was be respected at all times, and saliva samples would have been destroyed immediately after participant withdrawal. However, no participant withdrew from the study.

8.3.3 Study setting

The study was conducted at University College London (UCL). Data was collected in the first two weeks of the first term (last two weeks of September) of three consecutive academic years (2010-2013) and ran over the course of the academic year, with follow-up data collected in the last week of May at the end of the third term of the respective academic year. UCL is a large university with over 22.000 new undergraduate students enrolled each year. Most students are expected to attend the main campus at some point during the first few weeks of term (e.g. the welcome fayre, which attracts nearly 10.000 attendees over two days). However, data was also collected in student halls because most first-year students live in halls, and to give participants who would not attend the main campus the option to participate.

8.3.4 Interventions

Development of a low-intensity intervention to promote weight gain prevention

Habit theory proposes that behaviours frequently repeated in a consistent context will be initiated in that context without little conscious effort and 'willpower' (Neal, Wood, & Quinn, 2006). Therefore, establishing beneficial habits by context dependent repetition is desirable as they are, once acquired, resistant to change. Although long-term habit change is an integral component of most programmes aimed at weight control, they are usually not explicitly designed with habit theory in mind (Beeken et al., 2012).

In the first study assessing the efficacy of habit-formation for weight control, Lally and colleagues (2008) developed a leaflet with ten easy to follow tips for weight reduction alongside brief advice encouraging habit-formation. Tips in the leaflet were designed to create a daily caloric deficit of about 800-900 calories if all tips were followed (vs. none, although most people would probably already be doing some), but not to involve too much effort (e.g. choose low-calorie drinks, choose low-fat options, have small portions and no second helpings). The efficacy of the leaflet was piloted in a RCT involving 104 volunteers aged 18 and over. Participants in the intervention group received the leaflet; control participants no intervention (wait-list control). There was no contact with the research team from baseline assessment to the eight-week follow-up appointment. After 8 weeks, participants in the intervention group had lost on average 2 kg, which was significantly different from control participants who lost only 0.4 kg. Moreover, weight loss continued after the initial follow-up visit. At 32 weeks, weight loss in completers was 3.6 kg, with about half of the participants in the intervention group achieving weight reduction of 5% or more. Although the trial was only small, the results were encouraging and the efficacy of the Ten Top Tips programme is currently being investigated in a large population-based trial in primary care(Beeken et al., 2012).

I decided to base the weight control advice for the current study on the 'Ten Top Tips' system because of its strong theoretical background, promising results, and ease of application (no specific training required, non-labour intensive) which made it suitable for use in a large sample. Furthermore, the 'Ten Top Tips' intervention requires only minimal engagement from participants and was therefore well-suited for the current study population. However, we did not expect the pathway whereby genetic test feedback was assumed to influence motivation

for behaviour change (by increasing risk perceptions and perceived susceptibility as proposed by the Health Belief Model, Rosenstock, 1974) to be altered by basing the leaflet on Habit theory.

The weight control leaflet was developed together with Jane Wardle (Professor of Psychology), Helen Croker (a Dietician) and Rebecca Beeken (Project Manager of the 'Ten Top Tips' trial) and is shown in Appendix 9. The leaflet is divided in three short sections: The first section outlines why it is easy to gain weight at university, the second explains the contribution of genes to weight gain, and the third section consists of seven tips that may be helpful to counteract weight gain. My role was to identify a range of behaviours in students which were likely to lead to unhealthy weight gain and to draft the content of the leaflet. I was also responsible for overseeing its design. The final choice of tips to be included was made after joint discussions.

Identification of common health behaviours in students was based on the review of the literature discussed in Chapter 1. It was found that constraints of time and money lead to a lack of physical activity and the purchase of food focused on value and not on nutritional content (e.g.Serlachius, Hamer, & Wardle, 2007; Cluskey & Grobe, 2009; Provencher et al., 2009). Furthermore, it emerged that university provides a multitude of 'eating opportunities' which foster passive overconsumption; alongside frequent alcohol intake.

The set of tips chosen aimed at raising awareness of these 'weight gain promoting' aspects of university life and provided students with specific strategies for intervention at those

occasions. Furthermore, we ensured that the tips chosen would require minimal effort to implement to also reach students with little interest in weight control.

Following the concern that genetic test feedback may facilitate overly restrictive eating behaviour that emerged in study 3a, a paragraph was included about the importance of weight not dropping too low and where to find help and advice. My contact details were provided and students were encouraged to contact me if there were any concerns regarding their weight. However, none of the participants contacted me.

As in the original Ten Top Tips study, the tips are written to be short and easy to remember, each with a memorable heading followed by a short explanation, e.g. '*Stand back from that snack* – University offers plenty of 'eating opportunities'; many events and meetings offer free food and spending all day at university can lead to eating in between meals. Snack calories are not always compensated for at the next meal, so it is best to politely pass those 'extra' snacks'. Preliminary versions of the leaflet were piloted in 45 UCL students to ensure design and 'tone' was appropriate; amendments were made according to feedback to arrive at the final version. Readability was assessed with the Flesch Reading Ease formula and the Flesch-Kincaid Grade Level formula, and received a score of 70.6, which translates to the reading level expected in grade 6 (age 12).

Intervention group ('FA' group)

The FA group received the weight control leaflet described earlier (Appendix 9) and their *FTO* gene test result in an email with the following text sent by me approximately four months after baseline data collection in the respective wave was complete. *'Thank you very much for*

your patience. I am very happy to tell you that you will find your result in the attached letter. I have also attached two short information leaflets that you may find helpful. Should you have further questions or concerns about your test result, please find my contact details in your result letter and below, I am happy to answer questions you may have.' A similar format is used by internet-based genetic testing services and was also used in studies 2 and 2b and found acceptable to participants. The result letter was sent as an email attachment so that participants could open and read it at a convenient time. The letter contained the personal result in addition to information about prevalence in the population. The email also included the short *FTO* information leaflet used in Studies 2 and 2b, giving a brief overview about the *FTO* gene, its mode of inheritance, and magnitude of influence on body weight (Appendix 2). My contact details were included for questions about the test results. As described in the relevant section of Chapter 5,(p. 119), result letter and *FTO* leaflet were piloted and were deemed clear, easy to read and informative.

Control group ('AO' group)

Participants randomised to the AO control group received the weight control advice leaflet attached to an email from me in identical format to and at the same time as the intervention group. The email also informed them that they would receive their *FTO* genetic test result by the end of the academic year; resembling a 'wait-list control' group for the genetic test feedback condition. The email read the following: *'Dear Participant, thank you very much once again for your patience. We did not determine your test result at this stage because you were assigned by chance to the group that will receive their genetic test result by the end of May. I attached a short leaflet for your information that you might find helpful. You will still qualify for your reimbursement if you fill in any questionnaires we may send. I hope that the delay will*

not cause any inconvenience. Please feel free to contact me should you have further questions or concerns (details below).Thank you very much for your continued participation.'

8.3.5 Study objectives

Primary research Objective

The primary aim of the study was to test the hypothesis that adding *FTO* genetic test feedback to weight gain prevention advice would result in higher motivation to prevent weight gain one month after receiving genetic test feedback compared with receiving weight gain prevention advice alone.

Secondary Research Objectives

There were four secondary objectives. First, it was of interest to investigate differences in motivation to control weight in participants receiving genetic test feedback by risk status to explore whether receiving higher risk genetic test feedback would be more motivating than receiving a lower risk genetic test result. Based on findings from Study 1, I hypothesised that receiving higher risk genetic test feedback (AA/AT) would result in significantly higher motivation to control weight than receiving a lower risk (TT) genetic test result. Interactions with age and gender were also explored. It would have been of interest to explore interactions between gene status and BMI, and this point was specified in the protocol, but because of small sample sizes this was unfortunately not possible.

Secondly, one aim was to explore whether receiving genetic test feedback alongside weight control advice would be especially effective in subgroups. I explored effects of receiving genetic test feedback and advice by age, gender and BMI. I hypothesised that participants who were female or overweight/obese would be more motivated to control weight than older

participants, men or those of normal weight, based on the literature showing that pressures to be slim are higher for women and findings from Studies 2 and 2b showing that *FTO* feedback may have benefits especially for individuals having difficulties at weight control. Furthermore, I hypothesised that females or those with higher BMI receiving genetic test feedback and advice (FA) would be more motivated to control their weight than females or those with higher BMI receiving only weight control advice (AO).

Thirdly, I assessed whether recieivng genetic test feedback for weight gain susceptibility would translate into behaviour change. I investigated differences in adherence to the weight control advice (tips) and weight change from baseline to 8-month follow-up in those receiving genetic test feedback and weight gain prevention advice compared with those receiving advice alone. I hypothesised that participants receiving genetic test feedback would be more likely to adhere to the weight control advice, evident in the frequency and number of weight control tips followed. Furthermore, I hypothesised that participants receiving genetic test feedback and weight control advice would gain less weight over the study period than those receiving only weight control advice.

All secondary objectives were exploratory, because the sample size limited power.

8.3.6 Study materials and Measures

DNA Collection and genotyping

DNA was collected as described in Chapter 5 (Study 2). Briefly, participants were asked to give a saliva sample for DNA collection by placing some sugar onto their tongue to stimulate saliva

flow and then spitting into a plastic tube to generate 1.5 -2 ml of saliva. DNA was extracted and analysed at the Institute of Metabolic Sciences, Cambridge, UK.

Demographic characteristics

Demographic information was assessed in an online questionnaire. The link to the questionnaire was sent to participants the day after saliva collection and included age and gender. BMI was calculated using measured height and weight (described below). The email with the invitation to fill in the questionnaire is shown in Appendix 5 and the questionnaire is shown in Appendix 11.

Body composition was assessed upon enrolment in the study and at 8-month follow-up (end of the academic year). Participants were asked to remove shoes, socks and heavy items, but stay otherwise fully clothed. Height was measured, rounded up to the nearest centimetre, using the Leicester Height Measure (Marsden Group, UK) a standardized instrument for determining height. Weight and body fat was assessed using the TANITA TBF-300 MA Body Composition Analyzer (Sindlfingen, Germany) which uses electrical impedance to assess body fat and BMI. Electrical impedance usually compares well to other measures of body composition such as whole body magnetic resonance imaging and dual X-ray absorptiometry (Beeson et al., 2010). Antibacterial gel was applied to the footplate area to minimise risk of infection and facilitate contact. Participants could opt to receive a printout of the results together with an explanation by the research team or not. All participants opted to receive their printout and an explanation by the research team.

Although it was specified in the original protocol that we would also assess changes in body fat we decided to drop this outcome measure from the analyses because we found that the measure was not accurate (the correlation between BMI and body fat was only r = 0.047).

Motivation to control weight

Motivation to control weight was assessed using a validated measure of readiness for behaviour change (Sarkin, Johnson, Prochaska, & Prochaska, 2001) adapted to relate to prevention of weight gain. Participants were asked *'Please mark with an 'X' the statement out of the next four that best describes you': 'I am not trying to control my weight, and I have no intention of doing so in the next month', 'I am not trying to control my weight, but I am thinking of doing something in the next month', 'I started to try to control my weight within the last month, 'I have been trying to control my weight for more than a month'*. Responses were used to classify individuals into one of the five stages of behaviour change outlined by Prochaska and DiClemente (1984): Precontemplation, Contemplation, Preparation, Action and Maintenance. Table 8.1 displays the statements and corresponding stages of change. Because of difficulties in distinguishing meaningfully between Contemplation and Preparation stages with respect to weight control intentions, these two stages were grouped together. Furthermore, the time frame was adjusted to one month as opposed to six months in the original model to reflect the time frame of the current study.

Table 8.1 Stages of change and corresponding statements

Stage of Change	Questionnaire item
Precontemplation	I am not trying to control my weight, and I have no intention of doing so in the next month
Contemplation/preparation	I am not trying to control my weight, but I am thinking of doing something in the next month
Action	I started to try to control my weight within the last month
Maintenance	I have been trying to control my weight for more than a month

Behaviour change

Behaviour change was measured by adherence to the weight loss tips, which was assessed by asking: *'How often in the last month did you... watch portion sizes, avoid second helpings, slow down your eating, avoid eating mindlessly/focus on your food, pass up extra snacks between meals, avoid sweet drinks or chose a 'lite' drink, integrated some physical activity into your day'.* Response options were given on a 5-point Likert scale, with response options being *'never', 'occasionally', 'sometimes', 'most of the time'* and *'always'.*

Participants were not specifically instructed to read the weight control leaflet or adhere to the tips (other than mentioning in the email that they may find it helpful) because we were interested to explore whether genetic test feedback would raise self-motivation to seek out the information provided and initiate weight control more than receiving only weight control advice. Although one section of the weight control leaflet explained that tips were chosen with

the mechanisms of action of *FTO* in mind, it was pointed out that the tips would be helpful for anyone wanting to avoid weight gain regardless of genotype to ensure that students within the control group or TT genotype would not disregard the leaflet as not applicable to them.

Motivation to control weight and adherence to the weight loss tips were assessed one month after the intervention group received their genetic test result. We chose the respective time frame, because we saw it as crucial that participants would have had sufficient time to think about their result, to ask any questions, and to implement eventual behaviour change. Participants who reported having controlled their weight for more than one month were excluded from the analyses because the intervention was not applicable to them (they were already in the maintenance stage).

8.3.7 Randomization

I conducted all elements of the trial (study enrolment, data collection, group allocation, data analysis) myself. Although this is not desirable because it increases the risk of bias and data manipulation, it was difficult to circumvent because the study was part of the PhD. Ideally, group allocation and data analysis would have been conducted by independent parties to ensure that data was not manipulated. To minimise the risk of inadvertent data manipulation, all questionnaire data was collected online and anthropometric data were objectively assessed and print-outs of weight records were kept in locked filing cabinets according to university regulations.

Sequence generation

Data was anonymised using serial numbers immediately after saliva collection. The randomisation sequence was generated using the 'randomise' function of SPSS v. 19 which randomly assigns a set number of cases (here: 100%) to a specified number of groups (here: 2), corresponding to a 1:1 allocation ratio of treatment and control group. Group allocation occurred immediately after saliva collection of the respective wave was complete and before genetic test results became available. Genotypes within the intervention group are intrinsically randomised because they are assigned at birth (Mendelian randomization).

Allocation concealment

Group allocation was not concealed because I conducted all aspects of the trial myself. However, ideally, group allocation would have been concealed to avoid the possibility of selection bias and to protect the assignment sequence. One way could have been to use a third party to assign participants according to the random sequence. In hindsight, a third person (e.g. another PhD student) from a different department could have allocated participants but this was not considered at the time.

Blinding

Neither I nor the participants were blind to group allocation because they knew whether they received their *FTO* result after four months or at the end of the respective academic year. However, because participants were not specifically signing up for a weight gain prevention intervention (the main interest for most participants was to receive genetic test feedback) this should have not unduly influenced the results.

Minimising other sources of bias

Participants who selected themselves into the study were likely to be more positive towards genetic testing than the average student population. However, if genetic testing was offered through a healthcare provider or over the internet, the same situation would hold, i.e. only interested individuals would have chosen to take part.

8.4 Statistical Analyses

Sample size and assumptions

A power calculation conducted *a priori* using *GPower* (version 3.1) showed that a total sample size of n=340 should suffice to detect a small effect (d=0.25) for motivation to prevent weight gain between 'FA' and 'AO' group with 95% power or greater at the 5% significance level, accounting for an attrition rate of 60% (based on research with other student samples). The small effect size was chosen based on data from the vignette study and on *FTO*'s modest effects on weight.

However, because the final sample size was smaller than expected (n = 279 instead of expected n = 406), we decided to lower power to detect a small effect to 90% which is still acceptable for trials according to CONSORT. The new sample size required was n = 252. Therefore, the current study was adequately powered to detect a small effect (d=0.25) for motivation to prevent weight gain between 'FA' and 'AO' group with 90% power or greater at the 5% significance level, accounting for an attrition rate of 60% .

Analyses

Analyses were conducted per protocol (completers only) because of the anticipated large amount of missing data (attrition from baseline to one-month follow-up was 59.5%). Analyses on intention-to-treat basis would have resulted in imputation of more than half of the data points and because data was only available from one time point, this was likely to be inaccurate. Analyses were carried out using the Statistical Package for Social Sciences (SPSS) version 20.

Differences between completers and non-completers of follow-up 1 and follow-up 2 were assessed with chi-square tests for categorical variables and independent-samples t-tests for continuous variables. Participants who had been controlling their weight for more than one month were excluded from analyses (n = 104); because the intervention was not applicable to them (they already controlled their weight).

Descriptive information was based on frequency tables and cross-tabulation. All data were tested for assumptions of normality (Skewness, Kurtosis, Levene's Test) and results are only reported if these were violated. For Skewness and Kurtosis, values between -1 and + 1 were deemed acceptable.

Primary outcome

Ordinal logistic regression (Polytomous Universal Model, PLUM) was used to assess the difference in 'FA' vs. 'AO' group for motivation to prevent weight gain. In contrast to other multinomial methods of analysis, PLUM extends the general linear model to ordinal categorical data by taking the order of categories within a variable into account; predicting

membership to a certain category or less (Armstrong & Sloan, 1989). Therefore, it was an appropriate model to use for the current analyses because higher categories reflect a more advanced stage of change. It would not have been very meaningful to treat the main outcome variable as continuous; dichotomizing it for use in logistic regression (e.g. 'no intention to control weight' vs. all other categories) would have been possible but less desirable because information about the stage of change would have been lost using this method.

Secondary outcomes

Results from all secondary analyses were considered exploratory. For all models, analyses were run at first only including the predictor variable of interest. Thereafter, the models were run including age, gender and BMI as covariates. Where significant main effects of covariates were found, analyses were run a third time, including interactions between the respective covariate and main predictor variable. For the purpose of all analyses, age was dichotomized into 'younger' (aged 18-20) and 'older'(aged 21 and over); weight status was dichotomized into 'normal weight' (BMI < 25 kg/m^2) and 'overweight/obese' (BMI>25 kg/m^2).

To assess the effect of risk status on motivation to control weight, *FTO* status was dichotomized into higher/lower risk, with those having at least one risk allele being classified as higher risk in the FA group. Ordinal regression analyses were used to examine effects of risk status on motivation to control weight by first comparing higher/lower risk with the control group and then comparing higher vs. lower risk *FTO* status. For the latter analysis, data was recoded so that TT participants constituted the reference group (AA/AT = 0, control = 1, TT = 2). Age, gender and BMI were included as predictor variables in all models but it was only possible to test interactions between risk status and age and gender, respectively, but not BMI

because of the small sample size. To determine the effects of genetic test feedback on motivation to control weight in subgroups, the model included age, gender and weight status. Analyses were repeated as described above.

Group differences in actual behaviour change (as measured by adherence to the individual tips) were assessed with a one-way ANOVA followed by one-way ANCOVA including age, gender and BMI. In addition, I built a mean score of the frequency with which participants adhered to all tips by summing the frequency with which they adhered to each tip and dividing it by the number of tips. Furthermore, I built an additive score of the total number of tips adhered to at least 'occasionally'. Differences between groups were explored as described above. Bonferroni corrections for multiple comparisons were used in all analyses.

Repeated-measures ANOVAs were used to determine change in anthropometric measures (BMI, weight) within and between groups over time. Again, the models were re- run with covariates (including height for analyses where weight was the outcome) as described.

8.5 Results

8.5.1 Data checks

One assumption of PLUM is that '*the relationship between the independent variable and the logits is the same for all logits'* (Norusis, 2011). The test of parallel lines examines the accuracy of this assumption and was not significant for any of the analyses, indicating equal relationships between the independent variable (Treatment Group) and each category within the outcome variable (motivation to control weight). Because PLUM does not require data to be normally distributed (Anderson, 1984), skewness and kurtosis were not investigated.

8.5.2 Participant flow and Demographic characteristics

Participant flow through the study is shown in Figure8.1. Of 1016 participants taking part in the study, 7.5% (n = 77, intervention n = 26, control n = 51) had to be excluded because their genotype could not be determined. 939 participants were invited to complete the one-month follow-up questionnaire and 383 (40.7%) completed it; just attaining the expected 40% completion rate. Participants who completed the one-month follow-up (vs. those who did not) were more likely to be older, $t(937) = -1.99$, $p = 0.046$) women ($\chi^2(1) = 13.25$, $p < 0.001$), with lower BMI at baseline, but not 8-month follow-up ($t_{BMIBL}(937) = 2.77$, $p = 0.006$; $t_{BMIFU}(109) = 1.93$, $p = 0.054$). Drop-out was not related to group allocation ($\chi^2(1) = 1.00$, $p = 0.317$).

Participants who reported having controlled their weight for more than one month were excluded from further analyses because the intervention would not be applicable to them (27.2%, n = 104). These participants were more likely to be female (χ^2 (1) = 9.14, p = 0.002), with slightly higher BMI at both baseline and 8-month follow-up (t_{BMIBL} (381) = -3.29, p = 0.001; t_{BMIFU} (146) = -2.03, p = 0.045) with no differences in age. The final sample consisted of n= 279 participants.

Participant characteristics for each group are shown in Table 8.2. There were 139 participants in the FA group (49.7%), and 140 (50.3%) in the AO group. About half of the participants in each group were male (FA = 51.1%, n = 79; AO = 47.9%, n = 67). Mean age in intervention and control group was 20 (SD = 2.9) and 21 years (SD = 3.0), respectively. Mean BMI was about 21 in both groups (Mean BMI_{FA} = 21.0 kg/m^2, SD_{FA} = 2.5, Mean BMI_{AO} = 21.4 kg/m^2, SD_{AO} = 2.6) and most participants in either group were 'normal weight' (FA = 92.1%, n = 128; AO = 89.3%, n = 125).

Following CONSORT guidelines, differences between intervention and control groups were not assessed; therefore, no p-values are reported. The reason for this is that it is assumed that groups were assigned at random; therefore, there should be no differences between the groups.

Table 8.2 Participant characteristics

	Intervention (Feedback and Advice, n = 139)		Control (Advice only, n = 140)	
Gender male % (n)	51.1	(71)	47.9	(67)
Age (years) mean (SD)	20.2	(2.5)	20.9	(3.0)
Height (m) mean (SD)	1.70	(0.97)	1.7	(0.97)
Weight (kg) mean (SD)	62.3	(10.8)	63.0	(11.7)
BMI kg/m kg/m^2 mean (SD)	21.2	(2.5)	21.4	(2.6)
Normal weight % (n) <25	92.1	(128)	89.3	(125)
Overweight/obese % (n) >25	7.9	(11)	10.7	(15)
Motivation weight control mean (SD)	1.6	(0.8)	1.5	(0.7)
No intention % (n)	55.4	(77)	66.4	(93)
Thinking about it % (n)	23.0	(32)	15.7	(22)
Started % (n)	21.6	(30)	17.9	(25)
***FTO* status % (n)**				
AA	13.7	(19)	---	---
AT	39.6	(55)	---	---
TT	46.8	(65)	---	---

8.5.3 Primary outcome: Motivation to control weight

Mean scores and number of participants for each stage of are shown in Table 8.2. Participants in the intervention (FA) group were slightly more motivated to engage with weight control (Mean = 1.6, SD = 0.8) than participants in the control group (Mean =1.5, SD = 0.8); although low means in both groups indicated low motivation overall. However, eyeballing percentages for each stage of change, it appeared that fewer participants in the intervention group had 'no intention' to control their weight (55.4% vs. 66.4%) than participants in the control group. Furthermore, more participants in the intervention group thought about controlling their

weight (23.0% vs. 15.7%) or had already started to do so (21.6% vs. 17.9%) than in the control group

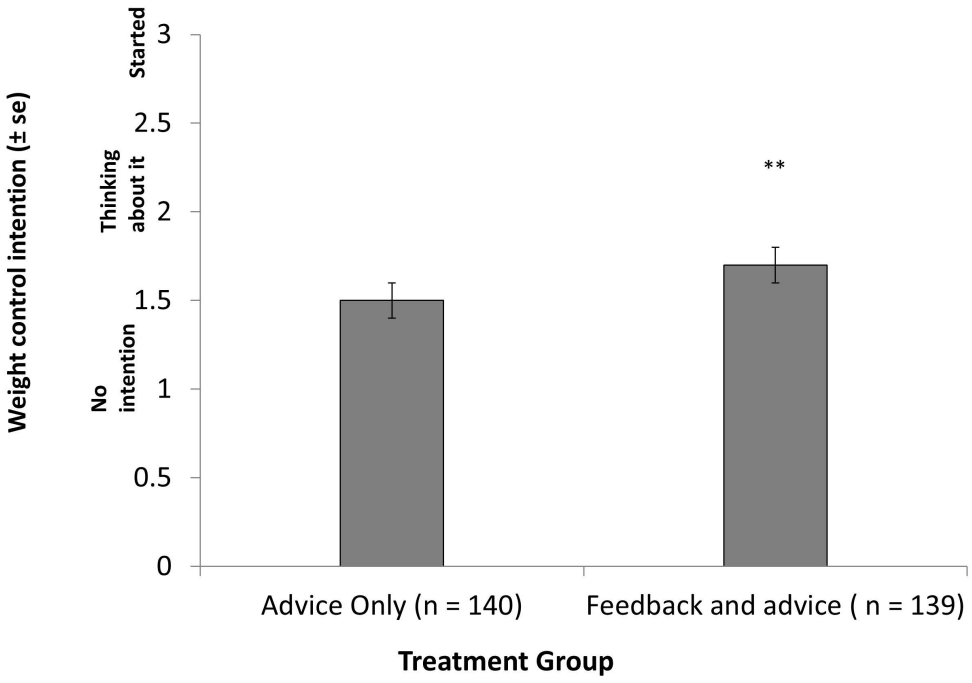
Table 8.3 Ordinal regression (PLUM) for the effect of the intervention on weight control intentions

Model	Dic only			Interaction Treat*age_DIC			Interaction Treat*gender			Interaction Treat*BMI_DIC		
	OR	**95%CI**	**Sig**	**OR**	**95%CI**	**Sig**	**OR**	**95%CI**	**Sig**	**OR**	**95%CI**	**Sig**
Gender												
Male	1			1			1			1		
Female	2.91	1.76-4.81	< 0.001	2.92	1.76-4.83	< 0.001	3.46	1.62-7.39	0.001	2.98	1.79-4.95	< 0.001
Age												
18-20	1			1			1			1		
21-30	0.87	0.53-1.44	0.594	0.40	0.19-0.82	0.803	0.88	0.53-1.47	0.626	0.89	0.53-1.48	0.646
BMI												
Nw	1			1			1			1		
Ow/ob	4.80	2.14-10.77	< 0.001	4.78	2.13-10.72	<0.001	4.83	2.14-10.89	< 0.001	2.32	0.79-6.83	0.127
Treatment Group												
AO	1			1			1			1		
F+A	1.77	1.08-2.89	0.023	2.00	1.06-3.76	0.061	2.12	0.97-4.64	0.059	1.46	0.87-2.45	0.127
TreatFA* age_18-20				1								
TreatFA* age_21-30	-	-	-	0.42	0.15-1.15	0.865	-	-	-	-	-	-
TreatFA* gender_male							1					
TreatFA* gender_female	-	-	-	-	-	-	0.73	0.27-2.01	0.547	-	-	-
TreatFA*BMI_Nw										1		
TreatFA* BMI_Ow/ob	-	-	-	-	-	-	-	-	-	6.67	1.13-39.25	0.036

Running PLUM without covariates yielded non-significant results (OR = 1.51, 95% CI = 0.94-2.41, p = 0.087). However, as shown in Figure 8.2, once age, gender and BMI were included, the effect of the intervention became significant. Participants receiving genetic test feedback in addition to weight control advice were significantly more likely to think about controlling their weight, or to had started to do so within the last month than participants receiving only weight control advice, OR = 1.77, 95% CI = 1.08-2.89, p = 0.023.

