TITLE
Genotype-based diet and physical activity advice: effects on behaviour change to reduce risk factors for cardiometabolic disease.

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Abstract:

Genotype-based diet and physical activity advice: effects on behaviour change to reduce risk factors for cardiometabolic disease.

The most important aspect of dietary or physical activity advice is that it results in a beneficial change in behaviour. Despite clear evidence that adherence to dietary and physical activity advice can reduce the risk of cardiometabolic disease, a significant proportion of the population do not meet recommendations. Personalised advice based on genetic variation has been proposed to motivate behaviour change, although research to date has been contradictory. The aim of this research was to determine the efficacy of genotype-based personalised advice to motivate and promote dietary and physical activity behaviour change, in the context of reducing the risk of obesity, type II diabetes (T2D), and cardiovascular disease (CVD). Four studies were conducted. The first two were intervention studies investigating: 1) dietary behaviour change following genotype-based personalised nutrition advice in participants (n = 114) informed of a risk versus a non-risk genotype (Study 1); and 2) healthy-eating motivation in young adults (n = 153) after receiving genotype-based personalised advice versus non-genotype-based personalised advice or no advice (Study 2). A systematic review and meta-analysis of 14 reports from 11 randomised controlled trials (RCTs) investigated the efficacy of genotype-based dietary or physical activity advice on behaviour change in the general population and individuals that are at-risk of CVD or T2D (Study 3). Finally, a survey (n = 396) was conducted to investigate the factors that influence the intention to adopt genotype-based personalised advice for diet and physical activity in young adults that perceive themselves to be a healthy weight versus those that perceive themselves to be overweight or obese (Study 4). Genotype-based personalised nutrition advice led to favourable dietary changes in participants who were not meeting dietary recommendations, but only those informed of a risk genotype met saturated fat recommendations following personalised nutrition advice (Study 1). Genotype-based personalised advice did not affect healthy-eating motivation in young adults (Study 2). The meta-analysis suggested that the use of genotype-based advice to promote dietary or physical activity behaviour is no more effective than general advice or advice based on lifestyle or phenotypic measures (Study 3). Background factors including belief composites, health locus of control (HLC), gender, physical activity, and food choice motives of 'health', 'price', 'familiarity', 'weight control', and 'convenience' interact with Theory of Planned Behaviour (TPB) constructs related to the intention to adopt genotype-based advice in young adults (Study 4). The findings from this programme of research suggest genotype-based advice does not motivate or promote greater behaviour change to reduce the risk of obesity, T2D and CVD, compared to non-genotype-based advice or general advice. However, recommendations are made for health care professionals and researchers to tailor genotype-based advice for young adults based on the findings of our survey. Finally, the effectiveness of the recommendations to motivate and change behaviour using genotype-based advice should be investigated in an intervention study in a young adult population.

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Summary:

The following section provides a summary of the programme of work, the aim of this section is to demonstrate how each study builds on the previous one to answer the overall aim of the PhD.

The most important aspect of any dietary or physical activity advice is that it results in a beneficial change in behaviour. Genotype-based personalised advice is delivered in combination with other levels of personalisation (phenotypic, clinical, dietary), with the aim of providing more precise and effective advice as well as encouraging behaviour change (Grimaldi et al., 2017). The overall aim of my research was to assess the second part of this aim, to determine the efficacy of genotype-based personalised advice to motivate and promote dietary and physical activity behaviour change, in the context of reducing the risk of obesity, T2D, and CVD.

The aim of the literature review was to provide context and a rationale for the area of research. Firstly, the prevalence and implications of obesity, T2D, and CVD is provided, and an overview of genetics, diet, and physical activity as risk factors for these conditions discussed. A greater understanding of the interaction between genes and life-style factors such as diet and physical activity has enabled greater personalisation of health advice based on an individual's genotype and is proposed as an alternative to the current 'one size fits all' approach to public health. These concepts are discussed and the research investigating the efficacy of this approach to diet and physical activity behaviour change is critically reviewed. A gap was identified in the literature investigating the use of genotype-based advice to motivate behaviour change, recently published studies have not been included in previous meta-analyses and the use of behaviour change theory is suggested as a framework to understand intention of the public to use genotype-based personalised advice. The aim of each study is stated at the end of the literature review.

Chapter two presents the findings of the first study of my PhD. The aim of this study was to determine the effect of genotype-based personalised nutrition advice on dietary intake in participants informed of a risk genotype compared to those informed of a non-risk genotype. The main findings from this study were that genotype-based personalised nutrition advice led to favourable dietary changes in participants who were not meeting dietary recommendations, irrespective of risk or non-risk genotype. However, in participants not meeting dietary

recommendations, only those with a risk Apolipoprotein E (*APOE*) genotype met saturated fat recommendations following genotype-based personalised nutrition advice. Therefore, incorporation of genotype-based personalised nutrition advice in a behaviour intervention may initiate favourable changes in dietary behaviour. This study was published in Nutrition and Health journal in November 2021.

In chapter three I present the second study of my PhD research. In the first study I used a pre-post-test design to compare the effect of genotype-based advice between participants with a risk genotype with those with a non-risk genotype. To enable the effect of genotype-based personalised advice to be isolated from other types of personalised advice, my second study included a control group as well as a group receiving personalised diet and physical activity advice without the addition of genetics. Unfortunately, due to COVID-19 it was not possible to collect all of the planned follow-up data (changes in measures of body adiposity and physical activity) for this study. As a consequence, the single outcome measure collected following advice was healthy-eating motivation. The aim of this study was to determine the efficacy of genotype-based personalised dietary and physical activity advice on healthy-eating motivation in young adults. Healthy-eating motivation was not significantly changed in young adults receiving genotype-based diet and physical activity advice, non-genotype-based personalised advice or no advice.

In the fourth chapter I present the third study of my PhD. The contradictory findings of my first two studies add to the already conflicting research to assess the effect of genotype-based diet and physical activity advice to promote increased motivation and behaviour change. The aim was to conduct a systematic review and meta-analysis to evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2D or obesity in the general population and individuals that are at-risk of CVD or T2D. The main finding was that genotype-based personalised advice is no more effective than general advice, or advice based on lifestyle or phenotypic measures, to change dietary or physical activity behaviour. This finding was consistent in studies that had recruited participants from the general population as well as studies that had recruited participants from populations at-risk of CVD or T2D. I concluded that future studies of genotype-based advice for changing behaviour should incorporate

behaviour change theory explicitly in their design and, where possible, behaviour outcomes should be measured objectively. This study was published in Nutrition Reviews in February 2023.

Chapter five presents the findings of my final study, the rationale for which was developed based on the findings of the first three studies. Previous findings suggest that personalisation of dietary and physical activity advice promotes behaviour change (Study 1 and 3), although the addition of genetics to other levels of personalisation may not be warranted (Study 3). Since, genotype-based personalisation of advice can be delivered earlier in the lifespan and therefore has the potential to prevent the development of unhealthy lifestyle behaviours, young people, stand to benefit from genotype-based dietary and physical activity advice. However, in Study 2, healthy-eating motivation in young adults was unaffected by any level of personalised advice. Therefore, the aim of Study 4 was to investigate the factors that influence the intention to adopt genotype-based personalised advice on diet and physical activity in young adults. Since, earlier research has suggested that individuals with a personal or family history of disease are more willing to engage with genotype-based advice, a secondary aim of this study was to investigate factors that influence the intention to use genotype-based personalised advice separately in young adults that perceive themselves to be a healthy weight versus those that perceive themselves to be overweight or obese. The main finding was that background factors including perceived body weight, behavioural beliefs, HLC, gender, physical activity, along with food choice motives of 'health', 'price', 'familiarity', 'weight control', and 'convenience' interact with TPB constructs that predict intention to adopt genotype-based personalised nutrition.