Table 8.4 shows the results of the PLUM including age, gender and BMI as covariates

Figure 8.2 Group differences in weight control intentions



**p = 0.023.

8.5.4 Secondary outcomes

Effects of the intervention in subgroups

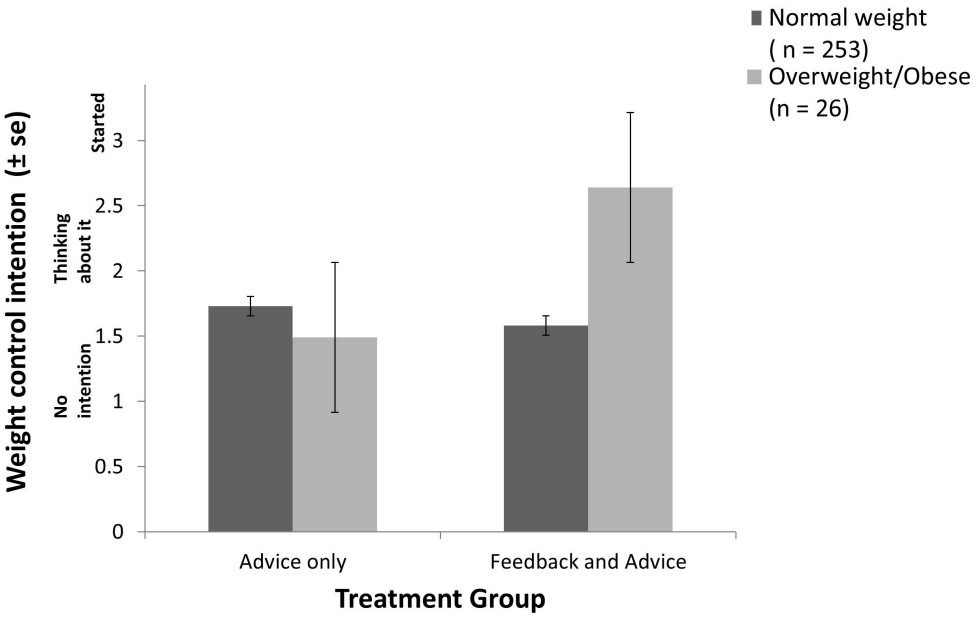
The model also revealed significant main effects for gender and BMI, suggesting that females and overweight participants were more likely to think about controlling their weight or had started to do so in the last month than males or those of normal weight (OR_{gender} = 2.91, 95% CI = 1.76-4.81, p<0.001; OR_{BMI} = 4.80, 95% CI = 2.13-10.77, p<0.001).

Models were run that included interactions with age, gender and BMI respectively. There was no significant interaction between Treatment Group* age (p = 0.865) and Treatment Group* gender (p = 0.547), indicating no difference in motivation to control weight by age or between genders in the intervention group. However, the Treatment Group*BMI interaction was significant. As shown in Figure 8.4, overweight/obese individuals in the intervention group were more motivated to think about controlling their weight or to had started to do so in the last month than normal weight individuals receiving the intervention (OR = 6.67, 95% CI = 1.13-39.25, p = 0.036).

Table 8.4 Ordinal logistic regression (PLUM) for the effect of the intervention on weight control intention

Model	Dic only			Interaction Treat*age_DIC			Interaction Treat*gender			Interaction Treat*BMI_DIC		
	OR	95%CI	Sig	OR	95%CI	Sig	OR	95%CI	Sig	OR	95%CI	Sig
Gender												
Male	1			1			1			1		
Female	2.91	1.76-4.81	<0.001	2.92	1.76-4.83	<0.001	3.46	1.62-7.39	0.001	2.98	1.79-4.95	<0.001
Age												
18-20	1			1			1			1		
21-30	0.87	0.53-1.44	0.594	0.40	0.19-0.82	0.803	0.88	0.53-1.47	0.626	0.89	0.53-1.48	0.646
BMI												
Nw	1			1			1			1		
Ow/ob	4.80	2.14-10.77	<0.001	4.78	2.13-10.72	<0.001	4.83	2.14-10.89	<0.001	2.32	0.79-6.83	0.127
Treatment Group												
AO	1			1			1			1		
F+A	1.77	1.08-2.89	0.023	2.00	1.06-3.76	0.061	2.12	0.97-4.64	0.059	1.46	0.87-2.45	0.127
TreatFA* age_18-20				1								
TreatFA* age_21-30	-	-	-	0.42	0.15-1.15	0.865	-	-	-	-	-	-
TreatFA* gender_male							1					
TreatFA* gender_female	-	-	-	-	-	-	0.73	0.27-2.01	0.547	-	-	-
TreatFA*BMI_Nw										1		
TreatFA* BMI_Ow/ob	-	-	-	-	-	-	-	-	-	6.67	1.13-39.25	0.036

Figure 8.3 Group differences in weight control intentions by weight status



8.5.4.2. Effect of *FTO* risk status on motivation to control weight

The *FTO* genotype was in Hardy-Weinberg equilibrium in the current sample (χ^2 (2) = 5.68p = 0.058). Nineteen (13.7%) participants had the higher risk AA genotype, 55 (39.6%) had the intermediate risk AT genotype and 65 (46.8%) had the lower risk TT genotype.

Two ordinal regression models were built to investigate the effect of *FTO* status on motivation to engage with weight control. The first model compared the effect on motivation by *FTO* status vs. no genetic test feedback; the second model explored the effect between higher risk and lower risk *FTO* status. Age, gender and BMI were included as covariates. Results are shown in Table 8.5.

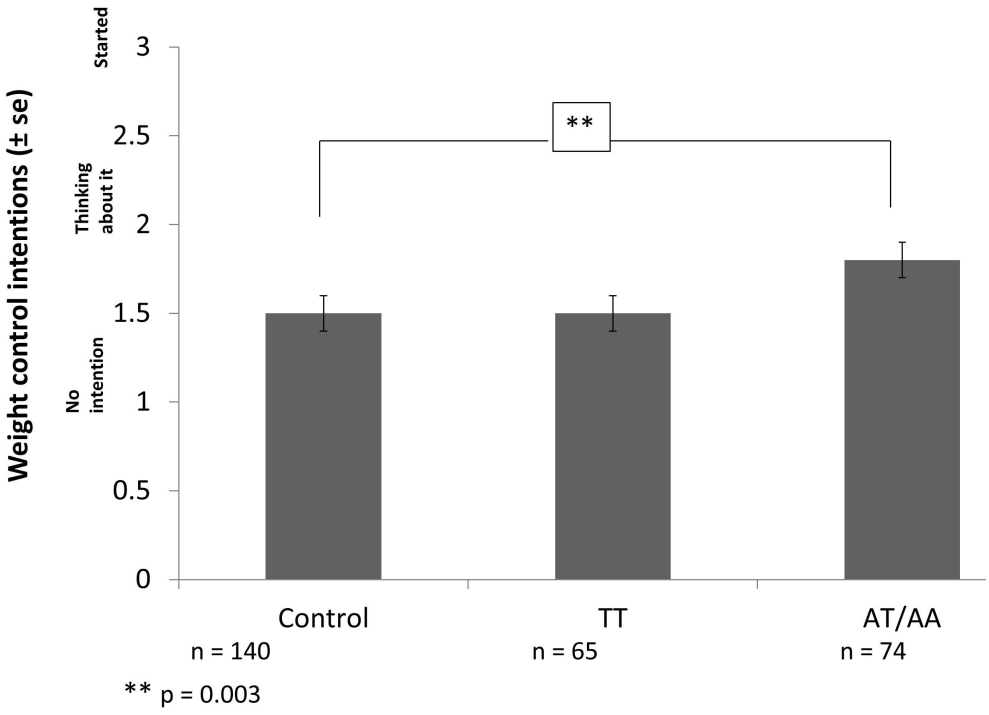
Table 8.5 Ordinal regression analysis (PLUM) for the effect of *FTO* status on weight control intentions

Model	Dic only			Interaction Feedback*gender		
	OR	**95%CI**	**Sig**	**OR**	**95%CI**	**Sig**
Gender						
Male	1			1		
Female	3.15	1.88-5.28	<0.001	3.59	1.68-7.69	0.001
Age						
18-20	1			1		
21-30	0.96	0.39-2.36	0.360	0.66	0.61-0.73	0.377
BMI						
Nw	1			1		
Ow/ob	4.90	2.17-11.07	<0.001	4.96	2.18-11.28	<0.001
***FTO* Feedback**						
Control	1			1		
TT	1.21	0.65-2.27	0.546	1.27	0.45-3.56	0.655
AT,AA	2.38	1.33-4.26	0.003	2.90	1.21-6.92	0.017
***FTO* Feedback**			-			
TT	1			1		
Control	0.82	0.44-1.54	0.546	0.79	0.28-2.22	0.119
AT,AA	1.97	1.00-3.88-	0.051	2.29	0.81-6.47	0.655
***FTO* Feedback*gender**						
Control *female				1		
AT,AA*female	-	-	-	2.90	1.21-6.92	0.017
***FTO* Feedback*gender**						
TT*female				1		
AT/AA*female	-	-	-	0.53	0.15-1.94	0.924

As shown in Figure 8.4, there was a significant effect of risk status on motivation to engage with weight control, with higher risk participants being more likely to think about controlling their weight or having started to do so in the last month than either control or TT participants;

although the latter was only borderline significant (OR $_{\text{no feedback}}$ = 2.38, 95%CI = 1.33-4.26, p = 0.003; OR_{TT} = 1.97, 95%CI = 1.00-3.88, p = 0.051). The significant main effects for gender and BMI were replicated, with female and overweight participants being more likely to think about controlling their weight or having started to do so in the last month than males or those of normal weight (OR $_{\text{gender}}$ = 3.15, 95%CI = 1.88-5.28, p< 0.001; OR_{BMI} = 4.90, 95%CI = 2.17-11.07, p < 0.001).The main effect of age was not significant (OR = 0.96, 95% CI = 0.39-2.36, p = 0.360), and therefore, interactions were not further investigated.

Figure 8.4 Intention to engage with weight control by *FTO* status



The main effect of gender was further investigated by including the *FTO* Feedback*Gender interaction in the model. Results were significant when comparing higher risk participants with the control group, indicating that females at higher risk were significantly more motivated to

control their weight than females not receiving genetic test feedback (OR = 2.90, 95%CI = 1.21-6.92, p = 0.017), but no more motivated than females receiving lower risk *FTO* feedback (OR = 1.88, 95% CI = 0.51-6.85, p = 0.924). Because of the small number of overweight and obese people in the sample (n = 11), it was not possible to investigate interactions of *FTO* risk status and BMI on motivation to engage with weight control.

Tips followed

Table 8.6 displays means and SDs for the adherence to the individual tips. Overall, adherence was very low with most participants only adhering 'occasionally' to each tip. Engagement with physical activity was slightly better, with most participants reporting to engage at least 'sometimes'. The overall mean score of all tips was equally low and identical in both groups, reflecting 'occasional' engagement.

Participants in either group followed on average 5 tips at least 'occasionally'; suggesting no significant group differences. Eyeballing means suggested no significant differences between groups for any of the variables, and this was confirmed using t-tests. However, ANOVAs, followed by ANCOVAs were run as described to conform to the protocol, and results from the ANCOVAs are shown in Table 8.6. Levene's test for homogeneity of variance was not significant for any of the variables.

Table 8.6 ANCOVA results for Tips followed

Outcome	Treatment group				
	FA (n= 139)	**AO (n = 140)**			
	mean ± sd	mean ± sd	F (df, error)	p-value	Cohen's d
Watch portion sizes	1.06 ± 1.11	1.00 ± 1.09	0.25 (1, 274)	0.471	0.054
Avoid second helpings	1.23 ± 1.33	1.02 ± 1.23	2.00 (1, 274)	0.158	0.163
Slow down eating	0.61 ± 0.83	0.64 ± 0.87	0.17 (1, 274)	0.679	-0.035
Avoid eating mindlessly	1.09 ± 1.14	1.34 ± 1.19	2.53 (1, 274)	0.112	-0.214
Avoid snacks	1.42 ± 1.24	1.50 ± 1.22	0.14 (1, 274)	0.708	-0.065
Avoid sweet drinks	1.99 ± 1.55	1.92 ± 1.52	0.27 (1, 274)	0.600	0.045
Engage in physical activity	2.56 ± 1.26	2.52 ± 1.21	0.05 (1, 274)	0.821	0.029
Mean frequency tips followed	1.42 ± 0.77	1.42 ± 0.72	0.03 (1, 274)	0.847	0.000
Total no of tips followed at least occasionally	4.51 ± 2.05	4.57 ± 1.97	0.01 (1, 274)	0.925	-0.029

Note: Results are adjusted for age (dichotomized), gender and BMI (dichotomized)

Tip 1: Watch portion sizes There was no significant difference between groups on this variable, p = 0.624, and this remained as such when covariates were added, p = 0.471. However, main effects of gender and BMI were significant, with females and overweight/obese participants being significantly more likely to watch portion sizes than males and normal weight participants (F_{gender} (1, 274) = 25.02, p <0.001; F_{BMI} (1, 274) = 5.10, p = 0.025). Age was not significantly associated with portion control (p = 0.595). Investigating Treatment Group*gender and Treatment Group*BMI interactions revealed a non-significant interaction of Treatment Group with gender (F (1, 273) = 1.88, p = 0.171). However, the Treatment Group*BMI interaction was significant, with overweight/obese participants receiving genetic test feedback in addition to weight control advice engaging significantly more often with portion control than overweight/obese individuals receiving only weight control advice(F (1, 274) = 5.05, p = 0.025).

Tip 2: Avoid second helpings Participants in both group avoided second helpings equally rarely, p = 0.176 and this did not change once covariates were added, p = 0.158. There was a significant main effect of gender, with females avoiding second helpings more often than males (F (1, 274 = 14.52, p = <0.001). Main effects of age and BMI were not significant (p_{age} = 0.136; p_{BMI}= 0.134); neither was the interaction of Treatment Group with gender (p = 0.757).

Tip 3: Slow down eating The intervention had no significant effects on eating speed, p = 0.759 and addition of covariates had no effect,p = 0.679. Main effects of gender and age were significant, with females and younger participants reporting to slow down their eating significantly more often than males or older participants (F_{gender} (1, 274) = 17.37, p <0.001; F_{age} (1, 274) = 5.78, p = 0.017); although low means indicate very modest effects. Main effect of BMI was not significant (F (1, 274) = 0.32, p = 0.571); neither were interactions of Treatment Group with either age or gender ($p_{Treatment\ Group*age}$ = 0.831; $p_{Treatment\ Group*Gender}$ = 0.079).

Tip 4: Avoid eating mindlessly Participants in both groups reported to refrain from eating mindlessly equally often, p = 0.077, even after adjusting for covariates, p = 0.112. The main effect of gender was significant and that of BMI approached significance (F_{gender} (1, 274) = 7.29, p = 0.007; F_{BMI} (1, 274) = 3.83, p = 0.051). Main effect of age was not significant (p = 0.895); neither were interactions with Treatment Group and gender or BMI ($p_{Treatment\ Group*Gender}$ = 0.157; $p_{Treatment\ Group*BMI}$ = 0.225).

Tip 5: Avoid Snacks The intervention had no effect on snacking frequency, p = 0.610 and results were unchanged once covariates were added, p = 0.583. Main effects of gender and

BMI were significant, with females and overweight/obese participants reporting to avoid snacks more frequently than males or those of normal weight (F_{gender} (1, 274) = 8.61, p = 0.004; F_{BMI} (1, 274) = 7.06, p = 0.008). Age was not significantly associated with snack avoidance (p = 0.451. Interactions between Treatment Group and gender or BMI, respectively, were also not significant ($p_{Treatment\ Group*Gender}$ = 0.545; $p_{Treatment\ Group*BMI}$ = 0.507).

Tip 6: Avoid sweet drinks There were no significant group differences for this variable, p = 0.699, and addition of covariates had no effect, p = 0.640. Female gender was significantly associated with avoidance of sweet drinks (F (1, 274) = 8.14, p = 0.744). Main effects of age and BMI were not significant p_{age} = 0.744; p_{BMI} = 0.832; neither was the TreatmentGroup*Gender interaction (p = 0.649), indicating equal effects of the intervention for both genders.

Tip 7: Engage in physical activity Participants in both groups engaged equally often in physical activity, p = 0.789 and this was not changed by addition of covariates, p = 0.793. Males reported to engage significantly more often in physical activity than females (F (1, 274) = 5.08, p = 0.025). Age and BMI were not significantly associated with the frequency with which participants engaged in physical activity (p_{age} = 0.750; p_{BMI} = 0.957). The Treatment Group*Gender interaction was also not significant (p = 0.885).

Mean frequency with which tips were followed Participants in both groups followed the tips equally rarely, p = 0.964 and adding covariates had no influence on the result, p =0.940. Females and overweight/obese participants followed the tips more frequently than males or normal weight participants (F_{gender} (1, 274) = 18.31, p <0.001; F_{BMI} (1, 274) = 4.25, p = 0.040).

Age was not significantly associated with the overall frequency with which participants followed the tips, p = 0.401. Interactions between Treatment Group and Gender and Treatment Group and BMI were also not significant ($p_{TreatmentGroup*Gender}$ = 0.199;, $p_{TreatmentGroup*BMI}$ = 0.067), indicating that the intervention was no more effective for some subgroups than for others.

Total number of Tips followed at least 'occasionally' Group differences in the number of tips followed were no significant, p = 0.802 and this remained unchanged after adjusting for covariates, p = 0.834. The only significant main effect was gender, with females following a greater number of tips at least occasionally, F (1, 274) = 32.65, p <0.001). However, there was no significant interaction of TreatmentGroup and Gender (p = 0.236).

Taken together, these results suggest that genetic test feedback has transient effects on weight control intentions which do not translate into behaviour change.

Anthropometric changes over time

Of the 279 participants included in the analyses, only 111 (39.7%) provided follow-up weight data (follow-up 2 completers). Differences between those who did and did not return for follow-up 2 are shown in

Table 8.7. Participants who returned for weighing (vs. those who did not) had significantly lower BMIs at baseline, t (1, 277) = 2.15, p = 0.032 and weighed less, t (1, 277) = 2.16, p = 0.031; although proportions of participants classified as normal or overweight at baseline did not differ, χ^2 (1) = 1.98, p = 0.159. Differences in mean age and gender were not significant

between participants who completed follow-up 2 and those who did not, t (1, 277) = 1.12, p = 0.340; χ^2 (1) = 0.91, p = 0.340; although a greater proportion of younger participants (aged 18-20) returned, χ^2 (1) = 5.22, p = 0.022. Treatment group allocation was unrelated to return for follow-up 2, χ^2 = 2.68, p = 0. 101.

Table 8.7 baseline differences between completers and non-completers of follow-up weighing

	Follow-up (n = 111)	**No Follow-up (n = 168)**	**χ^2 /t**	**Sig**
Weight BL (kg) mean (SD)	60.8 (10.8)	63.8 (11.4)	2.16	0.031
Weight FU (kg) mean (SD)	61.7 (10.9)	--- ---	---	---
5%weight gain % (n)	22.5 (25)	--- ---		
BMI baseline mean (SD)	20.9 (2.5)	21.6 (2.6)	2.15	0.032
Normal weight % (n)	93.7 (104)	88.7 (149)	1.98	0.159
Overweight/obese % (n)	6.3 (7)	11.3 (19)		
BMI Follow-up mean (SD)	21.2 (2.6)	-- --		
Normal weight% (n)	92.8 (103)	-- --		
Overweight/obese % (n)	7.2 (8)	-- --		
Gender male % (n)	45.9 (51)	51.8 (87)	0.91	0.340
Age years mean (SD)	20.4 (2.9)	20.7 (2.8)	1.12	0.263
Age 18-20 % (n)	68.5 (76)	54.8 (92)	5.24	0.022
Age 21-30 % (n)	31.5 (35)	45.2 (76)		
Treatment group % (n)				
FA	55.9 (62)	45.8 (77)	2.68	0.101
AO	44.1 (49)	54.2 (91)		

Anthropometric changes were modest in the 111 participants for which data was available, mean Δ weight = 0.83 kg, SD = 3.75, mean Δ BMI = 0.28 kg/m^2, SD = 1.29. Sphericity was investigated with Mauchly's test, and results were not significant, indicating that variances of differences were equal. Weight change over time was not significant, F (1, 566) = 0.14, p = 0.700; neither was the Treatment Group*Time interaction F (1, 566) = 0.57, p = 0.451, indicating equal weight change in both groups over the year. These results did not change

once covariates (age, gender) were added to the model F_{time} (1, 105) = 0.30, p = 0.864, $F_{Treat*Time}$ (1, 105) = 0.50, p = 0.500. Main effects for covariates were not significant.

Differences between groups in 5% weight gain

Because weight naturally fluctuates as discussed in the previous chapter, and it is difficult to determine whether weight fluctuations are meaningful, we decided to also explore whether the intervention had an influence on 5% weight gain in the sample.

Out of the 111 participants for whom data were available, 25 (9.0%) gained at least 5% of their body weight. Gainers were younger than non-gainers (t (1, 109) = 2.0, p = 0.045) but were otherwise no different from non-gainers with no significant differences in baseline BMI (t (1, 109) = 1.73, p = 0.85), baseline body weight (t (1, 109) = 0.07, p = 0.942, proportion of those classified as overweight (χ^2 (1) = 0.16, p = 0.692, or gender (χ^2 (1) = 2.56, p = 0.209). Binary logistic regression analyses revealed that treatment group allocation was not a significant predictor of 5% weight gain, OR = 0.64, 95%CI = 0.25-1.62, p = 0.353. This remained unchanged once covariates were added, OR = 0.73, 95%CI = 0.27-1.91, p = 0.523. Younger age remained the only significant predictor of 5% weight gain, OR = 0.21, 95% CI = 0.05-0.85, p = 0.029.

8.5.5 Potential Harms

We were not made aware that the intervention caused any harm; in fact, we got many positive comments, suggesting that it was well received.

However, we were aware that the topic of body weight is very sensitive and personal; especially for young adults or those struggling with weight control (REF). Therefore, I trained all researchers assisting with data collection to be sensitive to the individual participant and to be careful to avoid discriminating against anyone based on their weight (high or low) because it might impair help seeking. Everyone who opted to receive their body composition assessment got brief, personal recommendations with it. Furthermore, we decided to offer brief, general advice on available resources regarding concerns about body weight or eating (GP, student services) to all participants, so that those who wished to find help could do so. In case any of the participants had become distressed by their genetic test result, Jane Wardle would have been available for support. However, none of the participants required support.

As discussed in Chapter 2, there is a possibility that receiving genetic test feedback causes transient negative affect and fatalistic reactions. Therefore, we assessed psychological reactions immediately after participants received *FTO* feedback and these findings will be discussed in the next chapter. Participants were once again provided with my contact details at that stage and were encouraged to get in touch with any questions or concerns, but none of them did.

8.6 Discussion

To our knowledge, this is the first study that investigated the utility of *FTO* genetic test feedback to motivate young, healthy individuals to engage with weight gain prevention. In line with our hypothesis, returning weight control advice in conjunction with *FTO* genetic test feedback successfully increased individuals' motivation to engage in weight control behaviours

in comparison with receiving weight control advice without genetic test feedback. As hypothesised, receiving higher risk genetic test feedback (AT/AA) resulted in increased motivation to engage with weight control relative to receiving no feedback, in line with predictions from traditional models of health behaviour (Rosenstock, 1974). Importantly, receiving lower risk *FTO* feedback did not decrease individuals' motivation to engage with weight control, with effects being equivalent to receiving no genetic test feedback; lending no support to the concern that genetic test feedback may result in false reassurance and complacency. However, contrary to hypotheses, effects on motivation did not translate into behaviour change; individuals receiving genetic test feedback and weight control advice showed no more engagement with the weight control advice provided and gained equal amounts of weight compared to those receiving only weight control advice.

8.6.1 Study limitations

However, the study had many limitations. First, baseline weight control intentions were not assessed, so that no inferences about change in motivation as a result of genetic test feedback can be made. Secondly, although the weight control leaflet was evidence-based, it was not piloted in students. It is therefore not possible to discern whether the leaflet would have been effective at changing behaviour without genetic test feedback, and this may explain our lack of behavioural effects. It is possible that the intervention was not intense enough to engage this particularly unmotivated population. It would have been preferable to pilot the leaflet in students before administering it to the larger sample, but this was unfortunately not possible because of time constraints. Furthermore, participants were not specifically encouraged to engage with the tips on the leaflet, because we were interested to explore whether genetic test feedback would be sufficient to prompt participants to seek out information and initiate

weight control without additional support. In the original 'Ten Top Tips' study, participants were motivated to engage with weight loss and were given additional materials (booklets) to record their progress daily. It is also possible that participants engaged in alternative weight control behaviours which were not mentioned in the tips. However, differences in weight gain between the groups were non-significant, and therefore, this explanation appears unlikely.