In chapter six, I discuss the findings from the four research studies together to answer the overall aim. The findings from this programme of research add to those of previous researchers that suggest genotype-based advice does not motivate or promote greater behaviour change to reduce the risk of obesity, T2D and CVD, compared to non-genotype-based advice or general advice. A systematic review of the literature identified that behaviour change theory has not consistently been adequately considered in the design and implementation of interventions that have incorporated genotype-based advice. For prevention of non-communicable diseases (NCDs) in later life young adults were identified as a population that stand to benefit most from the use of genotype-based advice to motivate behaviour change. For the first time factors that may

influence intention to adopt genotype-based advice were investigated in young adults using all constructs of the TPB as a framework. Finally, recommendations are made for how genotype-based advice delivered to a young adult population could be tailored to motivate changes in dietary and physical activity behaviour. These recommendations should be used by health care practitioners and researchers that intend to use genotype-based advice in a young adult population.

Publications and conference presentations to date:

Publications

King, A., Graham, C. A.-M., Glaister, M., Da Silva Anastacio, V., Pilic, L., & Mavrommatis, Y. (2023). The efficacy of genotype-based dietary or physical activity advice in changing behavior to reduce the risk of cardiovascular disease, type II diabetes mellitus or obesity: A systematic review and meta-analysis. *Nutrition Reviews*, nuad001.

King, A., Saifi, S., Smith, J., Pilic, L., Graham, C. A.-M., Da Silva Anastacio, V., Glaister, M., & Mavrommatis, Y. (2022). Does personalised nutrition advice based on apolipoprotein E and methylenetetrahydrofolate reductase genotype affect dietary behaviour? *Nutrition and Health*, 28(3), 467–476.

Conference presentations

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King, A., Graham, C. A.-M., Glaister, M., Da Silva Anastacio, V., Pilic, L., & Mavrommatis, Y. (2022). The efficacy of genotype-based dietary or physical activity advice in changing behavior to reduce the risk of cardiovascular disease, type II diabetes mellitus or obesity: A systematic review and meta-analysis. Poster presentation at the NuGOweek 2022 18th edition August 29-September 1, Tarragona, Spain.

King, A., Pilic, L., Nixon, J., Mauro, E., Glaister, M., Mavrommatis, Y. (2021). The effect of genotype-based personalised diet and physical activity advice on healthy-eating motivation in university students. Poster presentation at the NuGO IV European Summer School on Nutrigenomics July 21-25, online.

King, A., Saifi, S., Smith, J., Pilic, L., Graham, C., Glaister, M., Mavrommatis, Y. (2019). Does personalised nutrition advice based on *APOE* and *MTHFR* genotype affect dietary behaviour? Poster presentation at the International Society of Nutrigenetics and Nutrigenomics annual congress, July 12-13, Cambridge, UK.

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α:	Cronbach's alpha
AD:	Alzheimer's disease
ANRIL:	Antisense noncoding RNA in the INK4 locus
APOE:	Apolipoprotein E
β:	Standardised coefficient
B:	Unstandardized regression coefficient
BCT:	Behaviour change techniques
BF%:	Body fat percentage
BMI:	Body mass index
CAD:	Coronary artery disease
CENTRAL:	Cochrane Central Register of Controlled Trials
CHD:	Coronary heart disease
CI:	Confidence interval
COMA:	Committee on Medical Aspects of Food and Nutrition Policy
Comp:	Comparator group
CrI:	Credible intervals
CRS:	Conventional risk score
CVD:	Cardiovascular disease
DTC:	Direct-to-consumer
DZ:	Dizygotic
EPAQ2:	Epic Physical Activity Questionnaire
EPPM:	Extended Parallel Process Model
FA:	Fatty acid

FFQ:	Food frequency questionnaire
FPG:	Fasting plasma glucose
FTO:	Fat Mass and Obesity Associated
GRS:	Genetic risk score
GWAS:	Genome-wide association studies
HDL:	High-density lipoproteins (HDL)
HEI:	Healthy Eating Index
HLC:	Health locus of control
HR:	Hazard ratio
HSPG:	Heparin sulfate proteoglycans
HTMT:	Heterotrait-monotrait ratio of correlations
IGT:	Impaired glucose tolerance
Int:	Intervention group
LD:	Linkage disequilibrium
LDL:	Low-density lipoprotein
LDL-R:	Low-density lipoprotein receptor
MAF:	Minor allele frequency
MDS:	Mediterranean Diet Score
MET:	Metabolic equivalent
MTHFR:	Methylenetetrahydrofolate reductase
MUFA:	Monounsaturated fatty acid
MZ:	Monozygotic
NCD:	Non-communicable diseases
NDNS:	National Diet and Nutrition Survey
NHS:	National Health Service
NICE:	National Institute for Health and Care Excellence
NRSI:	Non-randomised studies on interventions

NW: Participants that perceive themselves to be normal weight

OB: Obese

OR: Odds ratio

OW: Participants that perceive themselves to be overweight or obese

PA: Physical activity

PAL: Physical activity level

PBC: Perceived behavioural control

PN: Personalised nutrition

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

R^2: Coefficient of determination

Δ R^2: Adjusted R^2

RCT: Randomised controlled trial

RevMan: Review Manager

RoB 2: Risk of Bias 2

RR: Relative risk

SACN: Scientific Advisory Committee on Nutrition

SBP: Systolic blood pressure

SD: Standard deviation

SE B: Standard error of the coefficient

SMD: Standardised mean difference

SN: Subjective norms

SNP: Single nucleotide polymorphism

STREGA: Strengthening the Reporting of Genetic Association Studies

TAG: Triglyceride

TC: Total cholesterol

TCFL2: Transcription factor 7 like 2

TEI:	Total energy intake
TPB:	Theory of Planned Behaviour
T2D:	Type II diabetes
VLDL:	Very-low-density lipoproteins
WC:	Waist circumference

Chapter 1: Literature Review

This chapter reviews relevant literature to provide context and a rationale for the use of genotype-based dietary and physical activity advice to change behaviour. Firstly, the prevalence and implications of obesity, T2D, and CVD are provided, and an overview of genetics, diet, and physical activity as risk factors for these conditions is discussed. Personalisation of health advice based on an individual's genotype in addition to phenotypic, clinical, and dietary measures is proposed as an alternative to the current 'one size fits all' approach to public health. These concepts are discussed and the research investigating the efficacy of this approach to diet and physical activity behaviour change is critically reviewed. The use of behaviour change theory, in particular the TPB is suggested as a framework to understand intention of the public to use genotype-based personalised advice. The aim of each study is stated at the end of the literature review. Further focused literature reviews for each study are presented within the subsequent study chapters.

1.1 Non-communicable disease.

The leading cause of mortality worldwide is NCD. In 2019, 74% of all-cause deaths were due to NCDs (World Health Organisation, 2022). Furthermore, NCDs are responsible for 75% of 'premature deaths', classified as deaths of individuals aged between 30 and 69 years (World Health Organisation, 2018). The Global Burden of Disease (GBD) study provides mortality and morbidity data from over 160 countries (GBD, 2019). In the UK, 89% of deaths in 2019 were estimated to be a consequence of NCDs; of deaths linked to NCDs, the leading cause of death was due to cancer (32%), followed by CVD (30%) (GBD, 2019).

It is unsurprising that the prevention of NCDs has been identified as a key focus in the promotion of health globally. One target of the Sustainable Development Goals set by the United Nations in 2015 was to reduce premature mortality due to NCDs by one third by 2030 (UN General Assembly, 2015); the importance of prevention of NCDs has been further highlighted by the COVID-19 pandemic, since NCDs have been identified as a major risk factor for adverse outcomes

in individuals with COVID-19 (Department of Health & Social Care, 2020; Kluge et al., 2020; World Health Organisation, 2022).

NCDs are not only associated with premature mortality, they are also associated with morbidity (Public Health England, 2019b). Specific mortality and morbidity data for England is reported in the Health Profile for England: 2021 (Public Health England, 2021). Diabetes mellitus had the fourth highest morbidity rate after low back pain, depressive disorders, and headache disorders. Furthermore, the morbidity rate for diabetes mellitus has the greatest increase since 1990, increasing by 2.3 times in men and 2.2 times in women (Public Health England, 2021). It is important to recognise that due to the social inequalities of health, mortality and morbidity associated with NCDs are not distributed evenly across the population. Men and women living in the most deprived areas have a life expectancy of ten and eight years lower respectively than those living in the least deprived areas and can expect 19 years fewer of good health compared to those in the least deprived areas (Public Health England, 2021). Consequently, action taken in the prevention of NCDs will also contribute to reducing health inequalities (The Marmot Review, 2010).