Randomization procedures leave also potential for bias. Because all relevant procedures were conducted by me (enrolment, group allocation, and data analysis) there was considerable potential for data manipulation. Even with keeping the constraints of the PhD in mind, in hindsight, it would have been desirable to involve a third party at least with group allocation to minimise the risk of data manipulation. However, several steps were taken to ensure that data was safe from manipulation: Data was anonymised immediately after data collection and group allocation occurred as soon as data collection for each wave was complete and before genetic test results became available. Furthermore, all outcome data was collected electronically and print-outs of anthropometric data were kept to ensure that all data are verifiable.

The study suffered from high drop-out rates and poor follow-up, despite making every effort to retain participants (i.e. personal emails, several email reminders, reimbursement). Although this was anticipated (because we chose a population which was not particularly interested) and we chose our sample size accordingly, it nonetheless limits the generalizability of findings. Participants were more likely to enrol if they were normal weight, and less likely to return if they had a higher BMI at baseline which limited opportunities for exploring effects of *FTO* test feedback in individuals who were already overweight.

Lastly, although the study population was chosen to reflect levels of interest in disease prevention in young adults, results cannot be assumed to apply to the wider population. Students are commonly of higher SES, better educated and have higher literacy levels than young adults in the general population which may have affected the interpretation of their results (i.e. they may hold less deterministic beliefs than the general population). Therefore, it might be beneficial to explore effects of genetic test feedback for risk of weight gain in a sample more reflective of the general population.

8.7 Conclusion

The current study provides evidence that returning *FTO* genetic test feedback can successfully increase motivation to engage with weight control in a young, healthy population with low perceived risk and little interest to do so. However, *FTO* genetic test feedback was not sufficient to impact actual behaviour; although it also did not worsen any motivational or behavioural outcomes. These findings provide further evidence that returning genetic test results has transient motivational effects, but does not lead to actual behaviour change.

Chapter 9: Study 4b – Psychological reactions to receiving *FTO* genetic test feedback

9.1 Background

The previous chapter investigated motivational effects of adding *FTO* feedback to generic weight control advice. Results showed that receiving *FTO* feedback increased motivation to engage with weight control; receiving higher risk *FTO* feedback was more motivating than receiving lower risk, or no feedback; consistent with traditional psychological theories (Rosenstock, 1974).

However, as discussed in Chapter 2, one concern of using genetic test feedback to engage healthy individuals with disease prevention is the potential for adverse psychological reactions caused by genetic determinism; possibly resulting in fatalism (with a higher risk result) and false reassurance (with a lower risk result). Either reaction would be detrimental for obesity prevention and treatment because recommendations are primarily based on behaviour change.

Results from the vignette study (Study 1) suggested that a small proportion of participants anticipated mild adverse reactions to a higher risk genetic test result Furthermore, Study 2b showed that lower (and not higher) risk *FTO* feedback may lead to transient negative affect in individuals struggling with weight control; although genetic test feedback had no negative outcomes in the qualitative study with predominantly normal weight individuals (Study 2).

However, because in both qualitative studies samples were small and highly selected, the psychological impact of 'real' *FTO* genetic test required further investigation in a larger sample. Furthermore, no study to date has investigated affective reactions of genetic testing for obesity risk in a sample of young, healthy individuals with low interest to engage in weight control behaviours. However, if genetic test feedback for disease prevention was introduced on a large scale, the target group would be most likely young, healthy individuals unaware of their genetic risk.

9.2 Study aims and contribution to the literature

Therefore, the aim of the study was to investigate the short-term psychological reactions to 'real' *FTO* feedback in the student sample to begin answering the question whether *FTO* feedback is 'safe' to administer in this population. All analyses were exploratory because of the modest sample size.

Based on findings from Study 1, I hypothesised that participants receiving a higher risk genetic test result would show higher negative affect but not higher fatalism in response to their genetic test result compared with those receiving a lower risk genetic test result. Based on findings from Studies 1 and 2b, I also predicted that overweight/obese participants receiving a higher risk *FTO* result would value having an explanation for their weight more than those with normal weight, but that they would also show higher negative affect in response to receiving a lower risk (TT) result.

9.3 Methods and Procedure

9.3.1 Sampling and recruitment

This study used data collected in all waves (and not just from participants in the trial). All participants received an email with the link to a questionnaire assessing psychological reactions from me the day after they received their genetic test result, irrespective of wave in which the data was collected or group allocation (for participants in waves 2 and 3). Therefore, these data are analysed together to increase power.

Details of the recruitment process and sampling are described in the relevant sections (Chapter 7: p. 147; Chapter 7: p.179). Participant flow through the study is shown in Figure 9.1

9.3.2 Measures

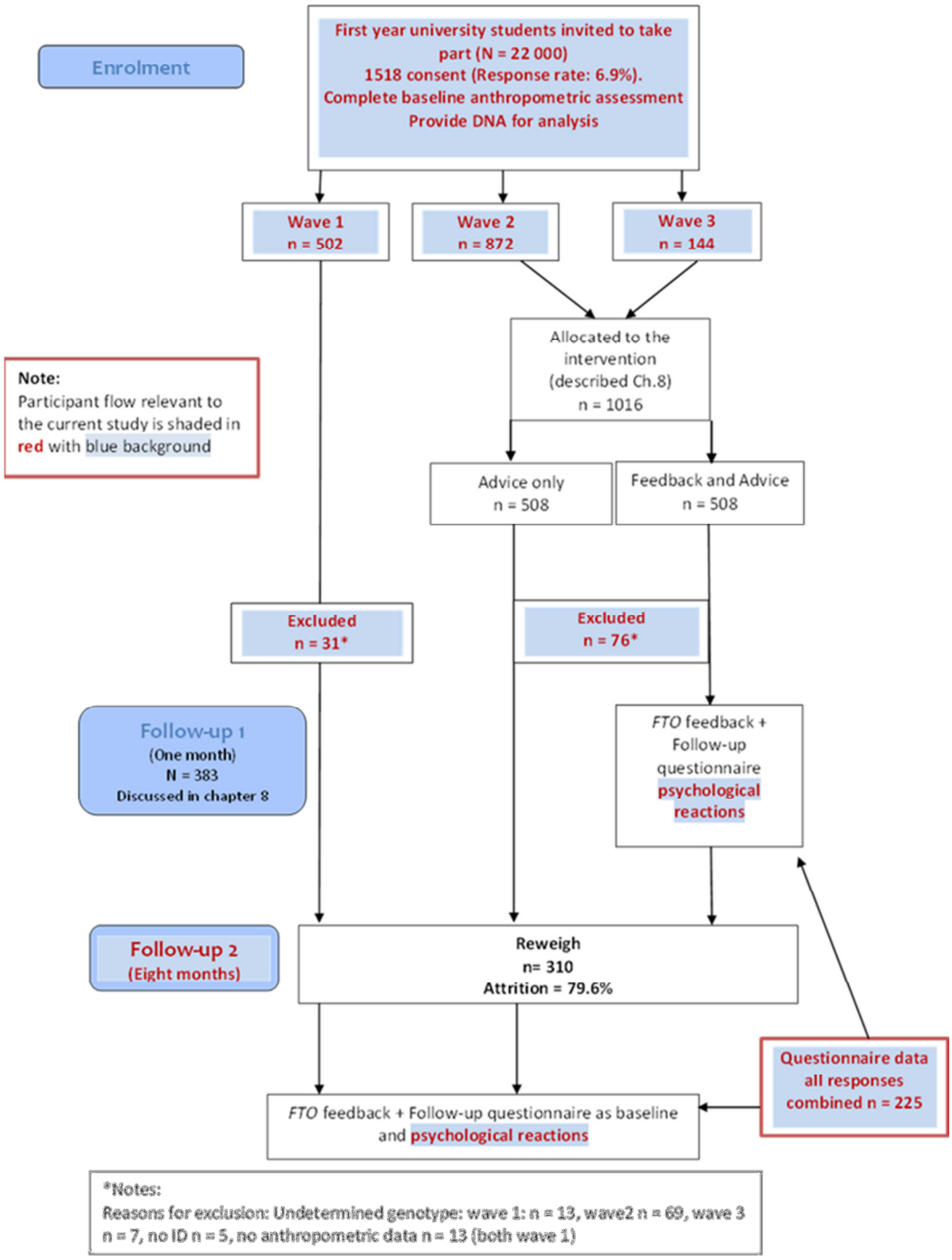
9.3.2.1 *Participant characteristics*

Age, gender and family history of obesity were assessed as part of the questionnaire. Family history was included because having overweight family members could increase perceived risk and potentially modify reactions to FTO test feedback. Effects could be positive if participants had seen family members cope with weight and therefore perceived it as less threatening or severe, or they could be negative if participants were more concerned about weight gain because of previous exposure (Wang, 2010; Acheson, 2010).

Participants were asked *'are/were any of your family members overweight?'* and a list of relatives consisting of mother, father, sister and brother (here participants were asked how many brothers/sisters they had and how many are/were overweight), grandmother on mother's side, grandfather on mother's side, grandmother of father's side and grandfather on father's side was provided . Response options of *'yes'*, *'no'*, and *'don't know'* were given for

each relative. Family history of obesity was coded as 'yes' if at least one parent or grandparent was reported to have been overweight/obese. BMI was calculated from height and weight measurements taken at baseline as described in Chapter 4 (pp.146).

Figure 9.1 Flowchart of study procedures



9.3.2.2 *Psychological reactions to FTO feedback*

A copy of the full questionnaire is included in Appendix 11. Constructs investigated were identical to those used in the hypothetical study (Study 1): Fatalism, Negative Affect, Explanatory value of the *FTO* result and Information Seeking. Motivation to engage with weight control was not included because it was the focus of the trial (Chapter 8). Agreement with each statement was rated on a 5-point Likert Scale, ranging from *strongly disagree* to *strongly agree.*

Question items of each construct are shown in Table 9.1. Question wording was adapted to capture responses to actual feedback but to remain as close as possible to the original items used in Study 1. Also, like in Study 1, scores of individual items in each construct were summed and their mean was calculated to obtain a composite score that was comparable across categories (referring to responses on a 5-point scale from *strongly disagree to strongly agree*).

Four items were newly developed based on review of the literature *('knowing my FTO gene result is useful', 'knowing my FTO gene test result is important for me', 'knowing my FTO gene result makes me think about my future health', 'knowing my FTO gene result will not change anything at all')* to explore potential benefits of genetic test feedback in more detail. These items remained individually assessed because they did not fall into any of the other constructs. Like the other items, responses were rated on a 5-point Likert Scale, with response options ranging from *strongly disagree* to *strongly agree*.

Table 9.1 Statements used to assess psychological reactions to *FTO* feedback

Scale items
Fatalism
Knowing my *FTO* gene test result makes me think that there is nothing I can do to prevent weight gain
Negative Affect
Knowing my *FTO* gene test result makes me regret having taken the test
Knowing my *FTO* gene test result makes me glad (reversed)
Knowing my *FTO* gene test result makes me feel angry
Knowing my *FTO* gene test result makes me feel disappointed
Knowing my *FTO* gene test result makes me feel depressed
Explanation for body weight
Knowing my *FTO* gene test result provides me with an explanation for my body weight
Knowing my *FTO* gene test result confirms what I have always thought of as the reason for my weight
Information seeking
Knowing my *FTO* gene test result makes me want to discuss my result with a health professional
Knowing my *FTO* gene test result makes me go to the Internet to find out more about what the result means
Knowing my *FTO* gene test result makes me want to know more about how the gene acts
Novel items (individually assessed)
Knowing my *FTO* gene test result is useful
Knowing my *FTO* gene test result is important for me
Knowing my *FTO* gene test result makes me think about my future health
Knowing my *FTO* gene test result does not change anything at all

9.3.2.3 *Correct recall of FTO genetic test result*

Correct recall of the *FTO* test result was assessed with two items because recall may also affect subsequent reactions. The first asked *'my FTO test result was…'* with response options being *'AA'*, *'AT'*, *'TT'* and *'don't remember'*. The second question asked *'My FTO test result puts me...'* with response options being *'at lower risk for gaining weight'*, *'at average risk for gaining weight', 'at higher risk for gaining weight'* and *'don't remember'* to determine whether participants understood the meaning of the genetic test result. Recall was coded as 'correct' if participants' answers to both questions matched their actual genetic test result.

9.4 Statistical Analyses

Analyses were carried out using the Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive information was based on frequency tables and cross-tabulation. All data were tested for assumptions of normality (Skewness, Kurtosis, Levene's Test) and results are only reported if these were violated. For Skewness and Kurtosis, values between -1 and + 1 were acceptable.

Differences between completers and non-completers of the follow-up questionnaire were assessed with chi-square tests for categorical variables and t-tests for continuous variables. Differences between participants who correctly recalled their genetic test result and those who did not were assessed with chi-square tests for categorical variables and t-tests for continuous variables.

FTO risk status was not dichotomized into higher (AT/AA) and lower risk (TT) for the current analyses because visual inspection of means suggested that effects differed according to each risk group; therefore, grouping variables together would not have been appropriate.

First, one-way ANOVAs, including only *FTO* status were run to examine short-term reactions to genetic test feedback for outcomes described above. These were followed by one-way ANCOVAs including age, gender, family history of obesity, BMI, correct recall and Treatment group to adjust for effects associated with trial participation. At first, analyses investigated only main effects. Thereafter, analyses were repeated for all outcome variables including *FTO**Gender and *FTO**BMI interactions. For all analyses, age was dichotomized into younger (aged 18-20 years) and older (aged 21 and over) and BMI was dichotomized into 'normal weight' and 'overweight/obese'. Where main effects or interactions were significant, post-hoc pairwise comparisons were carried out to investigate these further. Trends were analysed using polynomial contrasts. Bonferroni corrections were employed in all analyses.

9.5 Results

9.5.1 Participant characteristics

Out of 1518 participants who enrolled in the study, 94.2% (n = 1426) were invited to complete the questionnaire and 15.8% (n = 225) completed it. Participants whose genotype could not be determined (5.8%, n = 89) did not receive an invitation. Table 9.2 shows differences at baseline between completers and non-completers of the questionnaire. Completers were more likely to be female (χ^2 (1) = 16.0, p < 0.001), and to have a slightly lower BMI at baseline (t_{BMIBL} (1424) = 2.12, p = 0.034) than non-completers; although proportions of those classified

as normal weight and overweight/obese did not differ (χ^2 (1) = 2.14, p = 0.143). Mean age was similar between completers and non-completers, t (1424) = -0.78, p =0.434); although a greater proportion of older participants completed the questionnaire (χ^2 (1) = 4.30, p = 0.042).

Table 9.2 Baseline differences of questionnaire completers and non-completers

N = 1426	Completers (n = 225)	Non-completers (n = 1201)	χ^2 /t	Sig
Gender male % (n)	36.9 (83)	51.4 (610)	16.0	<0.001
BMI kg/m^2 mean (SD)	22.0 (2.9)	21.5 (2.8)	2.12	0.034
Normal % (n)	89.3 (201)	84.6 (1016)	2.14	0.143
Overweight/obese % (n)	10.7 (24)	15.4 (185)		
Age years mean (SD)	20.6 (2.9)	20.3 (2.4)	-1.81	0.069
Age 18-20 % (n)	56.4 (127)	63.7 (756)	4.30	0.042
Age 21-30 % (n)	43.6 (98)	37.1 (445)		
Treatment group % (n)				
Control	32.4 (73)	34.4 (413)	5.19	0.075
FA	40.4 (91)	32.5 (391)		
AO	27.1 (61)	33.1 (397)		
***FTO* test result % (n)**				
TT	40.9 (92)	42.2 (507)	0.86	0.649
AT	44.4 (101)	45.4 (546)		
AA	14.7 (32)	12.3 (148)		
Family history overweight				
Yes % (n)	68.4 (154)	--- ---		
No % (n)	31.6 (71)	--- ---		
Recall *FTO* result				
Correct % (n)	79.6 (179)	--- ---		
Incorrect % (n)	20.4 (46)	--- ---		

FTO genotype was in Hardy-Weinberg equilibrium, $\chi^2 = 1.57$, p = 0.454. Genotype status was unrelated to questionnaire completion ($\chi^2 = 0.86$, p = 0.649) and so was treatment group allocation (χ^2 (1) = 5.19, p = 0.075). The majority of participants had a family history of overweight (68.4%, n = 154), defined as having at least one overweight parent or grandparent.

9.5.2 Recall of the FTO result

Overall, accurate recall of the *FTO* test result was high. Nearly 80% of participants (n = 179) could remember their test result accurately, and a slightly fewer (76%, n = 170) could correctly explain its meaning. Participants who recalled their *FTO* result incorrectly (20.4%, n = 46), most commonly misreported a lower risk result as higher risk (37%, n = 17), followed by participants who could not remember their *FTO* result (34.8%, n = 16).

9.5.3 Psychological outcomes

Results of all ANCOVAs (main effects only), including means and standard deviations are shown in Table 9.3. Age was not significantly associated with any of the outcomes, so it is not further reported.

Table 9.3 ANCOVA results of psychological reactions to *FTO* genetic test feedback

Outcome (range 1-5)	Risk status (N = 225)			F (df, error)	Sig.
	TT (n = 92) mean ± sd	AT (n = 101) mean ± sd	AA (n = 32) mean ± sd		
Fatalism	1.73 ± 0.72	1.71 ± 0.78	2.03 ± 0.86	2.19 (2, 214)	0.217
Negative Affect	1.71 ± 0.55[a]	1.89 ± 0.77[a,b]	2.34 ± 0.75[c]	14.30 (2, 214)	<0.001
Information Seeking	3.08 ± 0.67	2.97 ± 0.82	3.20 ± 0.76	0.92 (2, 214)	0.397
Explanation	2.94 ± 1.01[a]	2.45 ± 0.93[b]	2.71 ± 1.07[a,b]	5.66 (2, 214)	0.004
Future Health	3.50 ± 0.80	3.46 ± 0.89	3.94 ± 0.50	2.85 (2, 214)	0.060
Personal utility	3.79 ± 0.79	3.56 ± 0.84	3.81 ± 0.73	2.37 (2, 214)	0.100
Personal importance	3.29 ± 0.90[a]	2.94 ± 0.97[b]	3.03 ± 0.78[a,b]	4.39 (2, 214)	0.015
Not change anything	3.26 ± 1.12[a]	3.47 ± 1.12[a,c]	2.63 ± 0.83[b]	5.77 (2,214)	0.004

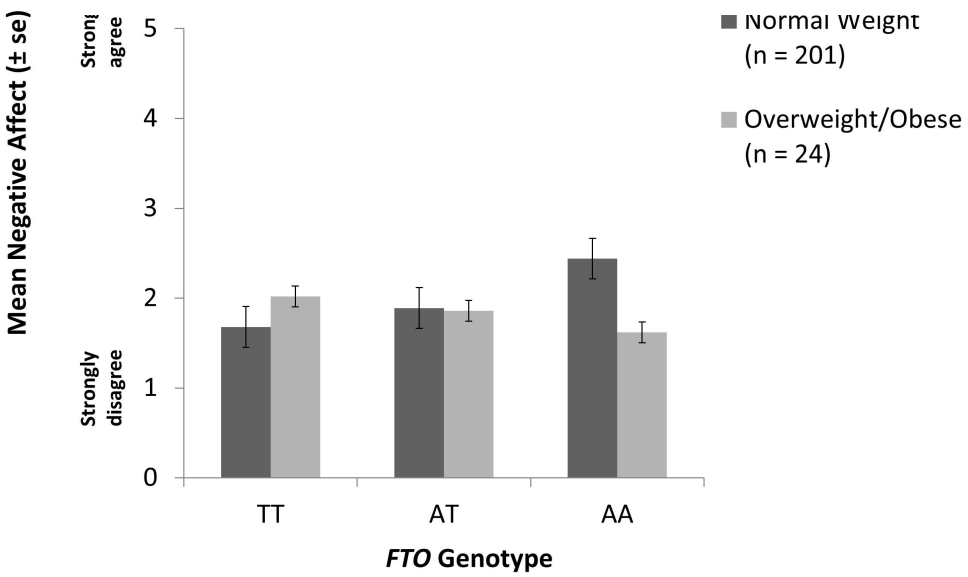
Notes: Results are adjusted for age, gender, BMI, Family history, correct recall and Treatment Group. Means that do not share superscripts differ by p <0.05.

Fatalism Fatalism did not differ by *FTO* risk status (F (2, 222) = 2.19, p = 0.113) and this remained unchanged when covariates were included in the analysis (p = 0.217). Gender was significantly associated with fatalistic attitudes to weight gain, with women being slightly more inclined than men to endorse the belief that there is nothing they could do to prevent it (F (1, 214) = 6.71, p = 0.010), although the very low mean (1.88) and the lack of scores at the extreme end of the scale (nobody scored 5) still reflects overall disagreement with this statement. Other covariates were not significant. Interactions of *FTO* status and gender or BMI were also not significant ($p_{FTO*gender} = 0.452$; $p_{FTO*BMI} = 0.234$).

Negative Affect Negative Affect differed significantly by *FTO* status ($F(2, 222) = 14.26$, $p < 0.001$) and this effect was maintained in the ANCOVAs ($F(2, 214) = 14.30$, $p < 0.001$). AA participants reported significantly higher negative affect than AT or TT participants ($p_{AT} = 0.002$, $p_{TT} < 0.001$). There was a trend for AT participants to report slightly higher negative affect than TT participants ($p = 0.053$); overall reflecting a linear increase in negative affect according to risk. The effect of gender was also significant, with women reporting significantly higher negative affect than men ($F(1, 214) = 4.69$, $p = 0.031$); although the low mean (2.03) indicates modest effects. Main effects of other covariates, including BMI were not significant ($F(1, 214) = 0.01$, $p = 0.985$); neither was the *FTO**gender interaction.

However, the *FTO**BMI interaction was significant ($F(2, 212) = 5.78$, $p = 0.004$). As shown in Figure 9.2, normal weight individuals reported to be most negatively affected receiving an AA result in comparison with those either receiving an AT or TT result ($p_{AT} = 0.001$, $p_{TT} < 0.001$); whereas there was only a trend for normal weight AT participants to report higher negative affect than TT individuals ($p = 0.083$); although, once again, low means and only a small percentage of individuals scoring at the extreme end of the scale (only two participants had a composite score of four and one participant of five) indicated that these effects were mild.

Figure 9.2 Differences in Negative Affect by *FTO*- and weight status

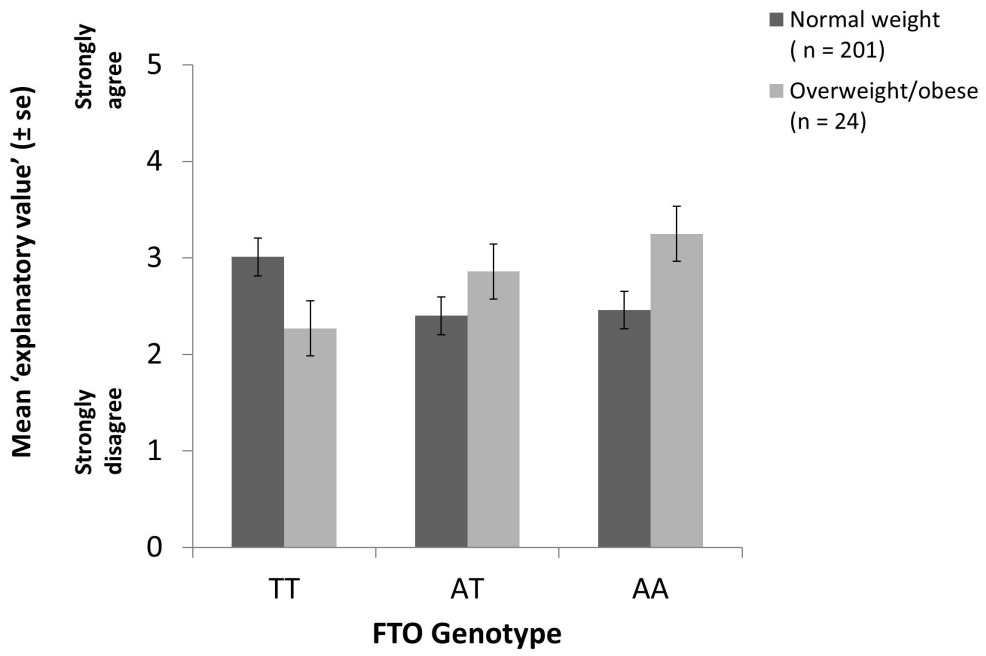


Information seeking Associations of *FTO* status with information seeking were not significant; neither in the univariate analysis (F (2,222) = 1.31, p = 0.270) nor in the ANCOVA (p = 0.397). However, the main effect of BMI was borderline significant, indicating a trend for overweight or obese participants to be slightly more inclined to seek information about *FTO* than those of normal weight (F (2, 214) = 3.86, p = 0.051). Other main effects were not significant. Interactions between *FTO* status and gender or BMI were also not significant ($p_{FTO*gender}$ = 0.487; $p_{FTO*BMI}$ = 0.126), indicating similar reactions for both genders and weight groups within each type of *FTO* result.

Explanation There was a significant association of *FTO* status with the perceived explanatory value of the result (F (2, 222) = 6.05, p = 0.003) and this effect remained significant in the ANCOVA (p = 0.004). Other main effects were not significant; neither was the *FTO**gender interaction (p = 0.260). However, interactions between *FTO* status and BMI were significant (F (2, 214) = 4.84, p = 0.009). As shown in Figure 9.3, unexpectedly, normal weight TT

participants reported to be most glad about having an explanation for their body weight compared with normal weight AT, but not normal weight AA participants ($p_{AT} < 0.001$; $p_{AA} = 0.490$). Differences between AT and AA participants were not significant ($p = 0.217$). Effects were not significant in overweight participants; although means indicated a trend towards a linear pattern in the opposite direction, with TT participants being least glad about having an explanation and AA participants reporting to be most glad to have an explanation for their weight status. However, the small sample size (n = 4) has to be taken into account when interpreting these findings.

Figure 9.3 Explanatory value of the *FTO* result by weight status



Future health considerations Differences by *FTO* status in thoughts about future health were significant in the univariate analysis ($F (2, 222) = 4.50$, $p = 0.012$), but this was not maintained once covariates were added ($p = 0.060$). The effect of gender was significant with women

being more likely to think about their future health in response to the *FTO* result (F (1,214) = 5.30, p = 0.022). Furthermore, correct recall of the genetic test result was associated with future health considerations (F (1, 214) = 5.05, p = 0.026), with individuals who recalled their genetic test result correctly being more likely to think about their future health; although these differences were modest. Other covariates were not significantly associated with future health considerations; neither were interactions with gender or BMI ($p_{FTO*gender}$ = 0.290; $p_{FTO*BMI}$ = 0.186).