NCDs carry not only a cost to the health of a population but also the economy. In 2011 it was estimated that the cost of NCDs globally would amount to $30 trillion over the following 20 years (Bloom et al., 2012). In the UK it was estimated that the cost of obesity to wider society was £27 billion per year (Public Health England, 2017). Recognition of the importance of tackling NCDs in England has been demonstrated by inclusion in the Public Health England strategy for 2020-25 (2019a) and the National Health Service (NHS) Long Term Plan (NHS, 2019).

The four major NCDs (CVD, cancer, T2D, and chronic respiratory disease) are associated with modifiable behaviours including smoking, physical inactivity, unhealthy diet and alcohol abuse. The increased risk of NCDs associated with these behaviours is mediated via metabolic and physiological conditions including raised blood pressure, obesity, high blood glucose and elevated blood lipids (World Health Organisation, 2018). The present literature review will focus specifically on the prevention of obesity, T2D and CVD. These prevalent conditions have a high burden for both the individual and the economy (Timmis et al., 2020) and are strongly linked to

poor dietary and physical activity behaviour. Therefore, the literature review will discuss the prevalence and health implications of each condition and the evidence suggesting that modifications in diet and physical activity behaviour can reduce their development. Genetic variations interact with lifestyle factors including diet and physical activity to affect the risk of an individual developing obesity, T2D and CVD (Kohlmeier et al., 2016). Researchers have suggested that genotype-based dietary advice may motivate individuals to change their dietary and physical activity behaviour more effectively than the current 'one size fits all' approach (Celis-Morales, Lara, et al., 2015). Literature that has investigated this to date will be critically reviewed.

1.2. Cardiovascular disease, type II diabetes and obesity

1.2.1 Cardiovascular disease

The National Institute for Health and Care Excellence (NICE) define CVD as disease of the heart and blood vessels that arises as a consequence of the process of atherosclerosis (NICE, 2014a). The mortality rate from CVD has been declining since the 1960s (Mensah et al., 2017). Despite this, CVD remains the most common cause of death worldwide. In 2019 it was estimated that 17.9 million deaths occurred globally as a consequence of CVD (World Health Organisation, 2021). Data from the UK in 2019 estimates that 188,113 or 30% of all deaths were due to CVD (GBD, 2019). The reduced mortality rate from CVD has occurred as a consequence of improved treatment and reduced prevalence of most major risk factors (systolic blood pressure, blood cholesterol and smoking); the exceptions being obesity and T2D (Mensah et al., 2017). In fact, it has been suggested that as a result of the increasing prevalence of obesity and T2D, the rate of decline in CVD mortality will decelerate (Mensah et al., 2017).

1.2.2 Type II diabetes

T2D is a chronic metabolic condition which occurs due to insulin resistance and insufficient pancreatic insulin production, leading to hyperglycaemia (NICE, 2015). In 2019 it was estimated that there were 463 million people, 9.3% percent of the population, living with diabetes globally, 50% of whom were undiagnosed (Saeedi et al., 2019). This represents an increase of 62% in prevalence of diabetes over 10 years. It is predicted that by 2045 there will be 700 million people

living with diabetes globally (Saeedi et al., 2019). Data obtained from the Quality and Outcomes Framework for 2019-20 show that 7.1% of people aged 17 years or above in the UK have diabetes; this data reflects the percentage of patients on GP practices' lists and therefore does not include undiagnosed cases (Quality and Outcomes Framework for 2019-20, 2020). The global rise in diabetes prevalence is reported to reflect an increase in type I diabetes in children and an increase in T2D in young people and adults (Saeedi et al., 2019). The majority of people with diabetes (90%) have T2D (Chatterjee et al., 2017).

1.2.3 Obesity

Obesity is the excessive accumulation of adipose tissue that results in mild, chronic, systemic inflammation (González-Muniesa et al., 2017). Obesity is most often defined by a disproportionate weight to height ratio using body mass index (BMI), a BMI of 30 kg/m^2 and above is considered obese and a BMI of 25-29.9 kg/m^2 is considered as being overweight (NICE, 2014b). In 2015, 603.7 million adults and 107.7 million children worldwide were estimated to be obese (The GBD 2015 Obesity Collaborators, 2017). Despite widespread acknowledgement of the problem that global trends in BMI indicate, the prevalence continues to increase, and the largest increases were reported in high-income English-speaking countries (NCD Risk Factor Collaboration, 2016). Data from The Health Survey for England (HSE) in 2019 showed that 68% of men and 60% of women were overweight or obese and, of those, 29% of women and 27% of men were obese (Moody, 2020). Prevalence of obesity increases with age; HSE data showed 36% of adults aged 65-74 years were obese compared to 13% of 16–24-year-olds (Moody, 2020).

1.2.4 Associations between obesity, T2D and CVD

The conditions of obesity, T2D and CVD are interlinked. The major concern regarding the increasing prevalence of obesity is the associated risks of poor health. Health risks associated with a high BMI were estimated to contribute to 4 million deaths and 120 million disability adjusted life years (DALYS). The leading cause of death and DALYS associated with a high BMI was CVD (2.7 million deaths, 66.3 million DALYS) and the second cause was T2D (0.6 million deaths, 30.4 million DALYS) (The GBD 2015 Obesity Collaborators, 2017). Research suggests that in 55–64-year-olds the relative risk (RR) for a 5 kg/m^2 higher BMI was 2.32 for T2D and 1.44 for

ischaemic heart disease (IHD). Furthermore, for a 1 mmol/L higher fasting plasma glucose (FPG) the RR was 1.81 for IHD and 1.14 for stroke (Singh et al., 2013). In the HSE a significant increase in diabetes prevalence was associated with BMI category; the prevalence in obese participants was 15%, compared to 9% in overweight and 5% in normal weight participants (Moody, 2020). Diabetes is associated with an increased risk of all-cause mortality and mortality associated with CVD (Tancredi et al., 2015). The Emerging Risk Factors Collaboration estimate that compared to people without diabetes, people with diabetes have a hazard ratio (HR) of 2.00 (95% confidence interval (CI) 1.83-2.19) for coronary heart disease (CHD), 2.27 (95% CI 1.95-2.65) for ischaemic stroke, and 1.73 (95% CI 1.51-1.98) for other vascular death (Emerging Risk Factors Collaboration et al., 2010). Risks for women (Emerging Risk Factors Collaboration et al., 2010), younger persons (<55 years), and in those with poorer glycaemic control are substantially higher (Tancredi et al., 2015). In summary, the prevalence of obesity and T2D continue to rise (Moody, 2020; Saeedi et al., 2019), and as a consequence the recent reduced prevalence of CVD has slowed (Mensah et al., 2017). CVD and T2D are associated with increased risk of mortality (GBD, 2019; Tancredi et al., 2015) and all three conditions are associated with increased risk of morbidity (The GBD 2015 Obesity Collaborators, 2017). Both obesity and T2D increase the risk of CVD and obesity is also associated with increased risk of T2D (Singh et al., 2013). The next section will discuss the role of genetics and lifestyle factors in the risk of developing obesity, T2D and CVD.

1.3. Risk factors for obesity, T2D and CVD

Much research has been carried out to determine the cause of the obesity epidemic and consequent rise in the prevalence of T2D. Environmental factors such as reduced physical activity and increased availability of energy dense highly palatable foods have played a substantial role (Swinburn et al., 2011), but research has also considered the role of genetics.

1.3.1 The role of genetics in obesity, T2D, and CVD.

The sharp rise in obesity since the 1990s suggests it is a result of environmental changes that have occurred during this time, such as reduced physical activity and increased availability of highly palatable energy dense foods (Speakman, 2007). However, twin studies of overfeeding

have suggested that weight gain is highly heritable (Bouchard et al., 1990). Although the prevalence of obesity has increased, the majority of the population have not become obese, suggesting that there is an interaction between genetics and the environment which influences the risk of obesity. It has been suggested that genetic variation has occurred due to random mutations or 'genetic drift' (Speakman, 2004), which has increased the likelihood of certain individuals developing obesity as a consequence of their genetics (Speakman, 2018; van der Klaauw & Farooqi, 2015). The increased prevalence of obesity has been identified as the primary driver of the corresponding increase in T2D (Smith, 2007). However, the likelihood of an individual developing T2D when exposed to a 'diabetogenic' environment (high energy diet with low physical activity) has also been related to genetics (Rathmann et al., 2013). Similarly, risk factors for CVD which include obesity and T2D along with dyslipidaemia, hypertension and smoking are under significant genetic control (Vrablik et al., 2021).