Perceived personal utility Perceptions of personal utility did not differ by *FTO* status (p = 0.095). This did not change when the analysis included covariates (p = 0.100) and there were no other significant main effects. Interactions of *FTO* status with gender or BMI were also not significant ($p_{FTO*gender}$ = 0.317; $p_{FTO*BMI}$ = 0.293).

Perceived personal importance However, perceptions of personal importance differed by *FTO* status in univariate analyses (F (2, 222) = 3.68, p = 0.027) which was maintained in the ANCOVA (F 2, 214) = 4.39, p = 0.014). Participants receiving a TT result found it more important than those receiving an AT result (p = 0.015), but not more important than those receiving an AA result (p = 0.204). There was no difference in perceived importance of the result between participants receiving AT vs. AA genetic feedback (p = 1.000). Family history of obesity was borderline significantly associated with perceived personal importance, with participants who had a family history of obesity attaching more personal importance to the *FTO* result than participants who had no family history of overweight (F (1, 214) = 3.84, p = 0.051). Other covariates were not significantly associated with perceived personal importance; neither were interactions with gender or BMI (F = 0.55, $p_{FTO*gender}$ = 0.576; $p_{FTO*BMI}$ = 0.852).

Perceived lack of impact Beliefs that awareness of *FTO* status would not change anything at all differed significantly by *FTO* status ($F(2, 222) = 7.31$, $p = 0.001$) and this effect was maintained in the multivariate analysis ($F(2, 214) = 5.77$, $p = 0.004$). Participants receiving TT feedback were more likely to agree that it would not change anything at all compared with AA but not AT participants ($p_{AA} = 0.032$; $p_{AT} = 0.843$) and AT participants were more likely to agree that it would not change anything at all compared with AA participants ($p = 0.003$). Main effect of gender was also significant with men being more likely to agree that the result would not change anything at all ($F(1, 214) = 3.88$, $p = 0.050$). Family history was also associated with the belief that awareness of *FTO* status would not change anything ($F(1, 214) = 8.02$, $p = 0.005$), with participants without family history of obesity being more likely to agree with this statement than individuals with family history. Other main effects were not significant; neither were interactions with gender or BMI ($p_{FTO*gender} = 0.123$; $p_{FTO*BMI} = 0.689$).

9.6 Discussion

This study investigated the short-term psychological reactions to *FTO* genetic test feedback in a sample of young, healthy individuals. In line with hypotheses, participants showed no evidence of fatalistic reactions in response to *FTO* genetic test feedback, regardless of *FTO* status. Although participants receiving a higher risk *FTO* result (AA) were more negatively affected than individuals receiving a lower risk (TT) result low overall means and a lack of scores at the extreme ends of the scale suggest that these effects were modest. Further investigation revealed that individuals of normal weight were more negatively affected receiving a higher risk AA result than overweight individuals, with a trend for the reverse

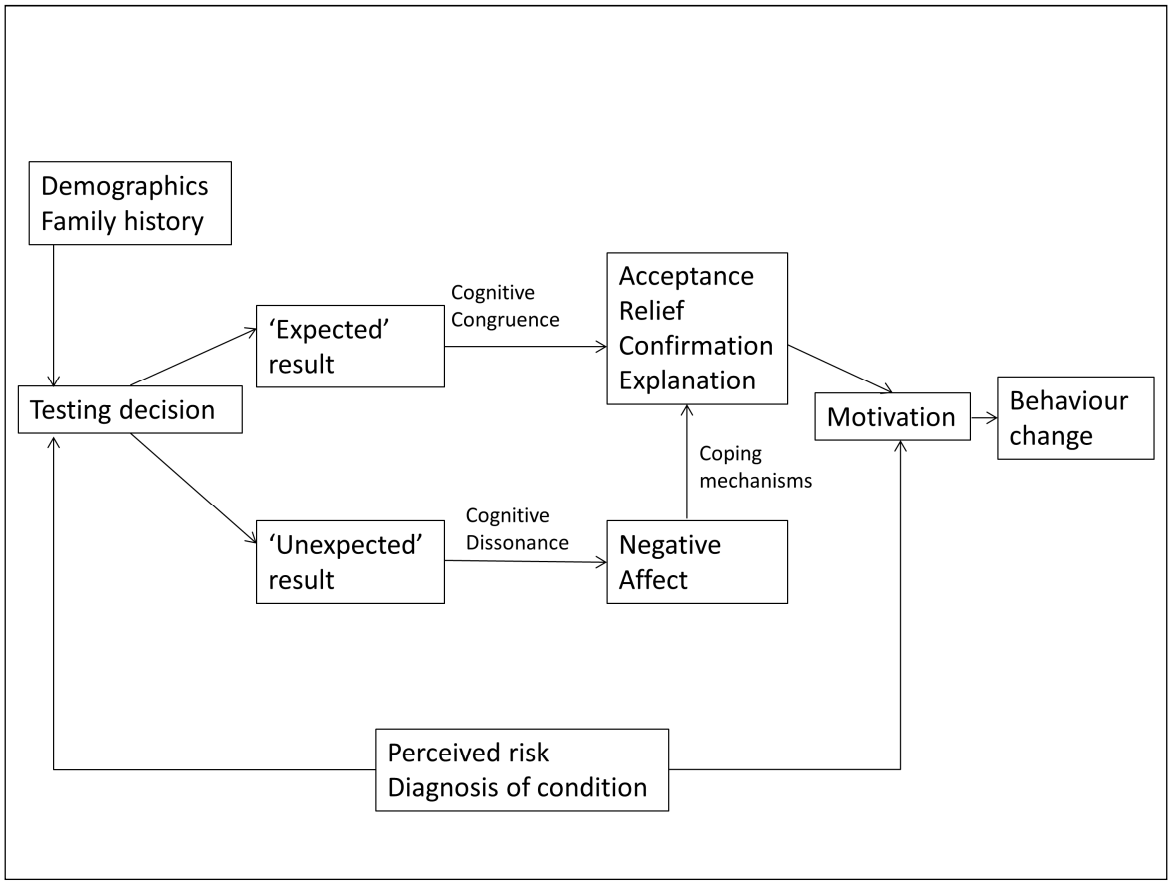
pattern in individuals receiving a TT result (overweight individuals were more negatively affected than normal weight individuals). In line with traditional health behaviour theories (Rosenstock, 1974), individuals anticipated that the knowledge of *FTO* status would lead only to change if it conferred a higher risk AA result. *FTO* status was not associated with information seeking, perceived personal utility or future health considerations. However, contrary to our hypothesis, overweight and obese participants were no more likely than normal weight participants to report that they were glad to have an explanation for their body weight.

9.6.1 A conceptual model of how genetic test feedback may influence psychological and behavioural reactions

Findings from all the studies in this thesis indicate that the impact of genetic test feedback for obesity risk may influence psychological and behavioural outcomes in the following manner (Figure 9.4): Demographic characteristics such as age, gender and education may impact on the decision to enrol for testing; in addition to perceived risk of the condition and existing diagnosis. If genetic test results are as expected (i.e. congruent with the participant's perceived risk or phenotype), I hypothesis that this will lead to acceptance of the result and perhaps some relief of stigma by providing a confirmation of private assumptions or a causal explanation, which will in turn impact on motivation to change behaviour (which is also influenced by perceived risk or an existing diagnosis). Ultimately these should result in actual behaviour change, although my study was as unsuccessful as those that have gone before in finding evidence for behaviour change.

If the result is unexpected to the participant (i.e. incongruent with their expectations, either because of prior perceived risk or current phenotype), this could result in cognitive dissonance and an increase in perceived risk, and potentially, negative affect. In my study, negative affective reactions were reported by some respondents but the reaction was transient, probably because coping mechanisms led to acceptance of the result, relief, confirmation and a causal explanation resulting in the increase in motivation to change behaviour as discussed above.

Figure 9.4 Proposed model of the mechanisms whereby genetic test feedback influences psychological and behavioural reactions



9.6.2 Study limitations

However, this study had several limitations. First, several constructs that may be important contributors to either testing decisions or psychological and behavioural reactions were not investigated (e.g. self-efficacy, tolerance of uncertainty, information avoidance) because it was beyond the scope of this thesis. However, these elements could be investigated in future research.

Secondly, the low overall response rate (15.8%) limits any conclusions that could be drawn for the student population at large. The long delay between providing saliva for analysis and receiving the genetic test result (either because of group allocation or because of delays in processing by the Institute of Metabolic Sciences) may have resulted in students being disinclined to return the questionnaire. Furthermore, it is possible that spamfilters and some results being returned near the holiday period (during which students may not check their university emails) precluded emails from reaching recipients. It is unlikely that questionnaire length contributed to the low response rate, because only two participants terminated the questionnaire before completion.

In addition, because of the observed differences between questionnaire responders and non-responders, particularly in the low number of overweight and obese individuals (n = 4) who returned the questionnaire; results from this group have to be interpreted with caution. It is possible that individuals who were more negatively affected by their genetic test result did not return the questionnaire.

Lastly, findings may also have limited application to the wider population because students tend to be better educated and have higher SES and literacy levels than the general population, as described in the previous chapter. Future research could explore reactions to obesity genetic testing in the wider population to allow for drawing more general conclusions.

9.7 Conclusion

Despite its limitations, findings from this study lend little support to concerns about fatalistic or complacent reactions in response to *FTO* genetic test feedback for the risk of weight gain in this young, healthy population; matching results from hypothetical and earlier small-scale studies. These findings are encouraging for aims of integrating predictive genetic testing into mainstream medicine.

Chapter 10: General discussion and Conclusions

The aim of the studies described in this thesis was to examine the emotional, motivational and behavioural effects of *FTO* genetic test feedback first in vignette studies, then in smaller scale qualitative research, then in a larger scale study, and finally to examine its contribution to promoting weight management. The key concern in all studies was psychological safety, with positive emotional, motivational and behavioural effects as a secondary focus.

10.1 Psychological impact of FTO genetic test feedback

The first set of research questions I tried to answer was: *'What is the psychological impact of anticipated and 'real' genetic test feedback for risk of weight gain? Will genetic test feedback cause fatalism (with a higher-risk result) or false reassurance (with a lower-risk result)? Will responses differ by weight status?'*

Results from the vignette study (Study 1) showed that the idea of a higher risk genetic test result did not result in a fatalistic attitude or false reassurance. Although fatalism increased slightly in the student sample, the increase was small, with the mean response increasing from 'strongly disagree' to 'disagree'; and only a very small percentage of students thought that they were destined to gain weight if their result showed the higher risk *FTO* variant. Vignette studies really only tell us what people *think* that they might feel, and they may not engage very hard in the thinking process. However, this reassuring result made it possible to move on to studies concerned with 'real' *FTO* feedback (Studies 2a, 2b and 4b). Results from these three studies confirmed that real genetic test feedback did not increase negative attitudes; regardless of risk status. In fact, far from fatalism, awareness of *FTO* status was perceived as

helpful and motivating; particularly for individuals who had difficulties at weight control. These findings contrast with some of the earlier work on smoking cessation (Sanderson & Wardle, 2005) and susceptibility to heart disease (Senior & Marteau, 1999). It is possible that causal attributions of obesity incorporate biological and environmental causes; whereas those for smoking or familial hypercholesterolemia are drawing predominantly on biological explanations (Senior, 1999) which may explain the discrepancy in findings.

Results from both my qualitative studies suggested that individuals' cognitive constructs of the causes of weight gain correctly incorporate multiple causes; so adding information about one gene that evidently only contributes very modestly to obesity development understandably had had little effect on altering obesity-related beliefs. Lock and colleagues (2006) discovered in interviews with 40 participants from the REVEAL study (Green et al., 2009) that personal beliefs about disease aetiology are resistant to change, and that new information encountered is made to 'fit' with previously held beliefs; a finding similar to that by Michie and colleagues (2005) about Familial adenomatous polyposis (FAP) aetiology, which remained wrongly perceived as multifaceted even after education sessions informing about dominant inheritance patterns. Alternatively, it is possible that only participants who anticipated not being negatively affected participated in the studies giving 'real' genetic feedback, as proposed in the self-selection hypothesis by Sanderson & Wardle (2005). Given that people are unlikely to get genetic feedback unless they volunteer, these results suggest that access to *FTO* genetic test feedback is not likely to contribute to fatalism.

This finding fits well with the current literature investigating fatalistic attitudes to genetic test feedback. As discussed in Chapter 1, on the whole, most studies have not found evidence that

awareness of genetic risk results in fatalistic attitudes (e.g. Marteau et al., 2004; Bloss et al., 2011), even for severe conditions, such as Alzheimer's or Huntington's Disease where to date no cure exists (Green et al., 2009; Wiggins et al., 1992). However, the low uptake rates of genetic testing in the population affected by Huntington's Disease (~ 30%) suggests that the self-selection argument has probably some validity and needs to be kept in mind when interpreting findings from any study on genetic test feedback.

The limitations inherent in self-report measures have also to be considered. Although survey items were based on a review of the literature, they did not stem from validated scales and may therefore be inadequate to correctly assess fatalistic responses. For example, Likert scales may not have been sensitive enough to account for any nuanced responses from individuals. I considered using visual analogue scales, as they have been found to have good ecological validity (Fields, 2005), but because they were not used in any other study, and coding them for statistical purposes can be challenging, I decided to use Likert scales in this thesis. However, despite including several items which were grouped into overarching scales by means of Principal Component Analysis to improve validity, fatalism remained assessed through a single item. Single item measures have been shown to have lower validity and reliability than composite scales (Fields, 2005). However, in the few other quantitative studies in the area (Sanderson & Wardle, 2005, Marteau et al., 2004), fatalism was also assessed through a single item, so that findings could at least be compared across studies.

Some increase in negative affect was anticipated in a small proportion of participants in the vignette study, and this was also observed the studies giving 'real' *FTO* genetic test feedback, with a small linear increase per higher risk allele. In contrast to the vignette study, results

from Studies 2b and 4b revealed that negative affect varied by risk-and weight status: normal weight participants showed mildly elevated negative affect in response to a higher risk genetic test result, but overweight and obese individuals reported increases in negative affect in response to a lower risk (TT) genetic test result.

Although these findings may be somewhat puzzling in isolation, when interpreted alongside the data for the perceived 'explanatory value' of *FTO* feedback, they are less surprising. Individuals struggling with weight control, appeared to benefit from receiving an 'explanation' for their weight status in the form of a higher risk result by reduced self-blame and a shift of focus towards taking action; suggesting that genetic feedback may have value beyond 'objective' clinical utility in participants struggling with weight control. In this respect, motivation to participate may have differed from those without difficulties at weight control. As shown in the qualitative studies, most normal weight individuals took part out of curiosity; whereas among individuals struggling with weight control, participation was unanimously driven by the desire to find an *explanation* for one's own 'battle' with weight. Therefore, a lower risk genetic test result led to disappointment because it lacked the anticipated 'genomic confirmation' of their weight problems. Alternatively, it is possible that slightly elevated negative affect is a necessary intermediate for shifting individuals towards taking action. Either way, it appears that coping mechanisms were relatively efficient because individuals in the qualitative studies insisted that negative effects were transient and nobody contacted us for advice in any of the studies. These findings are in line with the review by Heshka and colleagues (2008) who investigated responses to genetic feedback for more severe conditions and found that negative affect in response to genetic test feedback may be elevated in the short-term, but not the longer-term. Furthermore, humans have generally a high capacity to

adjust to adverse life experiences (Bonnano, 2004), and the response to genetic risk information appears to be no exception.

However, as these findings were obtained from qualitative work, which is limited by the small sample size and the potential for social desirability or researcher bias, they have to be viewed with caution and further quantitative work is needed to test the hypotheses that they generated.

A further limitation common to all studies in this thesis was that samples were self-selected and therefore, only individuals who had positive attitudes towards genetics and who anticipated no negative outcomes may have taken part which may have influenced reactions to genetic feedback. The small sample sizes in the qualitative studies (studies 2 and 2b) – which is usual with this methodology – primarily allows us to develop hypotheses for further research and cannot be generalised to other/larger populations. It would have been desirable to include a larger number of participants in the qualitative studies to improve validity; especially because I did not observe differences in explanatory value by weight status in Study 4b which investigated the psychological impact of FTO feedback quantitatively. However, trends were in the same direction as those from the qualitative studies and the discrepancy may be due to the small sample overall which meant that the power may not have been sufficient to detect differences in responses between participants.

The numbers of overweight and obese individuals in study 4b were low (n = 34); making it difficult to draw conclusions. Problems with participant retention had been expected because the study population was not particularly motivated, but this was made worse by the delays in

genotyping that were not in my control. The delay meant that students were not reachable anymore, so personal reminders were also ineffective. Furthermore, it may have caused individuals to be less cooperative when required to return the final questionnaire, contributing to the low response rates, as discussed in Chapter 7. It would have been desirable to build on findings from the qualitative studies with a quantitative study with a larger number of overweight/obese individuals to investigate the 'genetic confirmation' hypothesis further. If the search for 'genetic confirmation' was a motivation to seek testing that applies to a larger segment of the population, it would change the purpose of the genetic test from being 'predictive' to 'aetiological' in terms of its interpretation by the individual, which might need to be considered in the debate about clinical utility of genetic testing for common complex conditions.

It would have also been desirable to also include participants from different socioeconomic and ethnic groups. All the participants in my studies were highly educated and predominantly white, but attitudes towards genetic testing may differ among ethnic groups and across socioeconomic strata (Kaphingst et al., 2012). The generalisability of my findings would have been improved if a wider variety of participants had been included. Although the current findings replicate those from earlier studies and other areas of genetic testing (Bloss, Schork, & Topol, 2011b; Heshka, Palleschi, Howley, Wilson, & Wells, 2008; Conradt et al., 2009; Harvey-Berino, 2001), participants in these studies were also likely to have been 'early adopters' and therefore wealthier, better educated and with higher literacy levels than the general population (McGowan et al., 2010). Few studies have investigated effects of genetic test feedback in more varied population groups (e.g.McBride et al., 2002; Lipkus et al., 2004), and although findings are comparable to others (e.g. improvements in smoking cessation rates

in the short-but not the longer-term), the limitations of self-selection/early adopters may also apply in these samples.

The studies in this thesis concerned with genetic test feedback were all cross-sectional, so that inferences about longer-term impact cannot be made. Ideally, participants would have been followed up over a longer period of time to explore whether reactions to their result changed, but this was not possible because of the time constraints of the PhD.

10.2 Motivational and behavioural impact of *FTO* genetic test feedback

The second set of questions I tried to answer was *'What is the impact of genetic test feedback for weight gain susceptibility on motivation to avoid weight gain or to lose weight? Does it enhance or decrease motivation to control weight? Does the effect depend on genetic risk status? Does the effect depend on current body weight?'*

The results of the vignette study had indicated that motivation to prevent weight gain or to initiate weight loss in response to receiving *FTO* feedback would be high regardless of weight status, but would be higher in response to a higher risk result. These findings were supported in the studies giving 'real' feedback. In particular, results of the RCT (Study 4) showed that adding genetic test feedback to weight control advice increased weight control intentions in participants who received feedback and advice, compared with those receiving weight control advice alone. Within the feedback group, receiving higher risk genetic test feedback was more motivating than receiving lower risk, or no feedback; matching predictions from traditional Health Behaviour Models (Rosenstock, 1974) rather than those of illness perception models (Leventhal, 1997). Although the effects in response to the feedback were overall modest, and

smaller than anticipated in the vignette study, this may be due to people overestimating the impact of events in hypothetical scenarios; expecting generally a stronger emotional reaction than they will actually have (Persky et al., 2008; Armor et al., 2006;Ajzen et al., 2004). Furthermore, most students who participated in the RCT had very low motivation to control weight (because most of them were normal weight), which may have contributed to the small effect size.

Importantly, findings from the RCT showed that receiving lower risk TT feedback did not result in a decrease in motivation to avoid weight gain, with weight control intentions identical to those of receiving no genetic feedback. These findings further support the idea that lay beliefs about disease onset are multifactorial, and less genetically deterministic than predicted by some; although it is important to note that the information provided to participants clearly outlined the multifactorial causes of unhealthy weight gain and was reiterated at various time points throughout the study which may have influenced participants' deterministic beliefs. However, because findings from the studies presented here are in agreement with previous studies (e.g. Hollands et al., 2012; Bloss et al., 2011; Sanderson et al., 2008), they are likely to have some validity. Furthermore, there was no indication that overweight/obese individuals would disengage with efforts at weight control in response to a higher risk genetic test result (which might have been assumed following deterministic predictions). As discussed earlier, findings indicated that public confirmation of private assumptions about weight from a source perceived as 'objective' helped to alleviate some of the internalized stigma of obesity and shifted individuals' focus toward taking action. Considering that individuals did not enrol specifically in a weight loss intervention this is encouraging; although the small sample size of overweight and obese individuals limits any general conclusions.

The motivational effect of *FTO* genetic test feedback described here cannot be viewed in isolation, but has to be interpreted in conjunction with my third and fourth set of research questions: *Is FTO status associated with weight gain at university? Will returning genetic test feedback alongside weight control advice be effective at diminishing weight gain during this time period? Will awareness of genetic risk status result in behaviour change?*

I found that, despite low follow-up rates and a highly selected sample, *FTO* status is associated with clinically significant weight gain at university, which would warrant risk-stratified intervention at this time. However, unfortunately, the answer to the question of whether or not gene test feedback had a behavioural effect was 'No'. Although the intervention was successful in increasing weight control *intentions*, it had no impact on actual behaviour, or on weight change. There may be several reasons for these negative findings. First, behaviour change is complex and results from a multitude of factors, some of which are still not very well understood (Michie et al., 2009). Therefore, it would have been surprising if adding a single piece of information would have had enough impact to alter behaviour to any great extent; particularly, if disease representations are multifactorial. However, if there is a 'tipping point' for action, it is reasonable to aim at 'edging' people to that tipping point and Study 4 has shown that returning genetic test feedback for risk of weight gain may be one way of achieving this.

A second reason is that the participants in this study were young, healthy individuals not particularly concerned about weight gain, and therefore they may have seen little need to take immediate action at weight control; hence no effects on actual behaviour change. It is

possible that people will keep their result in mind and take action quicker than they would have otherwise once they begin gaining weight, as participants also reported in Study 4b that higher risk FTO feedback would make them think about their future health. However, the one-year follow-up results from Bloss and colleagues' study which recently became available (Bloss, Wineinger, Darst, Schork & Topol, 2013), found no differences in anxiety, diet or exercise behaviours between baseline and follow-up. The only effect was that participants were more likely to have shared their results with a physician, which resulted in more screening tests than reported in the short-term; especially in participants over 40 years old. This suggests that people may act on their test results once they feel it necessary, but as these are findings from a single study, results have to be viewed with caution. In the present study, it would have been valuable if I had been able to follow up participants for an extended period of time to ascertain whether awareness of FTO status would prompt earlier action.

One issue discussed in relation to Study 4 (p. 215), is that it is possible that the weight control leaflet was ineffective. As the students in the study did not specifically enrol in a 'weight control intervention', nor were they explicitly encouraged to follow the tips, the intensity of the intervention might not have been sufficient. Weight gain prevention studies in this age group have usually only been effective if they are very time- and resource intensive (e.g. weekly courses), as discussed in Chapter 2. It would have been interesting to offer an intervention with proven efficacy, but in that case, participation would have depended on interest in weight loss, and the potential value of a'light touch' prevention would be lost. I was also able to explore the effects of 'self-motivation' in response to FTO genetic feedback, which would not have been possible with a more structured intervention.

One limitation of all studies in this thesis was that genetic test feedback was given for a single gene implicated in a complex condition. As discussed above, any significant reaction (positive or negative) could be deemed inappropriate as the effect size is so small. This scenario is highly unlikely in clinical practice because steadily falling sequencing costs now allow for sequencing of gene panels, and most likely, whole genome sequencing in the foreseeable future, so that participants may assign a different meaning to these results. However, when this study was conceived (2008) the dramatic fall of sequencing costs was not predicted; therefore, studies presented here only focused on FTO and therefore, can only serve as a proof-of-principle investigation. A further shortcoming is that we did not provide participants with much specific information on how to counteract FTO's effects, as there have been no tests of the type of advice that would help to counteract the probable behavioural mechanisms of low satiety sensitivity and high food responsiveness. Advice tailored to the individual genotype result may have had a greater impact than generic weight control advice, but this hypothesis remains to be explored in further research.

10.3 Implications for clinical practice

Findings from the current thesis may have some implications for clinical practice; bearing in mind the many limitations discussed above; particularly, that studies in this thesis used only a single marker with modest effect size to assess weight gain susceptibility and the highly selected samples.

Results of the studies presented here showed that knowledge of genetic risk may be beneficial for individuals who have difficulties with weight control by diminishing negative emotions associated with this problem. The 'scientifically objective' genetic test result was perceived as

removing some of the stigma and shame attached to weight gain, permitting dialogue about the 'condition'. Therefore, it might be useful to include genetic test feedback as one component of weight loss intervention packages. However, if genetic feedback was offered in a clinical context, it would be crucial to determine beliefs about risk status beforehand to avoid negative impact.

Secondly, as demonstrated in the studies presented here, and in all other studies concerned with the psychological and behavioural effects of genetic test feedback, impact (positive or negative) appears to be much less than anticipated; suggesting that deterministic beliefs about disease development are not widespread and most people are unlikely to overestimate the predictive value of genetic tests; especially when feedback is concerned with a single gene implicated in the development of a complex condition. However, instead of dismissing genetic test feedback for behaviour change because these early studies have had little impact, we need to continue improving our understanding of how individuals make sense of and use their genetic data to discover how to best harness the potential of this new and exciting technology.

10.4 . Conclusion

Results from this thesis indicate that *FTO* genetic test feedback for weight gain susceptibility has little adverse psychological impact and may be beneficial for overweight and obese individuals by diminishing stigma and self-blame. Furthermore, normal weight individuals appreciated the information about their risk of weight gain, and FTO feedback was successful in increasing their readiness to change behaviour. Based on results of the current thesis it would also be expected that FTO feedback is be especially useful for normal weight women with a family history of obesity who receive AA feedback; although the studies here were not

sufficiently powered to draw firm conclusions. However, although *FTO* feedback was effective in increasing weight control intentions, it had no impact on behaviour change. Although the many limitations of the studies presented here have to be kept in mind, in particular the often small and highly selected sample sizes and the cross-sectional nature, findings are in agreement with those obtained from other studies in the field which increases confidence. With whole genome sequencing on the horizon, we need to continue to improve our understanding of how individuals 'make sense' of genetic risk to successfully harness the potential of genomic medicine to influence health behaviour change.