The heritability of a phenotypic trait such as CVD, T2D or obesity represents the amount of variation in that phenotypic trait that can be explained by genetic variation. Twin studies are used to make comparisons between monozygotic (MZ) twins and dizygotic (DZ) twins. Since MZ twins share all their genes and DZ approximately half, if genetics has a strong influence on the phenotypic trait of interest it should be more similar in MZ twins than DZ twins (De Caterina et al., 2020). The correlation of the phenotype between MZ twins is compared to the correlation of the phenotype between DZ twins, assuming that any difference between MZ and DZ twins is due to genetic differences, using Falconer's formula an estimate of heritability is calculated (Mayhew & Meyre, 2017). Twin studies suggest that CVD, T2D and obesity are highly heritable; the heritability of CHD mortality reported to be 57% in male and 38% in female twins (Zdravkovic et al., 2002), T2D to be 72% (Willemsen et al., 2015) and BMI to be 84% (Silventoinen et al., 2008). Alternative study designs used to estimate heritability of traits include adoption studies, family-based and population studies. Heritability estimates are usually higher in twin studies; for example, twin studies estimate the heritability of BMI to be 60-84% compared to 40-45% in family-based studies and 20-40% in population studies (Loos, 2018; Silventoinen et al., 2008). Assumptions are made in twin studies that may result in an overestimate of heritability. In twin studies gene-environment correlations and interactions are assumed to be minimal and shared

environmental factors of MZ and DZ twins are assumed to be identical, these assumptions may result in the attribution of environmental factors to genetics incorrectly (Mayhew & Meyre, 2017). Variability in heritability estimates between studies of the same phenotype may be explained by the age range of the cohort included. Heritability estimates for BMI have been demonstrated to reduce with age; from 77% and 75% in men and women aged 20-29 years to 57% in men aged 70-79 years and 59% in women aged ≥ 80 years (Silventoinen et al., 2017).

Heritability studies enable the estimation of the role of genetics in the development of CVD, T2D and obesity; however, these types of studies are not able not identify the genetic variation or mechanisms responsible for the heritability of the trait (Wardle et al., 2008). A greater understanding of how genetic variation contributes to the development of a disease may facilitate diagnosis, treatment and prevention (Manolio et al., 2009). There are different types of genetic variation that mediate the genetic effects on phenotypic traits; common examples include single nucleotide polymorphisms (SNPs), small insertions/deletions, and copy number variation. SNPs are the most common form of genetic variation. A SNP can be defined as a single base change in the DNA sequence that occurs in greater than one percent of a large population (De Caterina et al., 2020). SNPs can occur at any location in the DNA sequence; if the SNP occurs in a coding region it can be defined as either a synonymous or non-synonymous SNP. A synonymous SNP does not affect the protein product expressed by that gene because the base change does not change the amino acid coded for. A non-synonymous SNP results in a change in the amino acid coded; this may result in a different amino acid (missense SNP) or a stop codon (nonsense SNP), both of which affect the protein expressed by the gene and often the function of that protein. If the SNP occurs in the promoter region of a gene it may up regulate or down regulate gene expression (De Caterina et al., 2020).

The frequency of variants in the population can be described as common (observed in greater than 5% of the population), intermediate (observed in 1-5% of the population), or rare (observed in less than 1% of the population) (De Caterina et al., 2020). The effect size of variants also varies and in general is larger in rare variants (van der Klaauw & Farooqi, 2015). Mendelian disorders which result in phenotypes such as severe obesity or hypercholesterolaemia are rare and a consequence of monogenic mutations; these genetic disorders are inherited in an autosomal

dominant, recessive or X-linked manner and have large effects sizes (odds ratio (OR) > 5) (Bell et al., 2005; De Caterina et al., 2020; Kullo & Ding, 2007). As mentioned above, the frequency of these monogenic conditions is rare, although a mutation in the *MC4R* gene, involved in appetite signalling, has been reported to explain up to 6% of severe childhood obesity but only 0.5% of severe obesity in adults (Farooqi, 2008). Consequently, monogenic conditions cannot explain the relatively recent increase in common obesity; however, the research can be useful in understanding potential mechanisms of gene variants and it has been used in the development of treatments, such as statins (Kullo & Ding, 2007).

The common forms of obesity, T2D and CVD are termed polygenic traits; which means that the risk of developing these conditions is conferred by multiple, probably hundreds, of genetic variations each with a small to moderate effect size (OR < 2) (De Caterina et al., 2020). Much research has been carried out to try to identify these genetic variants. Association studies are utilised to determine the co-occurrence of genetic markers with phenotypic traits in unrelated participants (De Caterina et al., 2020). The two predominant approaches include candidate-gene studies and genome-wide association studies (GWAS). Candidate-gene studies evaluate the contribution of genes, selected by researchers, based on their functional or positional link to known pathways; comparisons are made to identify if variants are more common in cases or controls (Bell et al., 2005). Therefore candidate-gene studies can be described as hypothesis driven; conversely, the GWAS approach is described as hypothesis free (De Caterina et al., 2020).

GWAS identify differences across the genome between participants or cases that exhibit a phenotype of interest (obesity, T2D, hypertension) with a control group. This type of study design has been made possible following the completion of the Human Genome Project in 2003 (Lander et al., 2001) and the HapMap project in 2005 (International HapMap Consortium, 2005), which has provided a near complete catalogue of human genes. In addition to advances that have been made in large-scale genotyping and technologies (Arking & Chakravarti, 2009). GWAS identify common variants, those with a minor allele frequency (MAF) greater than 5%, with modest effect sizes (OR < 2, often 1.1-1.5 per allele) which explain a modest proportion of variability in the phenotype of interest (De Caterina et al., 2020; van der Klaauw & Farooqi, 2015). Very large GWAS have been carried out to identify common genetic variants that confer an increased risk

of developing obesity, T2D and CVD (Arking & Chakravarti, 2009; Hebebrand et al., 2010). A selection of some of the most researched genes with SNPs identified through GWAS and meta-analyses of case-control studies that have been associated with an increased risk of obesity, T2D and CVD are presented in Table 1.1.

Table 1.1. Selected examples of genes with SNPs associated with increased risk of obesity, T2D and CVD from GWAS and meta-analyses of case-control studies.

Gene	Condition	Reference
ANRIL	Heart disease	(Palomaki et al., 2010)
FTO	Obesity	(MAGIC et al., 2010)
TCF7L2	T2D	(Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research et al., 2007)
APOE	Plasma cholesterol	(Xu et al., 2016)
MTHFR	Heart disease	(Wald et al., 2011)

T2D: type II diabetes; CVD: cardiovascular disease; GWAS: genome-wide association studies; *ANRIL*: antisense noncoding RNA in the INK4 locus; *FTO*: fat mass and obesity associated; *TCF7L2*: transcription factor 7 like 2; *APOE*: apolipoprotein E; *MTHFR*: methylenetetrahydrofolate reductase.

The choice of phenotype will influence genes identified in GWAS for example, hypertension or dyslipidaemia (Arking & Chakravarti, 2009). A non-specific quantitative phenotype such as BMI, which reflects both fat and lean body mass may have many different genetic factors (Hebebrand et al., 2010). In a meta-analysis of 46 studies, the GIANT consortium identified 32 SNPs associated with BMI. However, the effect size of each allele on BMI was small (0.06-0.39 kg/m^2) and the 32 SNPs only explained 1.45% of BMI variance (Hebebrand et al., 2010). The number and size of GWAS has increased and as a consequence researchers are able to carry out meta-analyses of GWAS, which has enabled the identification of rare variants with an increased effect size on BMI (Turcot et al., 2018). However, a considerable gap remains between the proportion of variance

in phenotype explained by GWAS and even the most conservative estimates of heritability (Mayhew & Meyre, 2017).