Chapter 11: References

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Chapter 12: Appendices

12.1 Appendix 1: Tables of studies discussed in the Literature reviews

Literature Table FTO review, Chapter 1

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
FTO and measured food intake					
Cecil et al (2008)	Measured ad-libitum food intake at a test meal containing a selection of sweet and savoury foods after preloads of varying energy density	Foods weighed before and after consumption, caloric value calculated	Children with at least one higher risk FTO allele ingested food with significantly higher energy density, but not higher weight, than children with the lower risk genotype after receiving the no energy and low energy preload, with a similar trend for the high energy preload. This effect remained significant	76 schoolchildren aged 4-10 years	Experimental Preload conditions high-energy (389kcals), low energy (187 kcals), no energy (water)

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			after controlling for age and BMI.		
Wardle, Llewellyn, Sanderson & Plomin (2008)	Association of FTO and eating in the absence of hunger	Biscuits consumed 1 hour after a meal. Plate weighed before and after consumption	Food intake was significantly higher in children carrying one or two higher risk alleles than in children homozygous for the lower risk allele; following a linear trend. Results remained significant after adjusting for BMI.	131 children aged 4-5 years	Experimental Home-based Children could eat as much as they liked for 10 min.
Dougkas, Yaqoob, Givens, Reynolds & Minihane (2013)	Measured ad libitum food intake after preload (201 kcal or water)in overweight individuals	Appetite and hunger rated on VAS; foods weighed before and after lunch; KJ calculated.	Significantly lower reports of fullness and higher hunger after preload in carriers of at least 1 A allele, but no difference in energy intake	40 overweight men from gen pop, mean BMI 32.1, SD = 9.1	Randomised with-in subject experimental cross-over design Preload: 3 types of different dairy snack, given to each participant one wk apart
FTO and -self-reported food intake					

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
Children and adolescents					
Liu (2010)	Assoc of FTO with insulin resistance, energy intake, PA	Up to 7 24h diet recalls , PA self-report, fat, BMI w DXA	No significant association w FTO and energy intake, PA, no insulin resistance and %body fat	1978 youth (mean age 16.5 y) ,	Cross-sectional
Johnson et al (2009)	Assoc of FTO and dietary energy density	3-day unweighed diet diaries, completed by children w parental help when aged 10	No evidence for assoc of FTO w dietary energy density at age 10 w fat mass at 13	2275 children from ALSPAC	Cross -sectional
Timpson et al. (2008)	Association of FTO and dietary intake	Detailed 3-day parent completed dietary records	Per higher risk allele significantly higher consumption of total fat (1.5g higher/day) and energy (25kj/day). Difference persisted after adjusting for BMI	3641 children from ALSPAC	Diet diaries 3 day unweighed food records, incl portion sizes, and preparation methods
Adults					
Park et al. (2013)	FTO and energy intake in multiple racial/ethnic populations	FFQ, 180 items, incl. portion size for MEC, EAGLE:24 hour 24 hour dietary recall	Sig higher intake of calories from fat, but no assoc w energy intake	36973 adults from the MEC, EAGLE-NHANES III and PAGE studies, BMI ~26.1	Cross-sectional

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
Brunkwall et al (2013)	FTO and food preferences	7-day menu book, 168 item FFQ and Interview-based diet history, 7-day self-report	Sig higher intake of protein in AA carriers, sig higher intake of cals in AA	28098 adults, mean BMI ~25.6.	Cross-sectional Interview and menu book incl portion size, calculate daily calorie consumption
McCaffery et al (2012)	Discover assoc of obesity susceptibility loci (incl FTO) and dietary intake	FFQ, 134 main items, 20 line items can be added	Sig higher intake of calories in AT/AA carriers and more eating episodes/day but diminished after adjustment for weight	2075 participants in the LOOK AHEAD trial, all overweight or obese (mean BMI = 36, SD = 5.9) Mean intake 2000 kcals over 4.7 meals	Assesses food intake over previous 6 months portion size included (small, medium, large)
Hasselbalch et al (2010)	Investigated assoc of FTO and MC4R and dietary intake	247 item FFQ 1 month recall	No association of FTO with habitual dietary intake	756 adult twins from the GMINAKAR study cohort, mean BMI 27	Cross-sectional, FFQ validated against 2-d weighed food records
Holzapfel at al. (2010)	Associations of obesity genes with lifestyle factors (diet and PA)	FFQ with focus on fat and carbs, self-reported physical activity	No association for a direct lifestyle SNP association	12462 adults from the MOINICA/KORA study, , mean BMI 26.9.4.9	Cross-sectional
Bauer et al. (2009)	Association of obesity genes and energy-and macronutrient intake	178-item FFQ daily consumption during year preceding enrolment; portion sizes included	No association of FTO and food intake	1700 adults from the EPIC-DUTCH cohort, BMI 25.9, SD = 4.02	Cross-sectional Portion sizes assessed w pictures, calculate average daily calorie consumption
Sonestedt et al (2009)	Investigate whether FTO assoc with dietary factors and	7-day menu book and 168-item FFQ, PA: Minnesota	FTO higher risk allele effect on BMI only observed in	4839 adults from the Malmö study, mean BMI ~25.8.	Cross-sectional

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
	PA	Leisure Time Physical Activity Instrument	individuals w higher fat diet and lower carb intake and restricted to those w low leisure time PA		
Speakman, Rance & Johnstone (2008)	Discover whether FTO associated w variations in energy intake or expenditure	7-day diary, weighed food records and kept packaging; BMR and VO_2 max for energy expenditure	FTO genotype sig assoc w variation in energy intake TT: 9.0MJ/day; AT: 10.2MJ/day; AA: 9.5MJ/day. No variation in energy expenditure	150 White adults , BMI from 16.7-49.3	Cross-sectional
FTO and eating behaviours					
Satiety sensitivity					
Karra et al (2013)	Link between FTO, ghrelin, BMI	Test meal protocol, appetite assessed with VAS before, 20, 30 min after	AA homozygotes failed to suppress circulating levels of acetyl-ghrelin	359 males aged 18-35, normal weight (BMI 22.5, SD = 0.1) 10 were selected,	experimental

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
		meal ingestion and every 30 min after until 180min after	appropriately in response to the test meal and levels remained elevated for the duration of the study period. Correspondingly, AA participants also reported significantly higher levels of hunger after meal termination and for the remainder of the study period than TT homozygotes.	matched and consumed test meal	
Ibba et al (2013)	Assess influence of FTO on satiety sensitivity	CEBQ	No sig assoc of CEBQ Satiety Sensitivity scale and FTO genotype	412 obese Sardinian children and adolescents aged 4-20 years	Cross-sectional
Den Hoed, Westerterp-Plantenga, Bouwman, Mariman, & Westerterp, 2009;	Assess FTO and satiety responsiveness	Rate hunger and satiety on VAS before and after consumption of a fixed meal	Carriers of at least 1 A allele significantly higher hunger and reduced satiety after meal	103 adults, mean age 31, BMI 25	Experimental Fixed meal protocol

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			consumption		
Wardle et al., 2008	Assoc of FTO with habitual appetitive behaviour	CEBQ	AA sig reduced satiety responsiveness scores	3337 children aged 8-11 from TEDS	Cross-sectional
Tanofsky-Kraff (2009)	FTO and eating behaviours (incl. binge eating)	Ad libitum lunch after 6 hr fast, EDE, rate hunger and satiety on VAS	No sig differences in satiety responsiveness at ad libitum, lunch but sig higher rates of LOC eating episodes in carriers of at least 1 A allele Also select foods higher in fat, no diff in cals	289 children and adolescents aged 6-19 years , normal weight , 190 participated in the ad libitum lunch	Experimental
Aberrant eating behaviour					
Cornelis et al (2013)	Assoc of FTO and other obesity susc loci w with uncontrolled eating, emotional eating and eating restraint	TFEQ	*FTO* sig assoc with all three aberrant eating behaviours, with each higher risk allele resulting in modestly increased scores	3852 adults in mid-sixties slightly overweight (mean BMI women: 25.9, SD: 5.1; mean BMI men: 25.3, SD = 3.1).	Cross-sectional

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			(~0.12-0.33) on each TEFQ subscale. However, only the association with cognitive restraint remained sig after adjustment with BMI and none of the associations survived adjustments for multiple testing. also the case for assoc of the gen risk score w aberrant eating and for any of the other SNPs investigated.		
Jonassaint et al (2011)	Assoc of FTO and eating disorders	SIAB and clinical interviews	No sig assoc w AN irrespective of subtype	1085 AN patients, 677 HC, from 3 large clinical cohort studies	Cross-sectional
Mueller et al (2012)	Assoc of FTO with eating disorders	Clinical interviews, CIDI questionnaire	Sig assoc of *FTO* with Bulimia Nervosa (BN) although only evident in	477 participants with BN, 689 with AN, 984 non-population healthy controls and a	Cross-sectional

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			comparison with the non-population based sample of controls.	population sample of 3951 control participants	
FTO and physical activity					
Kilpeläinen et al (2011)	Investigate influence of PA on FTO activity	41 published studies, 13 unpublished PA dic into 'inactive' vs.'active → categorical: inactive < 1 hr. leisure time or commute + sedentary occupation; continuous: bottom 20% 'inactive'	PA sig attenuated the association of *FTO* with BMI, with the effect being reduced by 30% in physically active adults; odds of being overweight or obese were also significantly reduced in physically active individuals with the higher risk alleles (27% and 26%, respectively)	218.166 adults and 19.268 children	Meta-analysis

Review of psychological and behavioural outcomes of FTO genetic test feedback, Chapter 2

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
Psychological outcomes					
Fatalism					
Senior et al (1999)	to describe parents' perceptions of familial hypercholesterolaemia (FH), an inherited predisposition to heart disease, following population-based neonatal screening	Qualitative interviews questions about beliefs about high cholesterol in children; based on the self-regulation model of illness perceptions As the interview was designed to elicit perceptions of the screening test, rather than elicit perceptions of genetic testing, perceptions of genes were only explored if participants raised them first.	found that parents felt the condition was more dangerous and less controllable when they thought of the result as genetic rather than related to the mother's diet during pregnancy.	24 parents of infants aged 15-30 months	qualitative
Wiggins et al (1992)	To investigate psych effects of testing for Huntington's disease	Standardised questionnaires assessing distress, depression, well-being	Decreased risk lower scores for distress than before testing increased risk, no change at first, but over the year small linear declines in	135 participants	longitudinal

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			distress and increases in well-being. At 12 mo. Both increased and decreased risk group had lower scores on depression and higher scores for well-being than no-change group.		
Heshka et al (2008)	Psychological outcomes of genetic testing for nonpolyposis colorectal carcinoma, hereditary breast and ovarian cancer, and Alzheimer's disease	5 databases searched, terms related to genes, testing psych impact	No long-term impact on affect, increased screening for breast and crc, no impact on risk perceptions	35 articles, 30 studies	Review
False reassurance					
Sanderson & Wardle (2005)	explored factors associated with a motivated or a complacent reaction to genetic testing for risk of heart disease or cancer	Vignette study Single statement for each reaction of interest (motivation, complacency, and depression), perceived family history,	majority of smokers anticipated to find a high-risk result more motivating for smoking cessation than a result showing no increased risk.	186 smokers	Cross-sectional survery

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
		dispositional pessimism, desire to quit smoking, level of nicotine addiction, and understanding of genetic testing.	Over one third of the sample (39%) thought it safe to carry on smoking if they received a negative result. Out of those participants who thought that it was safe to carry on smoking, a higher percentage had less formal education and less understanding of genetic testing, in addition to a lower desire to quit and not falling into the middle-age category. However, in multivariate analyses, only age and level of education were maintained.		
Frosch et al (2005)	assess anticipated consequences of genetic test feedback for obesity risk	Vignette study two (hormone test vs. genetic test) by two (high-risk vs. low-risk) design; participants	High-risk feedback led to increased intentions to eat a healthy diet, regardless of feedback	249	Cross-sectional

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
		received one of the four vignettes in random order. Measures: intentions to eat a healthy diet, attitudes, perceived behavioural control, perceived social norms, and expectations about benefits of eating a healthy diet	type. Individuals receiving high-risk genetic feedback felt less in control than those receiving average feedback, whereas in hormone group: opposite pattern. Intentions to eat a healthy diet high when perceived control high, independently of risk status or feedback type. Having higher BMI was not related to feedback status although intentions to eat a healthy diet were relatively low. Individuals who scored low on perceived behavioural control imagining not having the high-risk gene combination for obesity reported less intention to eat a		

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			healthy diet.		
Stigma					
Conradt et al (2007)	Impact of gen feedback in weight loss programme	Measurements included restraint eating, body acceptance, feelings of guilt, self-efficacy, and affect.	The inclusion of genetic information led to a significant increase in genetic causal attributions of obesity in individuals, and those who also had a family history of obesity suffered from less negative affect after six months. Feelings of guilt were also reduced in the short-term, although this had disappeared at follow-up.	147 obese individuals who took part in a weight loss programme	Longitudinal, 6 mo 1 yr FU
Behaviour change					
Smoking cessation					
Lerman et al (1997) **Audrain et al (1997)**	impact of genetic test feedback on smoking cessation	assigned to receive counselling only, counselling and biomarker feedback or counselling, biomarker feedback and genetic test feedback	Feedback was successful in elevating perceived risk, perceived quitting benefits but also increased worry about lung cancer. No	427 smokers	Longitudinal, 2 mo, 6 mo, 12 mo FU

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			differences between groups in cessation rates and number of cigarettes smoked per day.at two-month follow-up After one year, however, participants receiving genetic test feedback in addition to counselling had made more quit attempts and were more motivated to quit than those only receiving counselling, although no differences in actual quit rates emerged		
McBride et al (2002)	Whether gene feedback could motivate smoking cessation	used genetic feedback in addition to a smoking cessation intervention	quit rates were nearly doubled at the six-month follow-up. 19% *versus* 10%, respectively; at 6 months but not at 12 months There were no increases in perceived risk or distress among	316 African-American smokers	Longitudinal, 6 mo and 12 mo FU

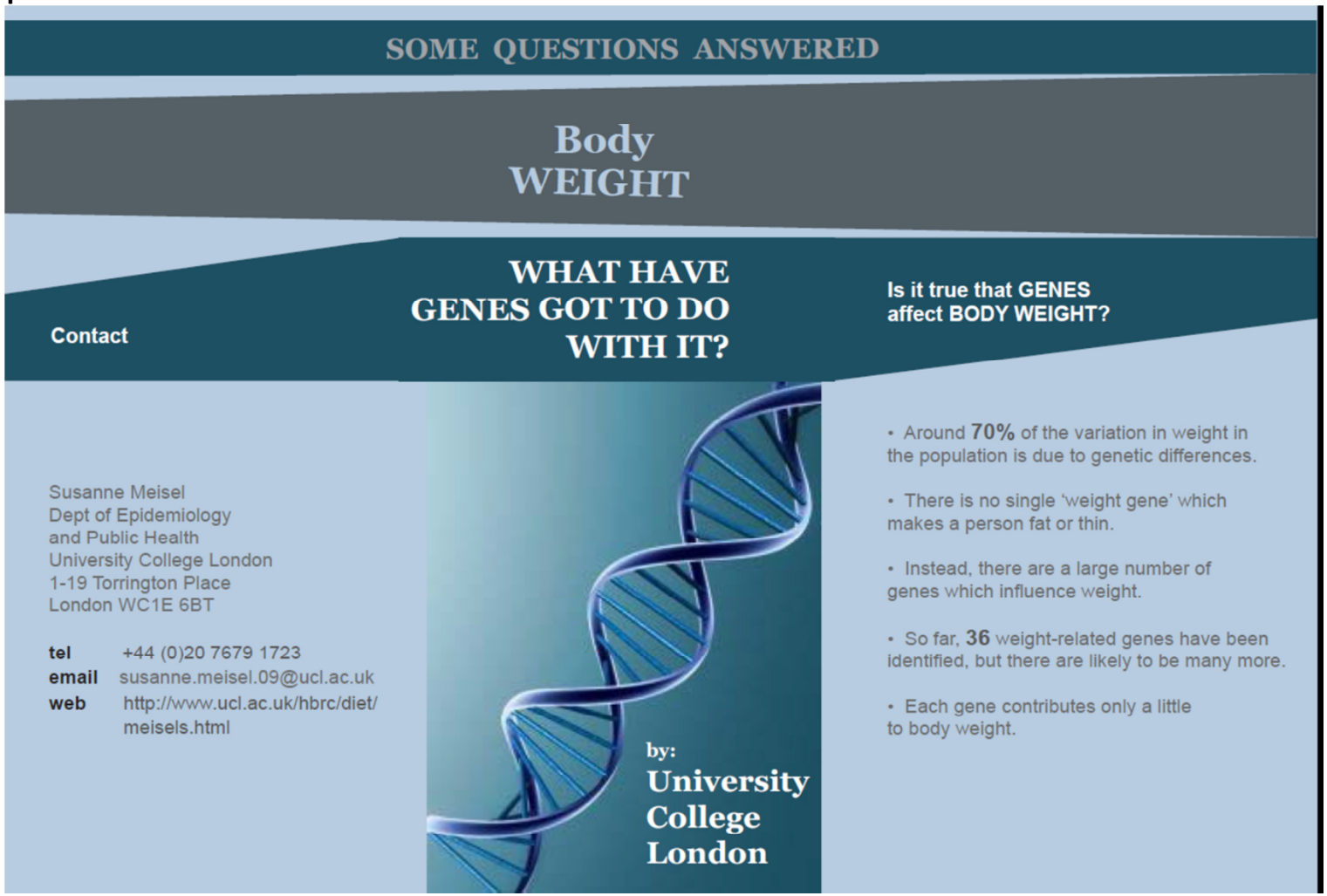
Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			participants. However, quit rates were high regardless of 'high-risk' or 'low-risk' genetic status for the GSTM1 gene.		
Sanderson et al (2008)	Gene feedback motivates smoking cessation?	smoking related outcomes, perceived risk and self-efficacy were also assessed	smoking cessation rates increased significantly one week after providing individuals with feedback for the GSTM1 gene, compared with control participants (35 % vs. 0%). However, the effect was no longer evident after the two-month follow-up	61 smokers	RCT, 2 mo FU
Hishida et al (2006)	Gene feedback to motivate smoking cessation?	Workplace intervention feedback vs. not	At one-year follow-up fewer people in the intervention arm had quit than in the control group (15 vs. 22 participants). However, negative	562 smokers	RCT, 1 y FU

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
			outcomes of gene feedback were also not reported.		
Ito et al (2006)	Gene feedback to motivate smoking cessation?	Attendees of a cancer centre, assess smoking status	There were no significant differences in quit rates between the groups; neither at three-, nor at nine months; although there was a trend for quit rates to be higher in participants receiving gene feedback.	617 smokers	RCT, 3 mo and 9 mo FU
Diet and exercise behaviours					
Harvey Berino et al (2001)	whether genetic testing would diminish self-efficacy and feelings of control over eating	Diet self-efficacy was measured with the Eating Self Efficacy Scale (Poston, 1997), and four statements assessed potential responses and beliefs about the effect of having an 'obesity	Feedback status had no impact on diet self-efficacy, confidence in the ability to lose weight, or attitudinal variables. Contrary to expectations, individuals who tested positive for the b3AR	30 postmenopausal obese women	Cross-sectional

Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
		gene'. Diet and weight history were assessed via self-report.	gene reported more confidence in the ability to overcome genetic predispositions with the right lifestyle choices		
Hicken and Tucker (2002)	whether a positive test result for the fictitious 'Asch syndrome' would affect individuals' dietary behaviour.	'family history' assessment, health behaviours, perceived risk for getting 'Ash syndrome', told soy would make it better	no differences between the groups emerged in intended soy consumption or dietary fat reduction	115 participants, particpants whose 'family history' supported Ash syndrome, 2 groups higher and lower risk gene feedback	RCT
Marteau et al (2004)	Impact of gene feedback for FH on health behaviours	randomly assigned to receive either a routine clinical diagnosis or the routine diagnosis and genetic test results. perceptions of control over FH, cholesterol and heart disease, and fatalism about FH, which were assessed with the respective scales of the Illness Perception Questionnaire-Revised	No effect of feedback was observed on perceived control on any of the tested variables, and neither was there an increase in fatalism.	341 individuals w FH, 128 affected relatives	

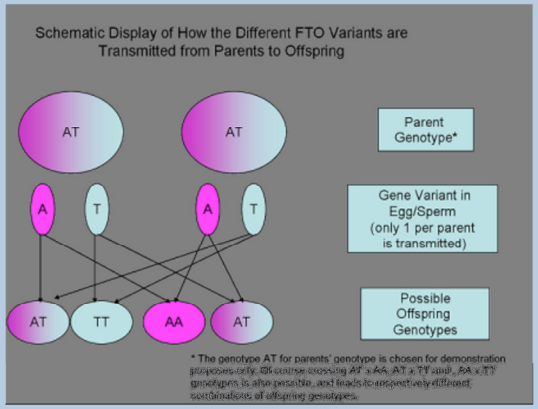
Study	Summary	Outcome measures and how assessed	Main findings	Sample description	Design
		(Moss Morris, 2002),			
Grant et al (2013)	whether returning genetic feedback about diabetes would improve outcomes in a 12-week validated diabetes prevention programme	self-reported attitudes, program attendance, and weight loss, separately comparing higher-risk and lower-risk result recipients with control participants.	No significant diff between either higher-or lower risk participants with control participants in any of the outcome variables	102 overweight adults at high risk of diabetes	Longitudinal, 12 wkFU
Hollands et al (2012)	Whether genetic susceptibility feedback and FH assessment for Crohn's would motivate smoking cessation in a sample of individuals with first degree reslatives with Chrohn's disease more than receiving only FH assessment	The primary outcome was smoking cessation for 24 hours or longer, assessed at six months	No effect on smoking cessation, or quit attempts	497 smokers, relatives of individuals w Chrohn's	RCT

12.2 Appendix 2: FTO information leaflet



What is the FTO gene?

- FTO was the first gene found to be associated with variation in weight in the general population
- There are two variants of the FTO gene, T and A.
- The A variant is associated with higher weight.
- As everyone gets one copy of the FTO gene randomly from each parent, they can end up with TT, AT, or AA combinations.
- About **37%** have the TT combination, **47%** the AT combination and **16%** the AA combination.



What does the A variant of the FTO gene do?

- People with two A variants (AA) are on average 3 kg (6.6lb) heavier than those with two T variants (TT).

- AA people are also at higher risk of becoming overweight or obese during their lifetime. AT people are 'in between'; on average 1.6 kg (2.6 lb) heavier than TT people.

How does the FTO gene affect body weight?

- Research from our department and others has shown that FTO probably works through affecting appetite, particularly by influencing sensitivity to the 'switch off' signal when enough food has been consumed.

- Diminished sensitivity to feelings of fullness, along with faster eating speed, can result in higher food intake that, over time, can affect weight.

Does that mean that it is all in the genes, and that my behaviour does not matter?

- Absolutely not. Having the genes that increase risk of weight gain is only part of the story.

- The environment is also important: Environments with lots of 'eating opportunities' and large portion sizes increase the risk of overeating and weight gain.

- Finally, people's efforts to choose healthier foods and keep up their levels of activity play an important role.

What does this mean for me?

- If you have the AA genotype, you might have to work harder than others to keep a healthy weight.

- Being strict about portion sizes and learning to eat more slowly could help to control any genetic tendencies to eat too much.

12.3 Appendix 3: Ethics approval letters

Approval letter Study 2

UCL RESEARCH ETHICS COMMITTEE
GRADUATE SCHOOL OFFICE

UCL Department of Epidemiology & Public Health
Health Behaviour Research Unit
1-19 Torrington Place
London
WC1E 6BT

14 May 2010

Dear Professor Wardle

Notification of Ethical Approval:
Ethics Application: 2471/001: Reactions to genetic testing for obesity risk

I am pleased to confirm that in my capacity as Chair of the UCL Research Ethics Committee I have approved your project for the duration of the study (i.e. until October 2010).

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The form identified above can be accessed by logging on to the ethics website homepage: http://www.grad.ucl.ac.uk/ethics/ and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

Reporting Non-Serious Adverse Events.
For non-serious adverse events you will need to inform Dr Angela Poulter, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Reporting Serious Adverse Events
The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

Ethics approval letter Amendment for Study 2b

From: E

Sent: 08 August 2011 17:47

To: I

Cc: ethics@ucl.ac.uk

Subject: UCL Research Ethics Committee - Approval of Amendment

Dear I ,

I am writing further to your recent submission to the UCL Ethics Committee of an Amendment Approval Request Forms for Project ID 2471/001 (form dated 29/07/11). I am pleased to let you know that the Chair of the Ethics Committee, Sir John Birch, has approved the application.