The gap between the percentage of phenotypic variance explained by common SNPs compared to the high heritability estimates from twin and family studies has been termed 'missing heritability' (De Caterina et al., 2020). There are a number of explanations for missing heritability. Firstly, the difference between heritability estimates is due to the method of estimation (Mayhew & Meyre, 2017). Genetic effects can be additive, which refers to the sum of the effect of each allele at all loci which influence the phenotype, or non-additive, which refers to the interaction between alleles at the same locus (dominance) or at different loci (epistasis). Twin studies capture all genetic effects (additive and non-additive) whereas GWAS only includes additive genetic effects. Furthermore, GWAS includes only SNPs that have been identified using a very stringent alpha level ($p < 5 \times 10^{-8}$) and excludes other types of genetic variation such as rare mutations and copy number variations (Mayhew & Meyre, 2017). One explanation for missing heritability is that there may be a large number of variants with small effect size or rarer variants with a larger effect size yet to be identified (Manolio et al., 2009). Furthermore, SNPs that are identified through GWAS may not be true risk alleles, they may be in linkage disequilibrium (LD) with a risk allele (Mayhew & Meyre, 2017). LD describes the co-inheritance of alleles within a population, as a haplotype at two or more loci, that is greater than would be expected by chance (De Caterina et al., 2020). Common SNPs that are in LD with a rare risk variant may lead to detection of a false association (Mayhew & Meyre, 2017). Epigenetics have also been identified as a potential source of missing heritability (Mayhew & Meyre, 2017). Epigenetics refers to chemical modifications that affect gene expression without affecting underlying DNA structure, which can be passed on to subsequent generations or spontaneously reversed (De Caterina et al., 2020; Mayhew & Meyre, 2017). Limited understanding of epigenetics means it is difficult to determine the contribution it could make to missing heritability (Mayhew & Meyre, 2017). Finally this 'missing heritability' may be explained by gene-gene or gene-environment interaction which GWAS studies currently have not investigated (De Caterina et al., 2020; Hebebrand et al., 2010; Manolio et al., 2009). An individual's risk of developing obesity, T2D and CVD is a product of both their genes (which are non-modifiable) as well as their environment (which is modifiable).

Consequently, there is global focus on the prevention of these conditions via the modification of risk factors including diet and physical activity.

1.3.2 Diet and physical activity as modifiable risk factors

Epidemiological data from large case-control and cohort studies have enabled the identification of risk factors for CVD and T2D. The INTERHEART study published in 2004 was a large case-control study of 52 countries, carried out to identify risk factors for myocardial infarction. They identified nine modifiable risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, low consumption of fruits and vegetables, high consumption of alcohol, and low regular physical activity) that explained 90% of the population attributable risk in men and 94% in women (Yusuf et al., 2004). Moreover, diet and physical activity are strongly linked to seven of these nine risk factors. To determine risk factors for the development of T2D Hu et al. (2001) analysed prospective data from the Nurses' Health Study and they found that being overweight or obese was the single most important predictor of T2D. Lack of exercise, poor diet, smoking and abstinence from alcohol were all significantly associated with the risk of developing T2D and this remained significant when controlling for BMI. Further analysis of data from the Nurses' Health Study and the Health Professionals Follow-up Study revealed the importance of preventing weight gain in early adulthood (Zheng et al., 2017). In their analysis weight gain from early to middle adulthood was associated with an increased incidence of T2D, hypertension, CVD and obesity related cancer. The findings of these studies clearly demonstrate the importance of maintaining a healthy diet and being physically active for the prevention of obesity, T2D and CVD.

Despite widespread acknowledgement of obesity as a public health concern, no country has yet managed to significantly decrease the prevalence (Kleinert & Horton, 2015; Roberto et al., 2015). In a recent policy paper, the Department of Health and Social Care (2020) in the UK have set out an updated strategy to prevent weight gain and support weight reduction in adults and children. They aim to encourage individual behaviour change via evidence-based tools and apps through the Public Health England 'Better Health' campaign in addition to the expansion of weight management and diabetes prevention programmes as set out in the NHS Long Term Plan. To

support better food choices, they also aim to change the environment through greater provision of food labelling for meals and alcohol consumed out of the home, and to restrict the promotion of high fat, salt and sugar foods in value-promotions and their advertisement on television before 9 pm.

Clinical trials have clearly demonstrated the benefits of intensive lifestyle interventions on reducing the risk of individuals with impaired glucose tolerance (IGT) developing T2D (Knowler et al., 2002; Tuomilehto et al., 2001). In the US Diabetes Prevention Program, a lifestyle intervention which included a greater than 7% weight loss, dietary advice and increased physical activity led to a 58% reduction in T2D incidence compared to a placebo group; pharmacological treatment also reduced T2D incidence by 31% (Knowler et al., 2002). Similarly, The Finish Diabetes Prevention Study reported that their lifestyle intervention group (counselling to reduce weight, decrease intake of total and saturated fat, increase intake of fibre and increase physical activity) had a 58% reduction in relative risk (RR) of developing T2D compared to a control group (Tuomilehto et al., 2001). Follow-up studies from both cohorts suggest that the reduction in T2D incidence following an intensive lifestyle intervention is maintained for up to 15 years (Diabetes Prevention Program Research Group, 2015; Lindström et al., 2006). The main determinant responsible for reduced T2D incidence is weight loss as a consequence of improved diet and increased physical activity (Hamman et al., 2006). However, the translation of these intensive lifestyle interventions from clinical trials into practice has been reported to result in smaller weight reductions and consequently a smaller, but still clinically significant, reduction in T2D incidence (Dunkley et al., 2014). The NHS Diabetes Prevention Programme was rolled out in England in 2016; the programme aims to prevent or slow the onset of T2D in 'at risk' individuals. A service evaluation of the programme reported a significant reduction in both body weight (- 2.3 kg) and $HBA1_C$ (2.04 mmol/mol). However, only 19% of referred people completed the programme (Valabhji et al., 2020). The most important risk factors for the development of T2D are an unhealthy diet and inactive lifestyle, which also increase the risk of developing overweight and obesity (Dunkley et al., 2014; Saeedi et al., 2019). Intervention studies have demonstrated that a modest change in dietary intake and physical activity can reduce the risk of T2D by greater than 50% in participants with IGT (Dunkley et al., 2014). In 2019 it was estimated that 373.9

million people had IGT globally (Saeedi et al., 2019); therefore, reducing their risk of developing T2D and its associated risks represents a substantial health benefit. However, interventions used in clinical trials are both intensive and expensive to translate into practice (Dunkley et al., 2014).

As outlined above, the health burden for obesity, T2D, and CVD in terms of morbidity and mortality is significant. The conditions of obesity, T2D, and CVD are inextricably linked; obesity increases the risk of developing T2D and both obesity and T2D increase the risk of CVD (de Gonzalez et al., 2010; Singh et al., 2013). It has been estimated that positive changes in behaviour could considerably reduce the prevalence of NCDs (Ezzati et al., 2003). Studies have demonstrated a significant reduction in the risk of T2D through weight reduction as a result of positive changes in dietary and physical activity (Knowler et al., 2002; Tuomilehto et al., 2001). However, what has also been identified is that without intensive support, changes in dietary and physical activity behaviours are difficult to achieve and, importantly, maintain (Dunkley et al., 2014).

1.3.3 Diet and physical activity recommendations

Dietary recommendations for energy and nutrients in the UK are made by the Scientific Advisory Committee on Nutrition (SACN) and previously by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) (Department of Health, 1991; SACN, 2011, 2015, 2019). Current dietary advice to reduce the risk of obesity, T2D, and CVD includes the increased consumption of fruits and vegetables, increased intake of fibre and oily fish, and reduced intake of saturated fat, salt, sugar, and alcohol (British Heart Foundation, 2017; Department of Health, 2016; Public Health England, 2016; SACN, 2003, 2015, 2019). Recommendations for physical activity in the UK are from the Chief Medical Officers (Department of Health & Social Care, 2019). Recommendations are for adults to accumulate, each week, at least 150 minutes of moderate-intensity activity (such as brisk walking or cycling); or 75 minutes of vigorous-intensity activity (such as running); or even shorter durations of very-vigorous-intensity activity (such as sprinting or stair climbing); or a combination of each. Muscle strengthening activities should also be carried out at least two days a week. For weight loss, more than 150 minutes of physical activity along with dietary restriction may be required. Findings from the National Diet and Nutrition Survey

(NDNS) of the UK population and HSE suggest that current dietary and physical activity advice is not being met by a significant proportion of the population (Health Survey for England, 2017; Roberts et al., 2018). UK dietary and physical activity recommendations to reduce the risk of obesity, T2D, and CVD, along with the level of adherence to those recommendations in adults aged 19-64 years are presented in Table 1.2.