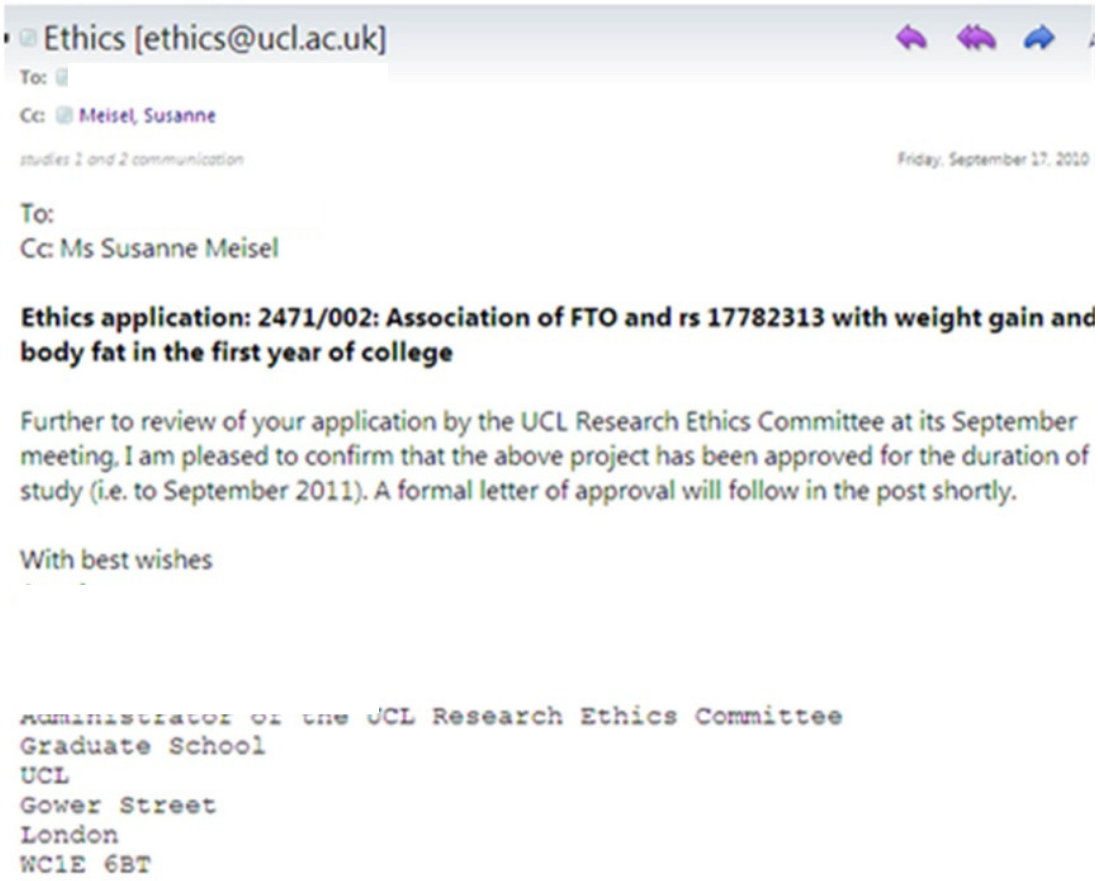
The secretary to the Ethics Committee, Helen Dougal, will be writing to you on her return from leave with a formal letter of approval, but in the mean time please accept this email as confirmation.

With best wishes,

Graduate School Administrator
Graduate School
North Cloisters
University College London
Gower Street
London WC1E 6BT

email:
direct tel: +44 (0) 20 7679 7841 (internal ext 37841)

Ethics Approval letter Study 3



Ethics [ethics@ucl.ac.uk]

To:

Cc: Meisel, Susanne

studies 1 and 2 communication

Friday, September 17, 2010

To:
Cc: Ms Susanne Meisel

Ethics application: 2471/002: Association of FTO and rs 17782313 with weight gain and body fat in the first year of college

Further to review of your application by the UCL Research Ethics Committee at its September meeting, I am pleased to confirm that the above project has been approved for the duration of study (i.e. to September 2011). A formal letter of approval will follow in the post shortly.

With best wishes

Administrator of the UCL Research Ethics Committee
Graduate School
UCL
Gower Street
London
WC1E 6BT

Ethics Approval letter Study 4

UCL

Sign out | Meisel, Susanne

Find Someone Options

Ethics Application 2471/003 - Approval

Ethics [ethics@ucl.ac.uk]

To:

Cc: Meisel, Susanne

Inbox Wednesday, September 14, 2011 9:40 AM

Ethics Application: 2471/003: Psychological and behavioural effects of genetic test feedback for weigh gain prevention in first year university students - a randomized controlled trial

I am pleased to confirm that your study has been approved by the UCL Research Ethics Committee for the duration of the project i.e until September 2013.

An approval letter, signed by the Chair, will be despatched to you shortly.

Administrator of the UCL Research Ethics Committee
Graduate School
UCL
Gower Street
London
WC1E 6BT

Tel: 020 7679 7844
Fax: 020 7679 7043
Email: ethics@ucl.ac.uk

12.4 Appendix 4: Information sheets and Consent Forms

Information sheet and Consent Form for Studies 2 and 2b – these were identical

Information Sheet for Participants in Research Studies

You will be given a copy of this information sheet.

Title of Project in lay terms: **Reactions to Genetic Testing for Risk of Overweight**

This study has been approved by the UCL Research Ethics Committee [Project ID Number 2471/001]:

Health Behaviour Research Centre
Department of Epidemiology and Public Health
University College London
1-19 Torrington Place, Room 203
London WC1E 6BT

T:+44 (0)20 7679 8306
F:+44 (0)20 7679 8354
Email:

Susanne Meisel
PhD Student
Health Behaviour Research Centre
Department of Epidemiology and Public Health
University College London
1-19 Torrington Place, Room 208
London WC1E 6BT

T: +44 (0) 20 7679 1723 (direct line)
F: +44 (0) 20 7679 8354
Email:

Aims of the research and possible benefits

- There is considerable evidence that becoming overweight has a genetic component. The aim of the study is to explore reactions to genetic test feedback for risk of overweight.
- Results from this study will help inform the debate about psychological effects of genetic tests. Furthermore, the results will help us to determine whether genetic testing for risk of overweight can be useful in combination with weight control advice.

What will be involved if you decide to participate?

- We will determine your genetic susceptibility to overweight by analysing DNA taken from saliva (by spitting into a test tube). We will then ask you some questions about your thoughts and your feelings after you receive your test result in a recorded telephone interview. The interview will last about 20 minutes, depending on your availability, and on how much information you would like to provide us with.
- It is important to note that genetic testing will only be done for one gene that makes a small contribution towards your susceptibility to overweight; it will not look at genetic markers for other diseases (such as Alzheimer's or breast cancer).

Are there any risks involved if you choose to participate?

- Some people could be upset by the test result, although in other studies related to genetic test feedback and cancer this was not the case. If you were upset, Susanne Meisel and Professor Wardle, who is also a clinical Psychologist, will be available to support you.

What are possible benefits for you as a participant?

- One possible benefit for you as a participant is knowledge of your genetic status on the FTO gene which is linked to overweight.
- You will receive detailed information from the charity Weight Concern on how to keep a healthy weight.
- You will also receive a copy of the final research report.

Arrangements for ensuring anonymity and confidentiality

- We will hold your demographic information, such as date of birth, and your test result which will be stored anonymously. In the transcripts we will use initials, so you will not be identifiable; this will also be the case for any statements that will be included in the final report.
- With your consent, recorded interviews will be transcribed (written up) and the tape will then be wiped clear
- Your saliva sample will be discarded after DNA analysis.
- Only the researchers immediately involved in the research (Susanne Meisel and Professor Wardle) will have access to the full results.
- All data will be kept confidential and stored in accordance with the Data

Protection Act.

- It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason.
- A decision to withdraw at any time, or a decision not to take part, will not affect the standard of education you receive.
- You may withdraw your data from the project at any time up until it is transcribed for use in the final report by October 2013.
- If you agree to take part, you will be asked whether you are happy to be contacted about participation in future studies. Your participation in this study will not be affected should you choose not be re-contacted.
- If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form.

Informed Consent Form for Students in Research Studies
Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Project: **Interest and attitudes towards genetic testing for obesity risk- an interview study**

This study has been approved by the UCL Research Ethics Committee [Project ID Number: 2471/001]

Thank you for your interest in taking part in this research. Before you agree to take part the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Participant's Statement

I …….

- I have read the notes written above and the Information Sheet, and understand what the study involves.☐
- I understand that participation involves taking a DNA test exclusively for the risk of becoming overweight.☐
- I understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.☐
- I consent to the processing of my personal information for the purposes of this research study.☐

- I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998. ☐

- I understand that my participation will be taped/video recorded and I am aware of and consent to, any use you intend to make of the recordings after the end of the project. ☐

- I agree that my non-personal research data may be used by others for future research. I am assured that the confidentiality of my personal data will be upheld through the removal of identifiers. ☐

- I agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study. ☐

- I agree to be contacted in the future by UCL researchers who would like to invite me to participate in follow-up studies. ☐

Signed: Date:

Information sheet and Consent form for Study 3

C10	**Information Sheets And Consent Forms**

Information Sheet for Students in Research Studies

You will be given a copy of this information sheet.

Title of Project in lay terms: **Associations between genes and body fat at the first year of college**

This study has been approved by the UCL Research Ethics Committee [Project ID Number 2471/001]:

Professor Jane Wardle
HBRC, UCL Epidemiology & Public Health,
UCL, Gower Street
London
WC1E 6BT, UK
Office: Room 203, 1-19 Torrington Place, London WC1E 6BT
Telephone:
+44 (0)20 7679 8306
Internal: x48306
Fax:
+44 (0)20 7679 8354
Email:

Susanne Meisel
PhD Student
Health Behaviour Research Centre
Department of Epidemiology and Public Health
University College London
1-19 Torrington Place, Room 208
London WC1E 6BT

T: +44 (0) 20 7679 1723 (direct line)
F: +44 (0) 20 7679 8354
Email:

important to read the following information carefully and discuss it with others if you wish. Ask us if anything is not clear or if you would like more information.

Aims of the research and possible benefits

- There is evidence that body fat is in part genetically determined, and one gene in particular – the FTO gene – has been linked with slightly higher body fat (equivalent to 5 lbs in weight)
- When young people go to university, some of them increase their body fat
- We are interested in testing a large sample of new students for the FTO gene and another gene with smaller effect to see if these genes are related to the tendency to gain body fat when people move into this new environment
- The results from this study may help identify health advice to reduce risk of body fat gain

What will be involved if you decide to participate?

- Participation will involve four things: i) assessment of body fat, ii) DNA collection and analysis, iii) filling out a questionnaire now and iiii) in 6 months time.

Assessment of body fat:

- Body fat is measured with a special scale. You will be asked to remove heavy garments (coat, belt) as well as your shoes and socks, but stay otherwise fully clothed. You will stand on the Tanita body fat scale for a few minutes. The scale will have an antibacterial gel in the area you place your feet. It works through *bioelectrical impedance* which involves a very low, safe current being sent through your body. Most people don't feel anything, although a few a slight tingling in hands and feet; but it is not painful or harmful in any way. This method is considered the most convenient way of assessing body fat and versions of the Tanita body fat scales are available in shops.

DNA Collection

- DNA for analysis of genes is collected with a saliva sample. This involves 'drooling' 1.5-2.0 ml of saliva into a plastic collection tube. This is painless.
- It is important that you don't eat, drink (except water), smoke, or brush your teeth for one hour before saliva collection.
- The DNA will be extracted from the saliva in the laboratory and we will carry out genetic testing for genes related to body fat. The samples will not be used to test for genetic markers for any other diseases such as Alzheimer's or breast cancer. You will be able to receive your result after 6 months if you wish, but you can also choose not to know.

Questionnaire

- We will ask you some questions on a computer about your eating habits, stress levels, physical activity levels and family history of overweight. Filling out the questionnaire should take no longer than 20 minutes. You can do it now, or if you don't have time, we can email you the link to the questionnaire, and you can fill it out when it suits you.

Follow-up

- After 6 months, we will email you another questionnaire to complete which will cover some of the same issues and we will invite you for a repeat assessment of body fat. The email will also remind you that your DNA results are ready for collection should you wish to know them.

Your test result

- You will be able to receive your test result either by email or over the phone as you choose, so that you have the opportunity to ask any questions. You will also receive the contact details of the researcher, should you have questions at a later stage.

Are there any risks involved if you choose to participate?

- During the assessment of body fat you might feel slight tingling in your hands or feet. Should that distress you, please let the researcher know, and we will terminate the assessment without any consequences for you.
- Some people could be upset by the test result, although in other studies related to genetic test feedback for genes that only confer a low risk, this was not the case. If you are upset, Susanne Meisel and Professor Wardle (who is a Clinical Psychologist), will be available to support you.

What are possible benefits for you as a participant?

- One possible benefit for you is knowledge of your genetic status on certain genes involved in body fat development (FTO and SNP rs 17782313 near the MC4R gene)
- You will receive an accurate assessment of your body fat percentage.
- You will also receive a copy of the final research report.

Arrangements for ensuring anonymity and confidentiality

- We will store any information about you and your test result anonymously. We will store your email address separately from other information for future contacts.
- Your saliva sample will be discarded after DNA analysis.
- Only the researchers immediately involved in the research (Susanne Meisel and Professor Wardle) will have access to the full results.
- All data will be kept confidential and stored in accordance with the Data Protection Act.
- It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason.
- A decision to withdraw at any time, or a decision not to take part, will not affect the standard of education you receive.
- You may withdraw your data from the project at any time up until it is transcribed for use in the final report by October 2011.
- If you agree to take part, you will be asked whether you are happy to be contacted about participation in future studies. Your participation in this study will not be affected should you choose not be re-contacted.

If you decide to take part in this study, you will be given this information sheet to keep and invited to sign a consent form.

Informed Consent Form for Students in Research Studies
Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Project: **Interest and attitudes towards genetic testing for obesity risk- an interview study**

This study has been approved by the UCL Research Ethics Committee [Project ID Number: 2471/001]

Thank you for your interest in taking part in this research. Before you agree to take part the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Participant's Statement

I …….

- I have read the notes written above and the Information Sheet, and understand what the study involves.☐
- I understand that participation involves taking a DNA test exclusively for the risk of becoming overweight.☐
- I understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.☐
- I consent to the processing of my personal information for the purposes of this research study.☐

- I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998. ☐
- I understand that my participation will be taped/video recorded and I am aware of and consent to, any use you intend to make of the recordings after the end of the project. ☐
- I agree that my non-personal research data may be used by others for future research. I am assured that the confidentiality of my personal data will be upheld through the removal of identifiers. ☐
- I agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study. ☐
- I agree to be contacted in the future by UCL researchers who would like to invite me to participate in follow-up studies. ☐

Signed: Date:

Information Sheet and Consent form Study 4

C10	Information Sheets And Consent Forms

Information Sheet for Students in Research Studies

You will be given a copy of this information sheet.

Title of Project in lay terms: **Psychological and behavioural effects of genetic test feedback for weight gain prevention in first year university students-a randomized controlled trial**

This study has been approved by the UCL Research Ethics Committee [Project ID Number 2471/003]:

Professor Jane Wardle
HBRC, UCL Epidemiology & Public Health,
UCL, Gower Street
London
WC1E 6BT, UK
Office: Room 203, 1-19 Torrington Place,
London
WC1E 6BT
Telephone:
+44 (0)20 7679 8306
Internal: x48306
Fax:
+44 (0)20 7679 8354
Email:

Susanne Meisel
PhD Student
Health Behaviour Research Centre
Department of Epidemiology and Public Health
University College London
1-19 Torrington Place, Room 208
London WC1E 6BT

T: +44 (0) 20 7679 1723 (direct line)
F: +44 (0) 20 7679 8354
Email:

We would like to invite you, as a UCL Student, to participate in this research project.

You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important to read the following information carefully and discuss it with others if you wish. Ask us if anything is not clear or if you would like more information.

Aims of the research and possible benefits

- There is evidence that body fat is in part genetically determined, and one gene in particular – the FTO gene – has been linked with slightly higher body fat (equivalent to 5 lbs in weight)
- When young people go to university, some of them increase their body fat
- It is possible to test for the FTO gene
- We are interested in testing a large sample of new students for the FTO gene to see whether knowing genetic risk status for weight gain will help to prevent weight gain in the first year of university
- We are also interested whether receiving an information leaflet with tips on weight management tailored to counteract the effects of FTO will be helpful in keeping a healthy weight
- The results from this study may help identify health advice to reduce risk of body fat gain

What will be involved if you decide to participate?

- Participation will involve five things: i) assessment of body fat, ii) DNA collection and analysis, iii) reading an information leaflet with tips on how to avoid weight gain iv)filling out a questionnaire now and v) in 8 month's time.
- You will be randomly allocated to receive your genetic test result either shortly after initial participation or at the 8 months follow-up.

Assessment of body fat:

- Body fat is measured with a special scale. You will be asked to remove heavy garments (coat, belt) as well as your shoes and socks, but stay otherwise fully clothed. You will stand on the Tanita body fat scale for a few minutes. The scale will have an antibacterial gel in the area you place your feet. It works through *bioelectrical impedance* which involves a very low, safe current being sent through your body. Most people don't feel anything, although a few a slight tingling in hands and feet; but it is not painful or harmful in any way. This method is considered the most convenient way of assessing body fat and versions of the Tanita body fat scales are available in shops.

DNA Collection

- DNA for analysis of genes is collected with a saliva sample. This involves 'drooling' 1.5-2.0 ml of saliva into a plastic collection tube. This is painless.
- It is important that you don't eat, drink (except water), smoke, or brush your teeth for one hour before saliva collection.
- The DNA will be extracted from the saliva in the laboratory and we will carry out genetic testing for one gene related to body fat. The samples will not be used to test for genetic markers for any other diseases such as Alzheimer's or breast cancer.

Your test result

- You will randomly be allocated to receive your test result shortly after enrolment, or at the end of the year. You can also choose not to know.
- You will be able to receive your test result either by email or over the phone as you choose, and you will have the opportunity to ask any questions. You will also receive the contact details of the researcher, should you have questions at a later stage.

Information leaflet

- You will receive an information leaflet with tips on how to keep a healthy weight. These tips are useful for anyone, but will be especially useful for you if you have the 'AA' or 'AT' FTO genotype. 'AA' and 'AT' genotypes have been linked with lower satiety sensitivity.

Questionnaire

- We will ask you some questions on a computer about your eating habits, stress levels, physical activity levels and family history of overweight. Filling out the questionnaire should take no longer than 20 minutes. You can do it now, or if you don't have time, we can email you the link to the questionnaire, and you can fill it out when it suits you.

Follow-up

- After 8 months, we will email you another questionnaire to complete which will cover some of the same issues and we will invite you for a repeat assessment of body fat. If you have not received your test result shortly after initial enrolment, you will now have the option to collect your test result.

Are there any risks involved if you choose to participate?

- During the assessment of body fat you might feel slight tingling in your hands or feet. Should that distress you, please let the researcher know, and we will terminate the assessment without any consequences for you.

- Some people could be upset by the test result, although in other studies related to genetic test feedback for genes that only confer a low risk, this was not the case. If you are upset, Susanne Meisel and Professor Wardle (who is a Clinical Psychologist), will be available to support you.

What are possible benefits for you as a participant?

- One possible benefit for you is knowledge of your genetic status on the FTO gene involved in body fat development
- You will receive an accurate assessment of your body fat percentage.
- You will also receive a copy of the final research report.

Arrangements for ensuring anonymity and confidentiality

- We will store any information about you and your test result anonymously. We will store your email address separately from other information for future contacts.
- Your saliva sample will be discarded after DNA analysis.
- Only the researchers immediately involved in the research (Susanne Meisel and Professor Wardle) will have access to the full results.
- All data will be kept confidential and stored in accordance with the Data Protection Act.
- It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason.
- A decision to withdraw at any time, or a decision not to take part, will not affect the standard of education you receive.
- You may withdraw your data from the project at any time up until it is transcribed for use in the final report by October 2013.
- If you agree to take part, you will be asked whether you are happy to be contacted about participation in future studies. Your participation in this study will not be affected should you choose not be re-contacted.

If you decide to take part in this study, you will be given this information sheet to keep and invited to sign a consent form.

12.5 Appendix 5: Recruitment materials

Email invitation for Study 2

Title: Genetic test feedback for weight gain – opportunity for participation
Dear Student,

I know I am writing to you very late, however i just wanted to inform you that a new opportunity has arisen to take part in the FTO study.

It is slightly different from the previous one in that you would be tested about your FTO status and then talk to me about your experience once you receive your result.

All interviews will be confidential, and you will not be able to be identified in any write -up.

The advantage of this study is that you would receive your result quite soon after you gave me your saliva, however talking to me might take a bit of time.

Please let me know if you are interested so I can send you further details.

Best Wishes,

Susie

Email invitation for Study 2b
Subject line: Big panel research – reactions to genetic test feedback for risk of overweight

Dear Big Panel Members,

You may remember taking part in a survey about attitudes towards genetic testing for risk of obesity that we organised last year. We have now moved on to the next stage of this research and are inviting a small number of people from the Big Panel for a genetic test of one of the genes that has been associated with increased risk for overweight. This gene is called the FTO gene. There would of course be no cost, but we are looking for participants who would be willing to take part in a short phone interview after the test to give us their views about the experience.

Please find an information sheet with further details about the study attached. If you are interested in the study, please contact me (Susanne.meisel.09@ucl.ac.uk) for further details.

Thank you very much for your time.

Kind Regards,

Susanne

Email invitation for studies 3 and 4
Subject line: how fat are your genes?-find out here!

Dear Student,

Are you a first year student at UCL aged between 18 and 25 years? If the answer is yes, we should like to invite you to participate in a study investigating the association of the FTO gene and the tendency to gain body fat in the first year of college.

Many Freshers already agreed to take part when they attended the Freshers' Fayre.

Those of you who didn't attend the Fayre, or were put off by the queue at our stall, now have the opportunity to help us find out more about how genes influence body fat gain.

What does participation involve?
Participation involves assessing your level of body fat, taking a saliva sample for DNA, and filling out a questionnaire now and in 6 months time.

These procedures are painless and should take in total no longer than 30mins.

Your DNA will be used solely to test for two genes associated with body fat gain, but not for any other condition or disease. Samples will be discarded after analysis. Results will be treated with strict confidentiality.

What are the benefits for me as a participant?
You will receive an accurate measurement of your body fat percentage, and see how it changes over time

You will receive feedback on your genet status for the two genes we test for

You will receive a copy of the final research report

Of course, you are under no obligation to participate; and if you did, you are free to withdraw at any time.

Please contact me by email (susanne.meisel.09@ucl.ac.uk) or on the phone number below if you would like to receive further information or discuss the study.

I look forward to hearing from you.

Susanne Meisel

Example of an advert distributed around campus for study 3 (Contact details were attached below)

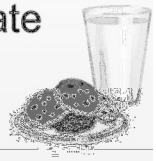
FREE Body composition measurement

Would you like to know how much body fat and muscle mass you have?

Are you aged between 18 and 25 years?

Are you curious about how your genes play a part in this?

Yes? Then you might be interested to participate in our study!



12.6 Appendix 6: Instructions for Saliva Collection Study 2b

Health Behaviour Research Centre
University College London
1-19 Torrington Place
London, WC1E 6BT
Tel: 0207 679 1736
November 28th 2011

Dear panel participant,

Thank you very much for your interest in the study.

Instructions on how to collect the saliva sample for the genetic analysis are on the back of this letter. Should you have any queries, please do not hesitate to contact me.

After you have posted your sample back to us, it will be analysed at the Institute for Metabolic Sciences in Cambridge. Although we are aiming for a speedy turnover, analysis may take a few weeks, but we will give you the result as soon as we can.

I will contact you by email as soon as your result is available. Then we will also make an appointment for the phone interview.

Meanwhile, please could you follow the link below, to fill out a brief baseline questionnaire.
www.attitudestohealth.co.uk/genesint

With best wishes,

Yours sincerely,
Susanne Meisel
Tel: 020 7679 1736
Email: _____

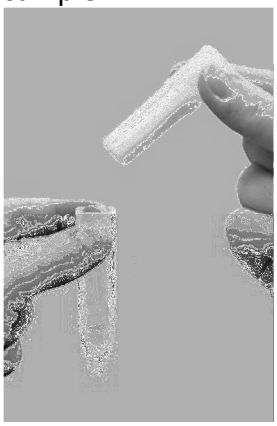
A guide to collecting your saliva sample

Before collecting your sample it is advisable not to eat, drink (except water), smoke, chew gum or brush your teeth 30 minutes before. Collection time is unimportant.

For collection, you will need:

- The salivette and about ¼ teaspoon of sugar/ sweetener.
- The sugar helps stimulate saliva flow. You will spit the sugar into the tube with the saliva. (Note for diabetics: you don't swallow the sugar but spit it into the tube, so it should not affect your blood glucose levels).

1. Open the salivette by pulling top and bottom half apart (as shown in the picture). You spit into the empty outer tube. Ignore the screw-cap that gives access to the cotton wool – you will NOT need the cotton wool to collect your sample.



2. Put the sugar onto your tongue and let it dissolve. Do not swallow for a few minutes.

3. When you feel saliva building up in your mouth, spit it into the test-tube.

4. The tube needs to be filled to at least the 1 ml mark, more is preferable. If you need to, repeat steps 2 and 3. Using sugar for each 'go' helps. Avoid 'frothy' saliva that is generated when you try and 'suck' saliva out of your cheeks. Do not drink water as it will dilute saliva.

5. Firmly close the lid (you should hear it 'click'). Wipe the tube, if necessary.

6. Write forename, last name and DOB on the label and stick it on to the tube (using a normal pen is fine). Sign and date the consent form.

7. Put the sample and the signed consent form in the prepaid envelope. Post it back as soon as you can, but you can store in your home fridge/freezer if you

are unable to post it the same day. This will not affect the result. The sample does not need to be frozen for transport.

8. Please do not forget to fill out the short questionnaire at www.attituedestohealth.co.uk/genesint

12.7 Appendix 7: Saliva Extraction Protocol

Saliva Spin Protocol

Notes:

• Equilibrate samples to room temperature.

• Heat a water bath or heating block to 56°C for use in step 4.

• Equilibrate Buffer AE or water to room temperature for elution in step 10.

• Ensure that Buffer AW1, Buffer AW2, and QIAGEN Protease have been prepared according to the instructions on page 24.

• If a precipitate has formed in Buffer AL, dissolve by incubating at 56°C.

• All centrifugation steps should be carried out at room temperature.

1. Add 4mls PBS (phosphate buffered saline) to 1ml sample. Centrifuge @ RT for 5mins 3000g. Resuspend the pellet in 180 PBS and 20 ul RNASE A (20mg/ul)

2. Add 200 µl sample to Eppendorf 1.5ml tube.

3. Add 200 µl Buffer AL to the sample. Mix by pulse-vortexing for 15 s.

4. Incubate at 56°C for 10 min.

5. Briefly centrifuge the 1.5 ml microcentrifuge tube to remove drops from the inside of the lid.

6. Add 200 µl ethanol (96–100%) to the sample, and mix again by pulse-vortexing for 15 s. After mixing, briefly centrifuge the 1.5 ml microcentrifuge tube to remove drops from the inside of the lid.

7. Carefully apply the mixture from step 6 to the QIAamp spin column (in a 2 ml collection tube) without wetting the rim, close the cap, and centrifuge at 6000 x *g* (8000 rpm) for 1 min. Place the QIAamp spin column in a clean 2 ml collection tube (provided), and discard the tube containing the filtrate.

8. Carefully open the QIAamp spin column and add 500 µl Buffer AW1 without wetting the rim. Close the cap and centrifuge at 6000 x *g* (8000 rpm) for 1 min. Place the QIAamp spin column in a clean 2 ml collection tube (provided), and discard the collection tube containing the filtrate.

9. Carefully open the QIAamp spin column and add 500 µl Buffer AW2 without wetting the rim. Close the cap and centrifuge at full speed (20,000 x *g*; 14,000 rpm) for 3 min. Continue directly with step 10, or to eliminate any chance of possible Buffer AW2 carryover, perform step 9a, and then continue with step 10.

9a. (Optional): Place the QIAamp spin column in a new 2 ml collection tube (not provided) and discard the collection tube with the filtrate. Centrifuge at full speed for 1 min.

10. Place the QIAamp spin column in a clean 1.5 ml microcentrifuge tube (not provided), and discard the collection tube containing the filtrate. Carefully open the QIAamp spin column and

add 50 µl Buffer AE or distilled water. Incubate at room temperature for 1 min, and then centrifuge at 6000 x *g* (8000 rpm) for 1 min.

For long-term storage of DNA, eluting in Buffer AE and storing at –20°C is recommended, since DNA stored in water is subject to acid hydrolysis.

.

Isolation of genomic DNA from Saliva

• Add isopropanol and ethanol to Wash Solution 1 Concentrate and Wash

Solution 2 Concentrate respectively. See the reagent bottles for preparation instructions. Store the solutions at room temperature.

• Prepare sufficient DNA Binding Bead Mix for your sample extraction and store at room temperature. If you are preparing multiple samples, prepare 5% excess to account for error.

• Confirm that your MagMAX™ Express-96 Deep Well Magnetic Particle

Processor has installed the 4413021 DW tissues protocol.

1. Add 1ml sample to 4mls PBS (phosphate buffered saline). Centrifuge @ RT for 5mins 3000g. Resuspend the pellet in 200 µL of Multi-Sample DNA Lysis Buffer

Disrupt the samples 1. For each sample:

a. Move samples into deep well plate.

2. Shake the plate on a plate shaker.

Perform the DNA extraction and elution

1. Add 160 µL of 100% isopropanol to each sample on the plate.

2. Seal the plate, shake for 3 minutes at on a plate shaker.

3. Remove the plate from the shaker, carefully remove the cover, add 20 µL

DNA Binding Bead Mix to each lysate on the plate. Seal then shake for a further 3 minutes

4. While the plate is shaking, prepare sufficient RNase A mix for the number of samples you are preparing. IMPORTANT! Prepare the RNase A mix just before use. Prolonged storage atroom temperature can reduce its efficiency.

5. Prepare the plates for the MagMAX instrument.

6. Start the protocol.

Component	Volume (µL)	
1 well 96-well plateRNase A	5	505
Water, nuclease-free	95	9595
Total (RNase A mix)	100	10100

Plate ID	Position		Reagent Volume per well (µL)
Binding	1	Lysate, isopropanol, and beads (from steps 1 to 3)	180 to 380
Wash 1	2	Wash Buffer 1	150
Wash 2	3	Wash Buffer 2	150
RNase	4	RNase A mixture (5 µL RNase + 95 µL water per well)	100
Wash 3	5	Wash Buffer 2	150
Wash 4	6	Wash Buffer 2	150
Elution	7	DNA Elution Buffer 1 for initial heated and elution	75

Load the plates into the loading station as prompted by the instrument.

Press start after loading each plate.

After the run is started, load the following reagents into the plates at the loading stations listed in the following table when prompted by the instrument.

ID	Position	Reagent	Volume per well (µL)
RNase	4	Multi-Sample DNA Lysis Buffer and isopropanol	220

Note: The instrument prompts you to add 100 µL lysis buffer and 120 µL isopropanol after the RNase digestion is complete.

Elution‡	7	DNA Elution Buffer 2 for equilibration	75§

Unload the instrument 1. When the instrument has completed the protocol, remove all plates from the loading station as prompted by the instrument. Press start after removing each plate.
IMPORTANT! After removing the elution plate (the first plate removed) from the MagMAX™ instrument, which contains the purified DNA, cover the plate immediately. To prevent evaporation, do not allow the sample to sit uncovered at room temperature for an extended time.
If precipitated DNA is visible in the samples, pipet up/down 5 to 10 times before covering the plate to ensure complete resuspension. Precipitate is common when preparing tissues that have a large amount of DNA (such as spleen or thymus).
2. When the MagMAX™ instrument displays END_OF_RUN, press stop.
3. Power off the MagMAX™ instrument.

STOPPING POINT. Use the purified samples immediately, or store the elution plate for later use at 2 to 6 °C for up to 24 hours or at − 20 to − 80 °C for prolonged storage.

12.8 Appendix 8: Result letters

Result letter AA

Health Behaviour Research Centre

1-19 Torrington Place

London

WC1E 6BT

Tel: 0207 679 1723

Dear Participant,

Thank you very much once again for your patience.

Please find your genetic test result below.

Your gene status for the FTO gene is AA.

16 out of 100 people have the AA genotype.

People with two A variants are on average 3 kg (7.3 pounds) heavier than those with two T variants.

They are also at slightly higher risk of becoming overweight during their lifetime.

I attached a short leaflet for your information that you might find helpful.

Please feel free to contact me should you have further questions or concerns (Details below).

We will also send you the link for a short questionnaire in the next few days about your experience.
It is very important that you fill it in as and when you get it to complete your participation.

Thank you very much once again for participating in my research.

Best wishes,

Susie

PhD Student -Cancer Research UK

Email

T: +44 (0) 20 7679 1736 (direct line)

Result letter AT

Health Behaviour Research Centre

1-19 Torrington Place

London

WC1E 6BT

Tel: 0207 679 1723

Dear Participant,

Thank you very much once again for your patience.

Please find your genetic test result below.

Your gene status for the FTO gene is AT.

47 out of 100 people have the AT genotype. This is the most common genotype in the population.

People with one A variant are on average 1.5 kg (3.3 lb) heavier than those with two T variants.

They are genetically at slightly higher risk of becoming overweight during their lifetime.

I attached a short leaflet for your information that you might find helpful.

Please feel free to contact me should you have further questions or concerns (Details below).

We will also send you the link for a short questionnaire in the next few days about your experience.
It is very important that you fill it in as and when you get it to complete your participation.

Thank you very much once again for participating in my research.

Best wishes,

Susie

PhD Student -Cancer Research UK

Email

T: +44 (0) 20 7679 1736 (direct line)

Result letter TT

Health Behaviour Research Centre

1-19 Torrington Place

London

WC1E 6BT

Tel: 0207 679 1723

Dear Participant,

Thank you very much once again for your patience.

Please find your genetic test result below.

Your gene status for the FTO gene is TT.

37 out of 100 people have the TT genotype.

People with two T variants are on average 3 kg (7.3 lb) lighter than those with two A variants.

They are genetically not at higher risk of becoming overweight during their lifetime.

I attached a short leaflet for your information that you might find helpful.

Please feel free to contact me should you have further questions or concerns (Details below).

We will also send you the link for a short questionnaire in the next few days about your experience.
It is very important that you fill it in as and when you get it to complete your participation.

Thank you very much once again for participating in my research.

Best wishes,

Susie

PhD Student -Cancer Research UK

Email [redacted]

T: +44 (0) 20 7679 1736 (direct line)

12.9 Appendix 9: Weight Control Leaflet

Why might WEIGHT change when starting University?

The transition to university life can be stressful. Some students gain weight after starting university and others lose weight, but gaining is more common.

Factors that can contribute to weight changes are:

- Missing home, family and friends
- Purchasing and cooking your own food
- Having many 'eating opportunities'
- Going out a lot, making new friends
- Having little time for exercise
- Work stress

Over time, changes in weight can lead to undesirable health consequences. Therefore, it is best to maintain a healthy weight from the start.

The following sections are about how to prevent weight gain, because weight gain is much more common than weight loss. However, being underweight is as harmful to the body as being overweight.

If you are concerned about your eating or weight, please let the researchers know.

Advice is available from the University health centre and the University counselling service (addresses overleaf). Alternatively, you can contact your GP.

Contact Details

UCL

Susanne Meisel
Dept of Epidemiology and Public Health
University College London
1-19 Torrington Place
London WC1E 6BT
tel 020 7679 1723
email

UCL Counselling Service
UCL Student Psychological Services
Ground Floor, 3 Taviton Street
London WC1H 0BT
web http://www.ucl.ac.uk/student-psychological-services/index_home

UCL Health Centre
3 Gower Place
London WC1E 6BN
tel 020 7387 6306
web http://www.gowerplacepractice.nhs.uk/index.php?pid=3

WEIGHTCONCERN

designed by zebrafishstudio.com

Starting UNIVERSITY

A TIME FOR WEIGHT GAIN?

University College London

What have GENES got to do with it?

- Body weight is influenced by genes.
- FTO was the first gene found to be associated with the weight in the general population.
- There are two variants of the FTO gene: T and A.
- As everyone gets one copy of the FTO gene randomly from each parent, they can end up with TT, AT, or AA combinations.
- People with an AA variant are at higher risk than AT or TT people of becoming overweight or obese during their lifetime.
- People with the AT combination are 'in between': slightly higher risk than TT for weight gain, but not as high as AA.
- Almost half (47%) the population have the AT combination, around 37% of people having the TT combination, and 16% the AA combination.

Does that mean that WEIGHT is all in the genes and behaviour does not matter?

- Absolutely not – having the genes that increase risk of weight gain is only part of the story.
- The environment is very important: environments with lots of 'eating opportunities' and large portion sizes increase the risk of overeating and weight gain
- People's own efforts to choose healthier foods and keep up their levels of activity also play an important role.

How does the FTO gene affect body weight?

- Research from our department and others has shown that FTO probably works through affecting appetite, particularly by influencing sensitivity to the 'switch off' signal when enough food has been consumed.
- Diminished sensitivity to feelings of fullness can result in higher food intake.

What does this mean for me?

- If you have the AA or AT genotype, the 7 tips below will be especially useful for you.
- The tips were chosen with genetic predispositions in mind, but are useful for anyone who wants to prevent weight gain.

7 EASY TIPS TO HELP AVOID WEIGHT GAIN AT UNIVERSITY

Tip 1: Ponder portion size
Cafes and canteens sometimes give very large portions. You are not obliged to finish them. Keep in mind that the stomach is roughly the size of your fist when judging portion size. Research has shown that saving as little as 100kcal/day can prevent weight gain.

Tip 2: Think twice about second helpings
Overeating just because food is left is easy. When cooking or having a large take-away meal, pack some of it away before starting to eat. This will help avoid 'picking' after finishing your portion. 'All you can eat' buffets may seem good value for money, but it is easy to misjudge the amount you have eaten.

Tip 3: Don't speed when you eat
Slowing down your eating gives your brain time to process the information that energy supply is on its way, and will help to 'feel' the fullness. Putting your fork down in between bites is a good way to slow down.

Tip 4: Don't eat mindlessly
Try to avoid eating while doing something else, such as browsing the internet, watching TV, or studying. Research shows that you eat more if you have your mind on something else. Sitting down and focusing on the food when you eat helps to feel more satisfied after eating.

Tip 5: Stand back from that snack
University offers plenty of 'eating opportunities'; many events and meetings offer free food and spending all day at university can lead to eating in between meals. Snack calories are not always compensated for at the next meal, so it is best to politely pass those 'extra' snacks.

Tip 6: Don't drink your calories
Sweetened drinks contain large amounts of sugar. That can include fruit juices (100% juice) and smoothies. Water or teas are best for staying well hydrated while saving calories. If you need a sweet drink, choose 'diet' or 'light'. And of course, alcohol calories can mount up!!

Tip 7: Walk off the weight
Get into the habit of walking or cycling as much as possible every day. Walking or biking to class and to see your friends are good ways to incorporate activity in your day. 10 000 steps are recommended, and a pedometer will help.

12.10 Appendix 10: Questionnaires

Questionnaire Study 1

Thank you very much for your participation in the survey asking about your attitudes towards genetic testing and risk of weight gain. Please answer the questions spontaneously, don't think about the answers in great detail.

Your Understanding of Genetics

	Much lower	Lower	About the same	Higher	Much Higher	I don't know anything about genetics
Compared with the average person, I believe my understanding of genetics is…	☐	☐	☐	☐	☐	☐

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I have a clear picture about what genetic testing is	☐	☐	☐	☐	☐
I am interested in the progress of genetic research, and I keep myself updated	☐	☐	☐	☐	☐
I am interested in genetic research, but I do not actively seek information about it	☐	☐	☐	☐	☐
I am very interested in genetic research in a specific area	☐	☐	☐	☐	☐

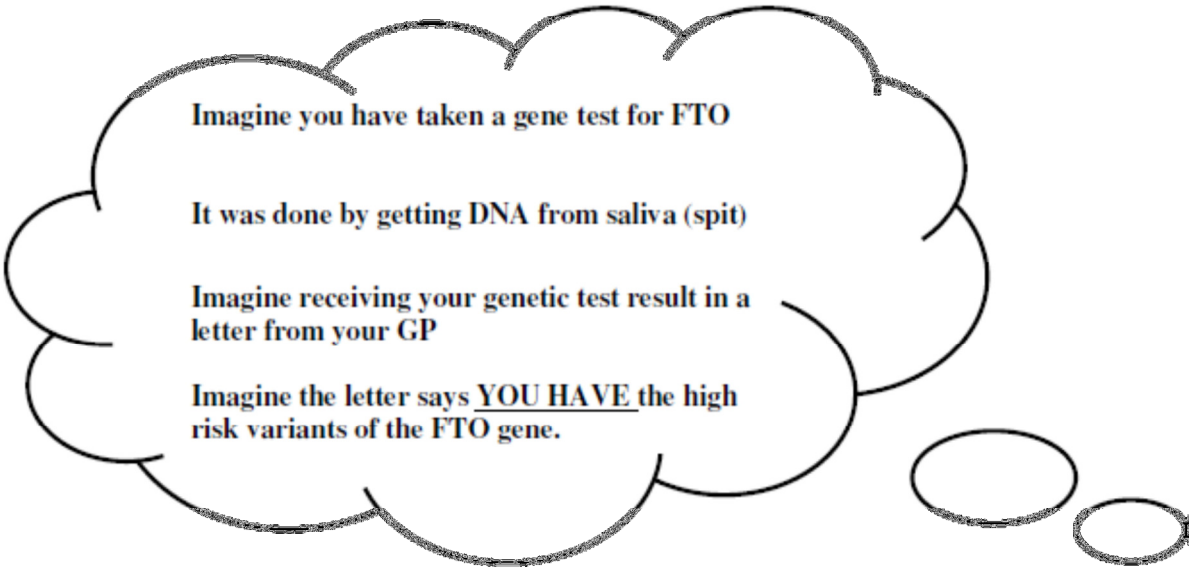
	Much lower	Lower	About the same	Higher	Much higher
Compared with someone of my age and sex, I think my chance of becoming severely overweight at some point in my life is…	☐	☐	☐	☐	☐

	Not at all	2	3	4	5	6	7	8	9	Entirely
Please indicate on a scale from 1-10 how much <u>you</u> believe <u>your</u> weight is determined by your genes?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

We would now like you to read some information about genetics and weight.

After reading each sentence please tick the box to show you have understood.

- One of the first genes linked with weight (called the FTO gene) was discovered in 2007. ☐
- About 1 in 6 people have the high risk variants of FTO. ☐
- Having the high risk variants of FTO makes a person more likely to put on weight. ☐
- Having the high risk variants of FTO increases your chance of becoming obese at some point in life by 20%. ☐



When you have finished reading this section, please think how this result would make you feel and answer the following statements…

2

	Much lower	Lower	About the same	Higher	Much higher
If you had the high risk variants of FTO, do you think your chance of weight gain compared to others would be	☐	☐	☐	☐	☐

If I received a genetic test result which put me at higher risk of gaining weight…

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I would try to change my lifestyle to prevent weight gain	☐	☐	☐	☐	☐
I would feel more conscious about my current weight	☐	☐	☐	☐	☐
I would feel that there is nothing I can do to prevent weight gain	☐	☐	☐	☐	☐
I would be more conscious about the amount of physical activity I do	☐	☐	☐	☐	☐
I would regret having taken the test	☐	☐	☐	☐	☐
I would take steps to prevent myself from gaining weight	☐	☐	☐	☐	☐
I would be glad that I knew about the genetic test result	☐	☐	☐	☐	☐
I would want to discuss my result with a health professional	☐	☐	☐	☐	☐
I would be more conscious about my diet	☐	☐	☐	☐	☐
I would be less inclined to take action to prevent weight gain	☐	☐	☐	☐	☐
I would be glad that I have an explanation for my body weight	☐	☐	☐	☐	☐
I would feel angry about the test result	☐	☐	☐	☐	☐

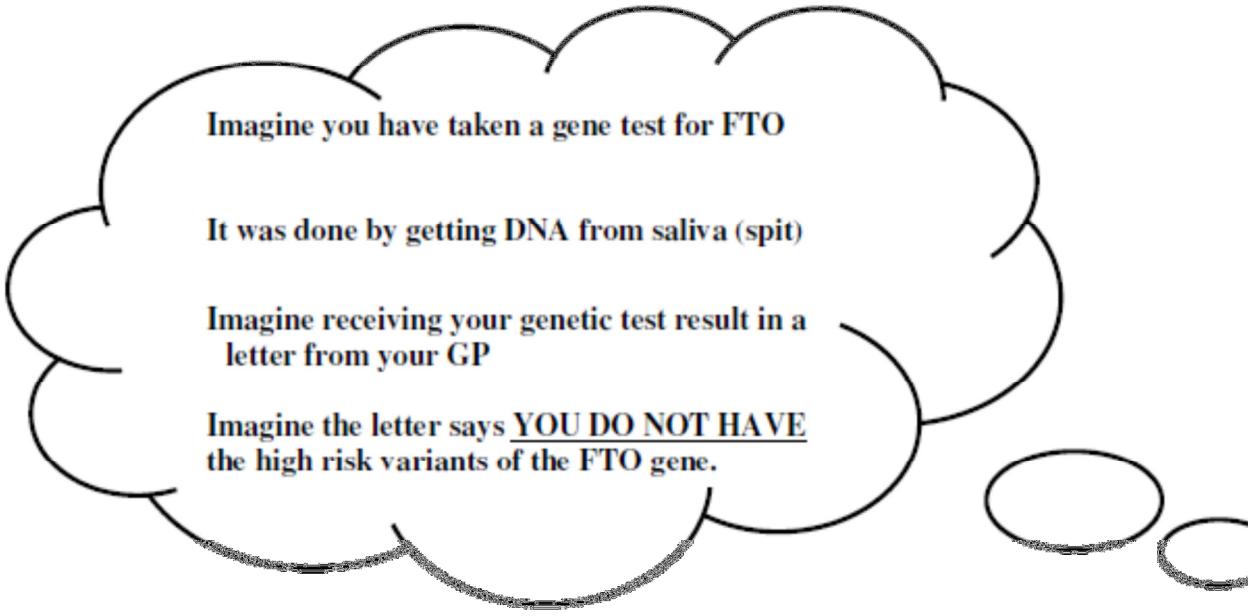
If I received a genetic test result which put me at higher risk of gaining weight…	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I would seek the advice of a dietician	☐	☐	☐	☐	☐
I would seek more information about weight loss programs	☐	☐	☐	☐	☐
I would go to the Internet to find out more about what the result means	☐	☐	☐	☐	☐
I would want to receive some more detailed information about how to prevent weight gain	☐	☐	☐	☐	☐
I would feel depressed	☐	☐	☐	☐	☐
I would want to take some action to prevent weight gain	☐	☐	☐	☐	☐
I would feel that this confirms what I have always thought of as the reason for my weight	☐	☐	☐	☐	☐
I would like to know more about how the gene acts	☐	☐	☐	☐	☐
I would feel more concerned about gaining weight	☐	☐	☐	☐	☐
I would take up exercise	☐	☐	☐	☐	☐
I would go to the Internet to find out more about how to prevent weight gain	☐	☐	☐	☐	☐

	Much lower	Lower	About the same	Higher	Much higher
If someone had the high risk variants of FTO, do you think their chance of weight gain compared to others would be…	☐	☐	☐	☐	☐

We should now like you to read some information about genetics and weight.

Please tick the box after reading each sentence to show you have understood.

- One of the first genes linked with weight (called the FTO gene) was discovered in 2007. ☐
- About 1 in 6 people have the high risk variants of FTO. ☐
- Having the high risk variants of FTO makes a person more likely to put on weight. ☐
- Having the high risk variants of FTO increases your chance of becoming obese at some point in life by 20%. ☐



When you have finished reading this section, please think how this result would make you feel and answer the following statements…

If I received a genetic test result which did not put me at higher risk of gaining weight…	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I would seek the advice of a dietician	☐	☐	☐	☐	☐
I would seek more information about weight loss programs	☐	☐	☐	☐	☐
I would go to the Internet to find out more about what the result means	☐	☐	☐	☐	☐
I would want to receive some more detailed information about how to prevent weight gain	☐	☐	☐	☐	☐
I would feel depressed	☐	☐	☐	☐	☐
I would want to take some action to prevent weight gain	☐	☐	☐	☐	☐
I would feel that this confirms what I have always thought of as the reason for my weight	☐	☐	☐	☐	☐
I would like to know more about how the gene acts	☐	☐	☐	☐	☐
I would feel more concerned about gaining weight	☐	☐	☐	☐	☐
I would take up exercise	☐	☐	☐	☐	☐
I would go to the Internet to find out more about how to prevent weight gain	☐	☐	☐	☐	☐

	Much lower	Lower	About the same	Higher	Much higher
If someone did not have the high risk variants of FTO, do you think their chance of weight gain compared to others would be	☐	☐	☐	☐	☐

Your Interest in Genetic Testing

If you were invited to take a free genetic test to determine your susceptibility to weight gain within the next 6 months, how interested would you be?	**Not Interested at all** ☐	**Slightly Interested** ☐	**Very Interested** ☐

What percentage of students do you think would be interested in taking a free test to determine their susceptibility to weight gain?	☐ %

If you were invited to take a free genetic test to determine your genetic susceptibility to weight gain within the next 6 months, would you take up the offer?	**No, definitely not** ☐	**No, probably not** ☐	**Yes, Probably** ☐	**Yes, Definitely** ☐

What percentage of students do you think would take up the offer of a free test to determine their susceptibility to weight gain?	☐ %

Your Beliefs About Overweight

There are many reasons why people become overweight. We are interested in what you believe. Please indicate how important you think each factor is for becoming overweight.

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Bad eating habits	☐	☐	☐	☐	☐
Stress	☐	☐	☐	☐	☐
Snacking	☐	☐	☐	☐	☐
Lack of exercise	☐	☐	☐	☐	☐
Watching a lot of TV	☐	☐	☐	☐	☐
Genes	☐	☐	☐	☐	☐
Late night eating	☐	☐	☐	☐	☐
Alcohol	☐	☐	☐	☐	☐
Slow metabolism	☐	☐	☐	☐	☐
Inactive lifestyle	☐	☐	☐	☐	☐
Drugs	☐	☐	☐	☐	☐
Negative emotions	☐	☐	☐	☐	☐
Runs in families	☐	☐	☐	☐	☐
Food constantly available	☐	☐	☐	☐	☐

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
How important do you think your genes are in determining <u>your</u> weight?	☐	☐	☐	☐	☐

Your Beliefs About Genetic Testing

There are many different views about genetic testing. We are interested in your thoughts. Please indicate how much you agree/disagree with each statement.

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Genetic testing will help scientists to cure many serious/ fatal inherited diseases	☐	☐	☐	☐	☐
People will benefit greatly from the advances in genetic testing	☐	☐	☐	☐	☐
Genetic testing will give people valuable information about their future	☐	☐	☐	☐	☐
Genetic testing will eventually lead to a better life for many people	☐	☐	☐	☐	☐
The government should put more money into research in genetic testing	☐	☐	☐	☐	☐
Overall genetic testing is a bad idea	☐	☐	☐	☐	☐
It is wrong for scientists to try to cure genetic diseases	☐	☐	☐	☐	☐
All genetic testing should be banned	☐	☐	☐	☐	☐
Genetic testing could be dangerous if conducted by the wrong people	☐	☐	☐	☐	☐
Genetic testing will cause many people a lot of unnecessary pain and anxiety	☐	☐	☐	☐	☐
Genetic testing will cause more problems than it will solve	☐	☐	☐	☐	☐

1

About you

To help us interpret the results, could you please answer some short questions about yourself.

What course are you studying?	**What year are you in?**
_____	_____
How old are you?	**What is your gender?**
_____*years*	Male ☐ Female ☐
What is your religion (even if you are not currently practising)?	**Do you consider that you are actively practising your religion?**
Christian ☐ *Buddhist* ☐ *Hindu* ☐	Yes ☐ No ☐
Jewish ☐ *Muslim* ☐ *Sikh* ☐	
Any other religion ☐ *No religion at all* ☐	
How tall are you?	**What do you weigh?**
_____*m or* _____*ft* _____*in*	_____**kg or** _____**st** _____**lbs**

About Your Lifestyle

	Very underweight	Slightly underweight	About the right weight	Slightly overweight	Very overweight
How would you describe your weight?	☐	☐	☐	☐	☐

	Neither gained nor lost	Gained weight	Lost weight	Don't weigh myself	Don't want to say
Since starting university, have you gained or lost weight?	☐	☐ _____st _____lbs or _____kg	☐ _____st _____lbs or _____kg	☐	☐

3

	Very dissatisfied	Fairly dissatisfied	Neither satisfied nor dissatisfied	Fairly satisfied	Very satisfied
How satisfied are you with your weight at the moment?	☐	☐	☐	☐	☐

Are any of your relatives overweight, or have they been overweight in the past?