Table 1.2 UK diet and physical activity recommendations to reduce the risk of obesity, T2D, and CVD, along with the level of adherence to those recommendations in adults aged 19-64 years.

Recommendation	Mean	Percentage meeting
Increase fruit and vegetables (≥ 5 portions /d)[1]	4.3[8]	33%[8]
Increase fibre (30 g/d)[2]	19.7 g[8]	9%[8]
Increase oily fish (1 portion/week; 140 g)[3]	56 g[8]	26%[10]
Reduce saturated fat (≤ 10% total energy)[4]	12.3%[8]	17%[8]
Reduce salt (≤ 6 g/d)[5]	8.4 g[9]	31%[9]
Reduce sugar (≤ 5% total energy)[2]	9.9%[8]	17%[8]
Reduce alcohol (≤ 14 units/week)[6]	_	60%[11]
Increase physical activity (150 mins of moderate-intensity/week)[7]	_	62%[11]

T2D: type II diabetes; CVD: cardiovascular disease; [1](Public Health England, 2016); [2](SACN, 2015); [3](COMA, 1994); [4](SACN, 2019); [5](SACN, 2003); [6](Department of Health, 2016); [7](Department of Health and Social Care, 2019); [8](Bates et al., 2020); [9](Ashford et al., 2020); [10](Derbyshire, 2019); [11](Health Survey for England, 2017).

In an attempt to tackle the discrepancy between dietary recommendations and reported intakes, nutritional education programmes aim to improve nutritional knowledge in populations to promote healthy dietary behaviour (Spronk et al., 2014). Change4Life, a national childhood obesity prevention campaign was launched in the UK in 2009. The campaign encouraged parents of children to complete a questionnaire after which they were provided with personalised feedback about their child's diet and activity and provided print and online guidance resources. An evaluation of the Change4Life intervention, suggested that the mass media campaign was successful in raising public awareness but failed to impact attitudes or translate into modification

of behaviour (Croker et al., 2012). Indeed, research suggests that nutritional knowledge is necessary, but not sufficient to induce behaviour change (Worsley, 2002). The relationship between nutritional knowledge and dietary intake was investigated in a systematic review by Spronk et al. (2014). Although most studies reported a positive relationship between nutritional knowledge and dietary behaviour, that relationship is weak ($r < 0.5$). Knowledge of dietary guidelines does not necessarily equate to understanding (Boylan et al., 2012); furthermore, procedural knowledge (how to reduce saturated fat in your diet) is as important as declarative knowledge (saturated fat can cause high cholesterol) to enable modification of behaviour (Boylan et al., 2012; Worsley, 2002).

Meta-analyses have reported that interventions designed to improve dietary and physical activity behaviour were effective for increasing physical activity (Whatnall et al., 2021), intakes of fruit and vegetables (Ashton et al., 2019; Rees et al., 2013; Whatnall et al., 2018) and fibre (Rees et al., 2013), and reducing intakes of fat (Rees et al., 2013; Whatnall et al., 2018) and saturated fat (Rees et al., 2013). These findings were reported in meta-analyses that included studies designed to reduce CVD risk in healthy adults (Rees et al., 2013), studies including healthy young adults (Ashton et al., 2019; Whatnall et al., 2021) and studies that included a brief nutrition intervention (Whatnall et al., 2018). Interventions that provided personalised instructions, feedback, and education were more likely to be effective than those that only included education with non-personalised advice (Whatnall et al., 2018). The findings of Whatnall et al. (2018) support those of an earlier systematic review of consumer responses to dietary and physical activity guidelines for weight management, which highlighted the importance of tailoring of guidelines where possible (Boylan et al., 2012). One way in which guidelines can be tailored is by personalising advice based on one's genotype.

1.4. Genotype-based personalised advice

1.4.1 Genotype-based personalised advice

The aim of personalised health advice is to provide an individual with more precise and effective dietary or physical activity advice, and to motivate behaviour change (Grimaldi et al., 2017). In contrast to the current dietary and physical activity recommendations outlined in section 1.3.3

that use a 'one size fits all' approach (Department of Health & Social Care, 2019; Department of Health, 1991; SACN, 2011, 2015, 2019). Personal salience of health advice is more difficult to achieve with a 'one size fits all' approach and increasing the personal salience of advice has been identified as a key concept in the successful delivery of behaviour change interventions (NICE, 2007). Advice is personalised by knowledge of genetic information in addition to phenotypic, clinical, dietary, physical activity and any other relevant information (Grimaldi et al., 2017). The use of technology, such as genotyping, to provide targeted personalisation of health advice was identified as a key public health priority by Public Health England in their strategy for 2020-25 (Public Health England, 2019a). SNPs have been utilised by researchers and commercial genotyping companies to provide individuals with information about their genetic risk for developing a disease (Horne, Gilliland, Madill, et al., 2020). The most useful SNPs in the provision of personalised advice are those which interact with modifiable risk factors for disease such as diet and physical activity (Kohlmeier et al., 2016). Consequently, when individuals are informed of their genetic risk, they can also be provided with advice to modify lifestyle behaviours in order to mitigate that risk.

Grimaldi et al. (2017) established a framework to enable scientists to determine which SNPs have sufficient evidence to support their use in the provision of valid genotype-based dietary advice. Firstly, the framework is used to assess the design and quality of studies that provide evidence of genetic interactions by determining if those studies have adhered to the Strengthening the Reporting of Genetic Association Studies (STREGA) guidelines (Little et al., 2009) also to determine if dietary intake data in the studies was measured quantitatively. Secondly, the framework is used to assess biological plausibility; this is defined as 'a particular physiological response to a dietary component which occurs only – or is more pronounced - in persons with a specific version of a gene (or genes).' The framework considers the gene-diet interaction as direct, indirect or complex as well as the nature of the genetic variant. In the present programme of research SNPs in the fat mass and obesity associated (*FTO*), apolipoprotein E (*APOE*) and methylenetetrahydrofolate reductase (*MTHFR*) genes were used to provide gene-based personal advice. These genes were selected because they have been used in previous research that has investigated the effect of genotype-based advice on behaviour (Celis-Morales, Livingstone, et al.,

2015; Chao et al., 2008; Meisel, Walker, et al., 2012), are often present in commercial genotyping (Floris et al., 2020), and have been widely researched (Dolgin, 2017), therefore there is robust research from which dietary and physical activity recommendations can be made. The following section will apply the framework proposed by Grimaldi et al. (2017) to provide a rationale for the inclusion of personalised advice based on *FTO, APOE* and *MTHFR* genotype.

1.4.2 Fat Mass and Obesity Associated gene.

A SNP in the first intron of the *FTO* gene was the first common variant identified that could affect the risk of obesity in the general population (Yeo, 2014). The *FTO* rs9939609 SNP was identified in a GWAS analysis for T2D; researchers found that the association between the SNP and T2D was no longer apparent when BMI was controlled for and, therefore, the effect of this SNP on T2D was driven by its effect on BMI (Frayling et al., 2007). Frayling et al. (2007) reported that participants homozygous for the rs9939609 risk allele (AA) weighed 3 kg more and had a 1.7-fold increased risk of obesity compared to those homozygous for the wild type (TT). The rs9939609 SNP has a MAF of 0.39, ranging from 0.12 in East Asian to 0.47 in African populations (*Rs9939609 RefSNP Report - dbSNP - NCBI*, n.d.). The *FTO* gene is highly polymorphic and subsequent GWAS have identified a cluster of highly correlated SNPs (r^2 = 0.52 - 1.0) in the first intron (Speakman, 2015). As GWAS have increased in size, a greater number of SNPs associated with obesity have been identified; however, *FTO* is consistently identified as explaining the largest proportion of inter-individual variation in BMI (MAGIC et al., 2010; Yeo, 2014). Carriers of the risk allele of *FTO* reported a significantly higher energy intake compared to participants homozygous for the non-risk allele; however, no significant differences were identified between genotype groups for measures of basal metabolic rate or VO_2 max (Speakman et al., 2008). Children with the *FTO* risk allele have been reported to have a significantly higher food intake than those with the non-risk allele (Wardle et al., 2008). Therefore, it is assumed that *FTO* exerts its effect on BMI via the energy intake rather than energy expenditure side of the energy balance equation. Macronutrient consumption has also been compared between genotype groups and some studies suggest a higher intake of protein and fat and a lower intake of fibre in those with the risk allele (Speakman et al., 2008). *FTO* is most highly expressed in the brain including the arcuate nucleus of the hypothalamus, which is the area of the brain responsible for energy homeostasis

(De Caterina et al., 2020). FTO protein levels in rodents have been demonstrated to decrease following a 24-48 hour fast and increase following 8-10 weeks of a high fat diet (De Caterina et al., 2020). The FTO protein is a nucleic acid demethylase and therefore has a potential role in nucleic acid repair and modification (Yeo, 2014). FTO has also been suggested to act as an amino acid sensor linked to the mammalian target of rapamycin complex 1 (Speakman, 2015). The cluster of SNPs in the first intron of *FTO* have also been suggested to exert their effect on BMI via other nearby genes such as *RPGRIP1L* and *IRX3* (De Caterina et al., 2020; Speakman, 2015; Yeo, 2014). Despite a large amount of research, the mechanism by which *FTO* affects BMI is still not clear (Loos, 2018; Yeo, 2014).

As discussed in section 1.3, compared to the heritability estimates of BMI from twin studies, the proportion of variance explained by SNPs identified through GWAS is small. One explanation for this 'missing heritability' is gene-environment interactions (Hebebrand et al., 2010). Studies have investigated the interaction of *FTO* genotype with several components of diet and physical activity on outcomes related to obesity (Graff et al., 2017; Kilpeläinen et al., 2011; Livingstone et al., 2015; Qi et al., 2014; Zhang et al., 2012). To facilitate changes in dietary behaviour it is recommended that individuals focus on few goals at a time, for the present programme of research one dietary goal was identified for each gene (Rosal et al., 2001). Although research has suggested that individuals with an *FTO* risk genotype would benefit from consumption of a high-protein diet for weight loss (Zhang et al., 2012), reduction of saturated fat was chosen as the dietary goal related to *FTO*. A reduction of saturated fat is one of the UK dietary recommendations to reduce the risk of obesity, T2D, and CVD, currently only 17% of the population are meeting this recommendation (Bates et al., 2020; SACN, 2019). Therefore, the present review will focus specifically on studies that have investigated the interaction between *FTO* genotype and saturated fat intake or physical activity on obesity.

Previous research had suggested an interaction between *FTO* rs9939609 genotype and dietary fat intake on BMI (Sonestedt et al., 2009). A cross-sectional case-control study by Sonesedt et al. (2009) on 4839 participants from the Malmo¨ Diet and Cancer study reported that within

participants with a high intake of fat, BMI was significantly higher in homozygous risk carriers of *FTO* rs9939609 compared to homozygous non-risk carriers. In participants reporting a low intake of fat there was no effect of genotype on BMI. Subsequent research has suggested that the interaction is driven by saturated rather than total fat intake (Corella, Arnett, et al., 2011). Corella et al. (2011) investigated the interaction of fat and carbohydrate intake with *FTO* genotype using a cross-sectional case-control design of 2163 participants from two studies - The GOLDN study, assessed *FTO* genetic variation at the rs9939609 SNP in 1069 participants, and the BPRHS study assessed *FTO* genetic variation at the rs1121980 SNP in 1094 participants. These two SNPs (rs9939609 and rs1121980) have been reported to be in high LD (Corella, Arnett, et al., 2011). In both studies a significant genotype-diet interaction was observed with saturated fat intake on BMI; furthermore, this interaction was stronger than that observed for total fat. In participants with a saturated fat intake above the mean (>27.6 g/d in GOLDN and >22.7 g/d in BPRHS), those that were homozygous for the *FTO* risk allele had a significantly higher BMI than heterozygous or homozygous non-risk participants. No interaction between saturated fat intake and genotype on BMI was observed in participants with a saturated fat intake below the mean. The LIPGENE-SU.VI.MAX study used a prospective case-control study design including 1754 participants to investigate the effect of *FTO* rs9939609 genotype on obesity indices and whether the effect was modulated by dietary fat intake. Phillips et al. (2012) reported that individuals with a high saturated fat intake (> 15.5% of total energy intake (TEI)) that have an rs9939609 risk genotype (A allele carriers) had a significantly higher BMI and waist circumference (WC) compared to those with a high saturated fat intake but a non-risk genotype. There was no significant difference in BMI or WC between the risk group and non-risk group when saturated fat intake was below 15.5% of TEI. Although subsequent studies have not reported an interaction between *FTO* rs9939609 genotype and saturated fat intake specifically with BMI, they have reported an interaction with intakes that are high in food containing fat, sugar and sweet snacks as well as fried foods (Livingstone et al., 2015; Qi et al., 2014).

As mentioned above, the *FTO* genotype does not appear to affect energy expenditure (Speakman et al., 2008); however, studies have suggested that being physically active may attenuate the

effect of *FTO* on BMI (Graff et al., 2017; Kilpeläinen et al., 2011). Although, an interaction between *FTO* genotype and physical activity level on BMI has not been identified in all studies (Jonsson et al., 2009). To determine the true effect of physical activity level and *FTO* genotype on BMI a large meta-analysis including 45 studies of adults (n = 218,166) and nine studies of children and adolescents (n = 19,268) was carried out by Kilpeläinen et al. (2011). They reported a significant attenuation of the effect of the rs9939609 risk allele on BMI in participants that were physically active (-0.14 kg/m^2). Physically active participants had a 30% lower effect of the risk allele on their BMI compared to inactive participants, although there was no interaction observed in studies of children and adolescents. Furthermore, when the analysis was carried out by geographical region, a stronger interaction between physical inactivity and *FTO* was observed in North American studies compared to studies carried out in Europe. Since the participants in the majority of the North American studies were likely to have European ancestry, it is unlikely that this difference was due to genetics. Physical activity levels were standardised in the meta-analysis by dichotomising them into active or inactive, since physical activity levels are lower in North America than in Europe (Hagströmer et al., 2010), the participants identified as inactive in North American studies may be less active than those identified as inactive in European studies (Kilpeläinen et al., 2011). A subsequent meta-analysis by Graff et al. (2017) was carried out to identify adiposity related loci that are modified by physical activity. *FTO* was the only loci identified that interacted with physical activity on BMI. Their findings replicated those of Kilpeläinen et al. (2011) also reporting an approximately 30% reduction in the effect of *FTO* risk allele on BMI in physically active compared to inactive participants (Graff et al., 2017).

In summary, there is strong evidence from large well-conducted trials and meta-analyses that *FTO* rs9939609 interacts with both saturated fat intake and physical activity to affect BMI. In terms of the design and quality of the studies, for the evidence related to saturated fat, both studies used a case-control design, adhered broadly to the STREGA guidelines, and provided quantification of dietary intake (Corella, Arnett, et al., 2011; Little et al., 2009; Phillips et al., 2012). The evidence for an effect of physical activity is from two well conducted meta-analysis, both of which utilised quality control criteria for inclusion of study data (Graff et al., 2017;

Kilpeläinen et al., 2011). Therefore, the quality of evidence for the interactions between *FTO* and both saturated fat intake and physical activity is strong. However, in terms of biological plausibility, the mechanism by which the *FTO* gene affects BMI is not clear. Therefore, this would be classed as an indirect interaction where the effect is unknown. As such, when assessed against the Grimaldi criteria there is probable evidence that *FTO* SNP rs9939609 interacts with saturated fat intake and physical activity level to affect BMI.