	YES	*NO*		*YES*	*NO*
Grandmother on mother's side	☐	☐	Grandmother on father's side	☐	☐
Grandfather on mother's side	☐	☐	Grandfather on father's side	☐	☐
Mother	☐	☐	Father	☐	☐
How many brothers do you have?	☐	☐	How many sisters do you have?	☐	☐
How many of them are overweight?	☐	☐	How many of them are overweight?	☐	☐

	Much lower	Lower	About the same	Higher	Much higher
Compared with other students your age and sex do you think the amount of physical activity you do is…	☐	☐	☐	☐	☐

	Much less healthily	Less healthily	About the same	More healthily	Much more healthily
Compared with other students your age and sex do you think you eat…	☐	☐	☐	☐	☐

	Much less healthy	Less healthy	About the same	More healthy	Much more healthy
Compared with other students your age and sex do you think your overall lifestyle is	☐	☐	☐	☐	☐

How true are the following statements for you?	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
If I don't watch what I eat I put on weight very easily	☐	☐	☐	☐	☐
I worry about becoming overweight	☐	☐	☐	☐	☐
I feel I am always struggling to keep my weight under control	☐	☐	☐	☐	☐
If I wanted to, I could easily eat a healthy diet from now on	☐	☐	☐	☐	☐

	Never	**Seldom**	**Sometimes**	**Often**	**Very often**
If food tastes good to you, do you eat more than usual?	☐	☐	☐	☐	☐
If food looks and smells good, do you eat more than usual?	☐	☐	☐	☐	☐
If you see or smell something delicious, do you have the desire to eat it?	☐	☐	☐	☐	☐
If you have something delicious to eat do you eat it straight away?	☐	☐	☐	☐	☐
If you walk past a shop or a café do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
If you see others eating, do you also have the desire to eat?	☐	☐	☐	☐	☐
Do you eat more than usual if you see others eating?	☐	☐	☐	☐	☐
When preparing a meal, are you inclined to eat something?	☐	☐	☐	☐	☐

5

	Never	Seldom	Sometimes	Often	Very often
When you have put on weight do you eat less that you usually do?	☐	☐	☐	☐	☐
Do you try to eat less at mealtimes than you would like to eat?	☐	☐	☐	☐	☐
Do you watch exactly what you eat?	☐	☐	☐	☐	☐
When you have eaten too much do you eat less than usual the following day?	☐	☐	☐	☐	☐
Do you deliberately eat less in order not to become heavier?	☐	☐	☐	☐	☐
How often do you try not to eat between meals because you are watching your weight?	☐	☐	☐	☐	☐
How often in the evening do you try not to eat because you are watching your weight?	☐	☐	☐	☐	☐

Thank you very much once again for your effort.

	YES	NO
Would you be willing to participate in further research on genetic testing?	☐	☐

If yes, please provide your email address below so we can contact you.

Email: _____

Baseline Questionnaire Study 4

Thank you very much for your participation in this study.

Please provide us with your contact details, so we can return your DNA test result to you.

Please note: Details are confidential; you will be assigned an ID to link the questionnaire and the DNA data. This information will solely be used to contact you when your test result is ready.

Name: _____

Email:_____

Phone:_____

Date of Birth: _____

Your Saliva ID no:

(In case you have not given saliva yet, or you cannot remember your number, please leave the field blank).

_____

About you

To help us interpret the results, could you please answer some short questions about yourself

What course are you studying	**Are you**
_____	**Male** ☐ **Female** ☐
Which year are you in?	
_____	**How old are you?** _____**years**

What is your Ethnicity?				
White	Black	Asian British	Mixed	Chinese or any other
White British ☐	Caribbean ☐	Indian ☐	White and Black Caribbean ☐	Chinese ☐
White Irish ☐	African ☐	Pakistani ☐	White and Black African ☐	Any other ☐
		Bangladeshi ☐	White and Asian ☐	
Any other White background ☐	Any other Black background ☐	Any other Asian background ☐	Any other mixed background ☐	Do not wish to answer ☐

	Very dissatisfied	**Fairly dissatisfied**	**Neither satisfied nor dissatisfied**	**Fairly satisfied**	**Very satisfied**
How satisfied are you with your weight at the moment?	☐	☐	☐	☐	☐

	Very underweight	Slightly underweight	About the right weight	Slightly overweight	Very overweight
How would you describe your weight?	☐	☐	☐	☐	☐

Are/were any of your relatives overweight?

	Yes	No	Don't Know		Yes	No	Don't Know
Grandmother on mother's side	☐	☐	☐	Grandmother on father's side	☐	☐	☐
Grandfather on mother's side	☐	☐	☐	Grandfather on father's side	☐	☐	☐
Mother	☐	☐	☐	Father	☐	☐	☐
How many brothers do you have?	☐			How many sisters do you have?	☐		
How many of them are overweight?	____			How many of them are overweight?	____		

4

About Your Diet

About how many times a week do you eat a serving of the following foods?

	Less than once a week	Once or twice a week	3-5 times a week	6 or more times a week	Never
Cheese (any except cottage)	☐	☐	☐	☐	☐
Beefburgers or sausages	☐	☐	☐	☐	☐
Beef, pork or lamb (if vegetarian: nuts)	☐	☐	☐	☐	☐
Beacon, meat pies, processed meat	☐	☐	☐	☐	☐

About how many times a week do you eat a serving of the following foods?

	Less than once a week	Once or twice a week	3-5 times a week	6 or more times a week	Never
Chicken or Turkey	☐	☐	☐	☐	☐
Fish (NOT fried)	☐	☐	☐	☐	☐
ANY fried food: fried fish, chips, cooked breakfast, Samosas	☐	☐	☐	☐	☐
Cakes, pies, puddings, pastries	☐	☐	☐	☐	☐
Biscuits, chocolate or crisps	☐	☐	☐	☐	☐

About how much milk do you yourself use in a day, for drinking in cereal, tea, or coffee?
What kind of milk do you usually use? (Choose the type you use most of)

	Less than quarter pint	About a quarter pint	About half a pint	1 pint or more	None
Full Cream (Silver Top) or Channel Islands (gold Top)	☐	☐	☐	☐	☐
Semi-skimmed (red-stripe top)	☐	☐	☐	☐	☐
Skimmed (blue-checked top)	☐	☐	☐	☐	☐

About how many pats or rounded teaspoons of margarine, butter, or other spread do you usually use in a day, for example on bread, sandwiches, toast, potatoes or vegetables?

Butter or Margarine: Flora, Vitalite, sunflower types, Golden Crown, Stork Light Summer Country	_____teaspoons
Low fat spread: Gold/Lowest, Outline, Shape, Flora Extra Lite, Delight, Half Fat Butter, Country Light	_____teaspoons

What sort of fat do you use?	Butter, dripping, lard, solid cooking fat	Hard or soft margarine, White Flora, Dairy blends, half fat butter	Poly-unsaturated/ sunflower margarine or low fat spread	Pure Vegetable Oil (sunflower, soya, olive, rapeseed)	No fat used
On bread and vegetables?	☐	☐	☐	☐	☐
For frying?	☐	☐	☐	☐	☐
For baking and cooking?	☐	☐	☐	☐	☐

About how many pieces of bread, rolls or chapattis do you eat on usual day?

	Less than 1 a day	1-2 a day	3-4 a day	5 or more a day	None
White Bread	☐	☐	☐	☐	☐
Brown or granary bread	☐	☐	☐	☐	☐
Wholemeal bread or 2 slices Crispbread	☐	☐	☐	☐	☐

About how many times a week do you have a bowl of breakfast cereal or porridge? What kind do you have most often?

	Less than once a week	Once or twice a week	3-5 times a week	6 or more times a week	Never
Sugar Type: Frosties, Coco Pops, Riccicles, Sugar Puffs	☐	☐	☐	☐	☐
Rice/Corn Type: Corn Flakes, Rice Krispies, Special K	☐	☐	☐	☐	☐
Porridge or Ready Brek	☐	☐	☐	☐	☐
Wheat Type: Shreddered Wheat, Weetabix, Puffed Wheat, Fruit 'n' Fibre, Nutri-Grain, Oat Crunches, Start	☐	☐	☐	☐	☐
Muesli Type: Alpen, Jordans,	☐	☐	☐	☐	☐
Bran Type: All Bran, Bran Flakes, Sultana Bran, Team	☐	☐	☐	☐	☐

About how many times a week do you eat a serving of the following foods?	Less than once a week	Once or twice a week	3-5 times a week	6 or more times a week	Never
Pasta or Rice	☐	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐	☐
Peas	☐	☐	☐	☐	☐
Beans (baked, tinned, dried) or lentils	☐	☐	☐	☐	☐
Other vegetables (any type)	☐	☐	☐	☐	☐
Fruit (Fresh, Frozen or Canned)	☐	☐	☐	☐	☐

	Much less healthily	Less healthily	About the same	More healthily	Much more healthily
Compared with other students your age and sex, do you think you eat…	☐	☐	☐	☐	☐

	Gain weight	Lose weight	Stay the same
Over the next year, do you think you will gain weight, lose weight, or stay the same?	☐	☐	☐
If you think you might gain or lose weight, about how much do you think you will gain/lose?	☐ *kg* ☐ *lb*	☐ *kg* ☐ *lbs*	

About your Physical Activity

How often do you engage in the following activities?	Times per week	Time per session (in min)
	☐	☐
Walking (as a means for transport or leisure)	☐	☐
Cycling (as a means for transport or leisure)	☐	☐
Watching TV	☐	☐
Playing video games	☐	☐
Jogging/running	☐	☐
Dancing	☐	☐
Tennis or badminton	☐	☐
Squash	☐	☐
Hockey	☐	☐
Netball, volleyball or basketball	☐	☐
Football	☐	☐
Rugby	☐	☐
Martial Arts, boxing or wrestling	☐	☐
Swimming	☐	☐
Cross-trainer/rowing	☐	☐
Aerobics	☐	☐
Yoga/Pilates	☐	☐
Frisbee	☐	☐
Other (please state) _____	☐	☐

	Much lower	Lower	About the same	Higher	Much higher
Compared with other students your age and sex, do you think the amount of physical activity you do is…	☐	☐	☐	☐	☐

9

About Your Eating Behaviour

	Never	Seldom	Sometimes	Often	Very often
If food tastes good to you, do you eat more than usual?	☐	☐	☐	☐	☐
If food looks and smells good, do you eat more than usual?	☐	☐	☐	☐	☐
If you see or smell something delicious, do you have the desire to eat it?	☐	☐	☐	☐	☐
If you have something delicious to eat do you eat it straight away?	☐	☐	☐	☐	☐
If you walk past the baker do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
If you walk past a snackbar or a café do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
If you see others eating, do you also have the desire to eat?	☐	☐	☐	☐	☐
Can you resist eating delicious foods?	☐	☐	☐	☐	☐
Do you eat more than usual if you see others eating?	☐	☐	☐	☐	☐
When preparing a meal, are you inclined to eat something?	☐	☐	☐	☐	☐

	Much lower	Lower	About the same	Higher	Much higher
Compared with other people your age and sex, do you think your chance of becoming seriously overweight at some point in your life is…	☐	☐	☐	☐	☐

10

	Never	Seldom	Sometimes	Often	Very often
When you have put on weight do you eat less than you usually do?	☐	☐	☐	☐	☐
Do you try to eat less at mealtimes than you would like to eat?	☐	☐	☐	☐	☐
How often do you refuse food or drink offered because you are concerned about your weight?	☐	☐	☐	☐	☐
Do you watch exactly what you eat?	☐	☐	☐	☐	☐
Do you deliberately eat foods that are slimming?	☐	☐	☐	☐	☐
When you have eaten too much do you eat less than usual the following day?	☐	☐	☐	☐	☐
Do you deliberately eat less in order not to become heavier?	☐	☐	☐	☐	☐
How often do you try not to eat between meals because you are watching your weight?	☐	☐	☐	☐	☐
How often in the evening do you try not to eat because you are watching your weight?	☐	☐	☐	☐	☐
Do you take into account your weight with what you eat?	☐	☐	☐	☐	☐

	Much less healthy	Less healthy	About the same	Healthier	Much healthier
Compared with other students your age and sex, do you think your overall lifestyle is…	☐	☐	☐	☐	☐

11

	Never	Seldom	Sometimes	Often	Very often
Do you have the desire to eat when you are irritated?	☐	☐	☐	☐	☐
Do you have the desire to eat when you have nothing to do?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are depressed or discouraged?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are feeling lonely?	☐	☐	☐	☐	☐
Do you have the desire to eat when somebody lets you down?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are cross?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are approaching something unpleasant to happen?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are anxious, worried or tense?	☐	☐	☐	☐	☐
Do you have the desire to eat when things are going against you or when things go wrong?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are frightened?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are disappointed?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are emotionally upset?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are bored or restless?	☐	☐	☐	☐	☐

How true are the following statements for you?	Definitely true	Mostly true	Mostly false	Definitely false
If I don't watch what I eat I put on weight very easily	☐	☐	☐	☐
I worry about being/becoming overweight	☐	☐	☐	☐
I feel I am always struggling to keep my weight under control	☐	☐	☐	☐
If I wanted to, I could easily eat a healthy diet from now on	☐	☐	☐	☐

	Never	Almost never	Some-times	Fairly often	Very often
In the last month, how often have you felt that you were unable to control the important things in your life?	☐	☐	☐	☐	☐
In the last month, how often have you felt confident about your ability to handle your personal problems?	☐	☐	☐	☐	☐
In the last month, how often have you felt that things were going your way?	☐	☐	☐	☐	☐
In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	☐	☐	☐	☐	☐

	Yes	No
Would you be willing to participate in further research on body weight, genes and health?	☐	☐

Thank you very much once again for your effort.

1-month follow-up questionnaire Study 4

Dear Participant

Thank you very much to everyone who already responded. You can ignore this email.

If you have not already done so, please fill out the short questionnaire below.

It is concerned with the leaflet on how to prevent weight gain, that I recently sent to you.

I would be grateful if you could answer the questions below by just replying to this email.

Once you click the 'reply' button you will be able to enter your responses.

You will be reimbursed for your time and effort at the final weighing session if you reply to this questionnaire.

Please mark with an 'X' the statement out of the next four that best describes you
1. I am not trying to control my weight, and I have no intention of doing so in the next month
2. I am not trying to control my weight, but I am thinking of doing something in the next month
3. I started to try to control my weight within the last month
4. I have been trying to control my weight for more than a month

In the past month, how often did you …	Not at all	Occasionally	Sometimes	Most of the time	Always
Watch portion sizes? (Tip 1)					
Avoid second helpings? (Tip 2)					
Consciously slow down your eating? (Tip 3)					
Avoid eating mindlessly/focus on your food? (Tip 4)					
Pass up 'extra' snacks between meals? (Tip 5)					
Avoid sweet drinks or choose a 'lite' drink? (Tip 6)					
Integrate some physical activity into your day? (Tip 7)					

All things considered, in the past month…	Not at all	Occasionally	Sometimes	Most of the time	Always
I was motivated to control weight					
I was committed to weight control					
I made weight control a priority					

Did you do anything else to control weight or do you have any other comments?

Reactions to genetic test feedback questionnaire Study 4

Thank you very much for taking part in the study. We would like to ask you a few questions about your reactions to the test result, as well as your eating habits since you started university.

Thank you very much for your participation in this study.

Please provide us with your contact details, so we can link your questionnaire to the data already provided.

Please note: Details are confidential; you will be assigned an ID to link the questionnaire and the DNA data

Name: _____

Email:_____

Date of Birth: _____

Your Saliva ID no (if you cannot remember, leave the field blank):

_____

About your test result

	AA	AT	TT	Don't remember
My FTO test result was…	☐	☐	☐	☐

	At lower risk for gaining weight	At average risk for gaining weight	At higher risk for gaining weight	Don't remember
My FTO test result puts me…	☐	☐	☐	☐

	Not at all	2	3	4	5	6	7	8	9	Entirely
Please indicate on a scale from 1-10 how much <u>you</u> believe <u>your</u> weight is determined by your genes?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Knowing my FTO gene test result encourages me to change my lifestyle to prevent weight gain	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me think that there is nothing I can do to prevent weight gain	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me more conscious about the amount of physical activity I do	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me regret having taken the test	☐	☐	☐	☐	☐
Knowing my FTO gene test result encourages me to take steps to prevent myself from gaining weight	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me glad	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me want to discuss my result with a health professional	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me more conscious about my diet	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me feel disappointed	☐	☐	☐	☐	☐
Knowing my FTO gene test result provides me with an explanation for my body weight	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me feel angry	☐	☐	☐	☐	☐
Knowing my FTO gene test result does not change anything at all	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me think about my future health	☐	☐	☐	☐	☐

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
Knowing my FTO gene test result makes me go to the Internet to find out more about what the result means	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me want to some more detailed information about how to prevent weight gain	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me feel depressed	☐	☐	☐	☐	☐
Knowing my FTO gene test result is useful	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me want to take some action to prevent weight gain	☐	☐	☐	☐	☐
Knowing my FTO gene test result confirms what I have always thought of as the reason for my weight	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me want to know more about how the gene acts	☐	☐	☐	☐	☐
Knowing my FTO gene test result is important for me	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me more concerned about gaining weight	☐	☐	☐	☐	☐
Knowing my FTO gene test result makes me take up exercise	☐	☐	☐	☐	☐

	No, definitely not	Not yet, but I might in the future	Not yet, but I will in the future	Yes, I have told already
I will tell a family member about my test result	☐	☐	☐	☐
I will tell a friend about my test result	☐	☐	☐	☐

	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I would recommend the gene test to other students	☐	☐	☐	☐	☐
I would recommend the gene test to other people in my family	☐	☐	☐	☐	☐
I would like to see genetic tests available as part of routine health care	☐	☐	☐	☐	☐

	Gained weight	Lost weight	Gained and lost weight	Stayed the same weight	Prefer not to say
Since starting University I have…	*In pop up window:* ☐ *st/lb* ☐ *kg*	*In pop up window :* ☐ *st/lb* ☐ *kg*	*In pop up window: gained* ☐ *st/lb,* ☐ *kg* *Lost* ☐ *st/lb* ☐ *kg*	☐	☐

	Much lower	Lower	About the same	Higher	Much higher
Compared with other people of my age and sex, I think my chance of becoming severely overweight at some point in my life is…	☐	☐	☐	☐	☐

	Never	Almost never	Some-times	Fairly often	Very often
In the last month, how often have you felt that you were unable to control the important things in your life?	☐	☐	☐	☐	☐
In the last month, how often have you felt confident about your ability to handle your personal problems?	☐	☐	☐	☐	☐
In the last month, how often have you felt that things were going your way?	☐	☐	☐	☐	☐
In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	☐	☐	☐	☐	☐

About your behaviour

Since starting university I....	Less often than before	The same as before	More often than before
eat breakfast	☐	☐	☐
eat snacks	☐	☐	☐
eat late at night	☐	☐	☐
eat big portions	☐	☐	☐
eat second helpings	☐	☐	☐
skip meals	☐	☐	☐
cook for myself	☐	☐	☐
drink caffeinated drinks	☐	☐	☐
sleep 7 hours or more	☐	☐	☐

	Never	Seldom	Sometimes	Often	Very often
If food tastes good to you, do you eat more than usual?	☐	☐	☐	☐	☐
If food looks and smells good, do you eat more than usual?	☐	☐	☐	☐	☐
If you see or smell something delicious, do you have the desire to eat it?	☐	☐	☐	☐	☐
If you have something delicious to eat do you eat it straight away?	☐	☐	☐	☐	☐
If you walk past the baker do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
If you walk past a snackbar or a café do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
If you see others eating, do you also have the desire to eat?	☐	☐	☐	☐	☐
Can you resist eating delicious foods?	☐	☐	☐	☐	☐
Do you eat more than usual if you see others eating?	☐	☐	☐	☐	☐
When preparing a meal, are you inclined to eat something?	☐	☐	☐	☐	☐

	Never	Seldom	Sometimes	Often	Very often
Do you have the desire to eat when you are irritated?	☐	☐	☐	☐	☐
Do you have the desire to eat when you have nothing to do?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are depressed or discouraged?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are feeling lonely?	☐	☐	☐	☐	☐
Do you have the desire to eat when somebody lets you down?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are cross?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are approaching something unpleasant to happen?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are anxious, worried or tense?	☐	☐	☐	☐	☐
Do you have the desire to eat when things are going against you or when things go wrong?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are frightened?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are disappointed?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are emotionally upset?	☐	☐	☐	☐	☐
Do you have the desire to eat when you are bored or restless?	☐	☐	☐	☐	☐

	Never	Seldom	Sometimes	Often	Very often
When you have put on weight do you eat less that you usually do?	☐	☐	☐	☐	☐
Do you try to eat less at mealtimes than you would like to eat?	☐	☐	☐	☐	☐
How often do you refuse food or drink offered because you are concerned about your weight?	☐	☐	☐	☐	☐
Do you watch exactly what you eat?	☐	☐	☐	☐	☐
Do you deliberately eat foods that are slimming?	☐	☐	☐	☐	☐
When you have eaten too much do you eat less than usual the following day?	☐	☐	☐	☐	☐
Do you deliberately eat less in order not to become heavier?	☐	☐	☐	☐	☐
How often do you try not to eat between meals because you are watching your weight?	☐	☐	☐	☐	☐
How often in the evening do you try not to eat because you are watching your weight?	☐	☐	☐	☐	☐
Do you take into account your weight with what you eat?	☐	☐	☐	☐	☐

How true are the following statements for you?	**Definitely true**	**Mostly true**	**Mostly false**	**Definitely false**
If I don't watch what I eat I put on weight very easily	☐	☐	☐	☐
I worry about being/becoming overweight	☐	☐	☐	☐
I feel I am always struggling to keep my weight under control	☐	☐	☐	☐
If I wanted to, I could easily eat a healthy diet from now on	☐	☐	☐	☐

About Your Diet

About how many times a week do you eat a serving of the following foods?

	Less than once a week	Once or twice a week	3-5 times a week	6 or more times a week
Cheese (any except cottage)	☐	☐	☐	☐
Beefburgers or sausages	☐	☐	☐	☐
Beef, pork or lamb (if vegetarian: nuts)	☐	☐	☐	☐
Beacon, meat pies, processed meat	☐	☐	☐	☐

About how many times a week do you eat a serving of the following foods?

	Less than once a week	Once or twice a week	3-5 times a Week	6 or more times a Week
Chicken or Turkey	☐	☐	☐	☐
Fish (NOT fried)	☐	☐	☐	☐
ANY fried food: fried fish, chips, cooked breakfast, Samosas	☐	☐	☐	☐
Cakes, pies, puddings, pastries	☐	☐	☐	☐
Biscuits, chocolate or crisps	☐	☐	☐	☐

About how much milk do you yourself use in a day, for drinking in cereal, tea, or coffee? What kind of milk do you usually use? (Choose the type you use most of)

	Less than quarter pint	About a quarter pint	About half a pint	1 pint or more
Full Cream (blue Top) or Channel Islands (gold Top)	☐	☐	☐	☐
Semi-skimmed (green top)	☐	☐	☐	☐
1 % fat (orange top)	☐	☐	☐	☐
Skimmed (red top)	☐	☐	☐	☐

About how many pats or rounded teaspoons of margarine, butter, or other spread do you usually use in a day, for example on bread, sandwiches, toast, potatoes or vegetables?

Butter or Margarine: Flora, Vitalite, sunflower types, Golden Crown, Stork Light Summer Country	_____teaspoons
Low fat spread: Gold/Lowest, Outline, Shape, Flora Extra Lite, Delight, Half Fat Butter, Country Light	_____teaspoons

What sort of fat do you use?	Butter, dripping, lard, solid cooking fat	Hard or soft margarine, White Flora, Dairy blends, half fat butter	Poly-unsaturated/ sunflower margarine or low fat spread	Pure Vegetable Oil (sunflower, soya, olive, rapeseed)	No fat used
On bread and vegetables?	☐	☐	☐	☐	☐
For frying?	☐	☐	☐	☐	☐
For baking and cooking?	☐	☐	☐	☐	☐

About how many pieces of bread, rolls or chapattis do you eat on usual day?

	Less than 1 a day	1-2 a day	3-4 a day	5 or more a day
White Bread	☐	☐	☐	☐
Brown or granary bread	☐	☐	☐	☐
Wholemeal bread or 2 slices Crispbread	☐	☐	☐	☐

About how many times a week do you have a bowl of breakfast cereal or porridge? What kind do you have most often?

	Less than once a week	Once or twice a week	3-5 times a week	6 or more times a week
Sugar Type: Frosties, Coco Pops, Riccicles, Sugar Puffs	☐	☐	☐	☐
Rice/Corn Type: Corn Flakes, Rice Krispies, Special K	☐	☐	☐	☐
Porridge or Ready Brek	☐	☐	☐	☐
Wheat Type: Shreddered Wheat, Weetabix, Puffed Wheat, Fruit 'n' Fibre, Nutri-Grain, Oat Crunches, Start	☐	☐	☐	☐
Muesli Type: Alpen, Jordans,	☐	☐	☐	☐
Bran Type: All Bran, Bran Flakes, Sultana Bran, Team	☐	☐	☐	☐

About how many times a week do you eat a serving of the following foods?

	Less than once a week	Once or twice a week	3-5 times a week	6 or more times a week
Pasta or Rice	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐
Peas	☐	☐	☐	☐
Beans (baked, tinned, dried) or lentils	☐	☐	☐	☐
Other vegetables (any type)	☐	☐	☐	☐
Fruit (Fresh, Frozen or Canned)	☐	☐	☐	☐

	Much less healthily	Less healthily	About the same	More healthily	Much more healthily
Compared with other students your age and sex, do you think you eat...	☐	☐	☐	☐	☐

About your Activity

How often do you engage in the following activities?	Times per week	Time per session (in min)
	☐	☐
Walking (as a means for transport or leisure)	☐	☐
Cycling (as a means for transport or leisure)	☐	☐
Watching TV	☐	☐
Playing video games	☐	☐
Jogging/running	☐	☐
Dancing	☐	☐
Tennis or badminton	☐	☐
Squash	☐	☐
Hockey	☐	☐
Netball, volleyball or basketball	☐	☐
Football	☐	☐
Rugby	☐	☐
Martial Arts, boxing or wrestling	☐	☐
Swimming	☐	☐
Cross-trainer/rowing	☐	☐
Aerobics	☐	☐
Yoga/Pilates	☐	☐
Frisbee	☐	☐
Weight training	☐	☐
Climbing	☐	☐
Other (please state) _____	☐	☐

	Much lower	Lower	About the same	Higher	Much higher
Compared with other students your age and sex, do you think the amount of physical activity you do is…	☐	☐	☐	☐	☐

12

Do you have any other comments concerning your participation? Please feel free to use the space below

Thank you very much for your time and your effort.

Please contact Susanne Meisel [redacted] should you have any questions

12.11 Appendix 11: CONSORT Checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	201
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	N/A
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	201
	2b	Specific objectives or hypotheses	202
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	203
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	204, 221
Participants	4a	Eligibility criteria for participants	205
	4b	Settings and locations where the data were collected	207
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	207
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	212
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	220
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	219
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	219
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	219
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	219/220
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	220