1.4.3 Apolipoprotein E

The *APOE* gene is one of the top five most researched genes in the human genome (Dolgin, 2017) and encodes for the APOE protein; which is involved in the regulation of plasma lipid concentrations. APOE circulates in the plasma and is associated with chylomicrons, very-low-density lipoproteins (VLDL) and high-density lipoproteins (HDL). Chylomicrons and VLDL are lipolysed by lipoprotein lipase to form remnant particles (Phillips, 2014). The APOE associated with remnant particles binds to the low-density lipoprotein receptor (LDLR), LDLR-related protein and heparin sulfate proteoglycans (HSPG) on hepatocytes and is subsequently endocytosed and removed from circulation. Excess APOE and other surface components are released into the HDL pool (Phillips, 2014). APOE is expressed mostly in the hepatocytes where it promotes VLDL assembly and secretion: consequently, optimal gene expression is required for normal metabolism of triglyceride-lipoproteins. A small amount of APOE also originates in macrophages, promoting cholesterol efflux from the arterial wall and thereby reducing atherogenesis (Phillips, 2014). There are two common missense SNPs resulting in three APOE isoforms (E2, E3 and E4) and six haplotypes (Fallaize et al., 2016). E3 is the wildtype isoform and has an allele frequency of 0.78. The E4 isoform has an allele frequency of 0.14 and occurs due to an interchange at position 112 of cysteine for arginine, resulting in structural differences that affect the binding ability of APOE (Phillips, 2014). APOE4 has preferential binding to VLDL and reduced binding ability to HDL, resulting in reduced lipolysis of VLDL and reduced HDL formation (Phillips, 2014). It has also been suggested that APOE4 may cause VLDL to compete with low-density lipoprotein (LDL) for hepatic uptake by the LDLR resulting in more LDL remaining in circulation (Griffin et al., 2018). Indeed, studies of LDLR binding have demonstrated that following a high saturated fat

meal, postprandial triglyceride (TAG)-rich lipoproteins of E4 carriers reduce LDL cholesterol uptake by LDL receptors (Calabuig-Navarro et al., 2017). E2 is the least common APOE isoform (allele frequency of 0.07) and occurs due to an arginine to cysteine interchange at position 158 and results in a reduced ability of APOE2 to bind to LDLR (Phillips, 2014). However, due to HSPG binding, remnant clearance is not usually impaired and therefore lipid levels are normal (Koopal et al., 2016). A positive dose response has been reported between *APOE* genotype and LDL cholesterol, with the lowest concentrations in E2/E2 carriers and the highest concentrations in E4/E4 carriers (Bennet et al., 2007; Khan et al., 2013). In a meta-analysis of 121 coronary outcome case-control studies (37850 cases and 82727 controls), Bennet at al. (2007) reported that compared to E3/E3, E2 carriers have a 20% lower risk of CHD, whilst E4 carriers have a 6% higher risk of CHD. Nevertheless, in a subsequent meta-analysis of 41 ischaemic stroke case-control studies (9027 cases and 61730 controls), Khan et al. (2013) did not find a significant increase in ischaemic stroke for E3/E4 (OR 1.05; 95% credible intervals (CrI): 0.99–1.12) or E4/E4 1.12 (95% CrI: 0.94–1.33) genotypes compared to E3/E3. The authors reported a significant linear relationship between APOE genotype (E2<E3<E4) and LDL cholesterol and ischaemic stroke ($p < 0.001$), and that a 1 mmol/L increase in LDL cholesterol corresponded to an OR of 1.33 (CrI: 1.17-1.52) for ischaemic stroke. Finally, a meta-analysis of 30 CHD case-control studies (11804 cases and 17713 controls) reported that compared to E3/E3 participants, E3/E4 participants had an OR for CHD of 1.48 (CI 1.26-1.75) and E4/E4 participants of 1.45 (CI 1.23-1.71) (Xu et al., 2016). A reduced risk of CHD was only evident in E2 carriers when sub-group analysis was carried out by ethnicity, in Caucasian populations an OR of 0.84 was reported for E2 carriers (CI 0.74–0.96), but this was not observed in Mongolians (OR 1.18, CI 0.94–1.46) (Xu et al., 2016). These findings suggest a relationship between *APOE* genotype and CVD that is mediated by LDL cholesterol. Epidemiological and intervention studies have demonstrated a positive relationship between increased dietary intake of saturated fat and increased LDL cholesterol levels (Hegsted et al., 1965; Keys et al., 1986). Furthermore, a recently updated meta-analysis confirmed that reducing saturated fat intake reduced the risk of combined cardiovascular events by 17% (Hooper et al., 2020). However, responsiveness to dietary manipulation is not consistent. Inconsistency in

trial outcomes can be the consequence of both genetics and environmental factors such as diet (Minihane et al., 2007).

Genotype-diet interactions affect the relationship between genotype and CVD phenotype, and studies have attempted to understand those interactions to increase the potential for reducing CVD risk through dietary modification (Griffin et al., 2018; Keathley et al., 2022; Masson et al., 2003; Rathnayake et al., 2019). For example, following a systematic review of genotype-diet interactions related to omega-3 fatty acid intake a significant reduction in plasma triglyceride levels was reported in male carriers of E4 in response to omega-3 fish-oil intake (Keathley et al., 2022). However, as with *FTO*, only one dietary goal was selected to provide genotype-based advice (Rosal et al., 2001). A greater percentage of the UK population are currently meeting recommendations for oily fish intake (26%) than saturated fat (17%), therefore saturated fat was selected as the dietary component upon which to provide dietary advice related to *APOE* genotype (Bates et al., 2020; COMA, 1994; Derbyshire, 2019; SACN, 2019). Consequently, the following section will review literature related to a genotype-diet interaction with *APOE* and saturated fat. Several studies have examined whether *APOE* genotype affects CVD risk in response to modification of dietary fat; findings from case-control studies have not shown a clear gene-nutrient interaction. A Costa Rican study to determine the effect of *APOE* genotype and saturated fat intake on risk of myocardial infarction (1,927 case and 1,927 control) reported that a diet high in saturated fat was associated with an OR of 1.49 (95% CI, 1.16-1.92) in E3/E3 participants, an OR of 2.59 (95% CI, 1.38-4.87) in E4 carriers and an OR of 3.17 (95% CI, 1.58-6.36) in E2 carriers (Yang et al., 2007). However, in a nested case-control study of the Spanish EPIC cohort, a significant interaction between a high saturated fat intake (≥10% TEI) and APOE genotype on CHD risk was reported. The risk of CHD was significantly greater in E4 carriers compared to E2 carriers (OR = 3.33; 95% CI, 1.61-6.90). There was no significant effect of genotype when saturated fat intake was below 10% TEI (Corella, Portolés, et al., 2011).

Masson, McNeill, & Avenell (2003) carried out a systematic review of the effect of genetic variation on the responsiveness of fasting lipids to dietary manipulation. Of the 46 dietary fat intervention studies, they reported that 11 showed a significant effect of *APOE* genotype on total cholesterol with eight showing an effect on LDL cholesterol. The authors summarised that E4

carriers were generally more responsive to changes in dietary fat compared to E3 and E2 carriers. A secondary analysis of the 'RISCK' study by Griffin et al. (2018) investigated the impact of replacing saturated fat in the diet with monounsaturated fat, high glycaemic index carbohydrate, or low glycaemic index carbohydrate in 389 participants (E2 carriers (n = 70), E4 carriers (n = 125) and E3/E3 (n = 274). Similar to Masson et al. (2003), following a 24-week intervention E4 carriers had a significantly greater reduction in total cholesterol compared to E3/E3 (TC −0.28 mmol/L, p = 0.03) participants when saturated fat was replaced with low glycaemic index carbohydrate as part of a low-fat diet. Finally, retrospective analysis of the DIVAS study of 159 adults with moderate risk of CVD (E4 carrier (n = 52) and E3/E3 (n = 107) investigated the effect of *APOE* genotype on responsiveness to diets of varying fat composition. A significant diet-gene interaction was reported when saturated fat was replaced by monounsaturated fatty acid (MUFA), whereby TAG concentrations increased in E3/E3 (TAG mmol/L 0.10 ± 0.06) and decreased in E4 carriers (TAG mmol/L −0.23 ± 0.10) (Rathnayake et al., 2019).

In summary, there is a plausible biological mechanism by which *APOE* genotype influences blood cholesterol levels that explains the association with CVD (Phillips, 2014). Moreover, this mechanism could also explain the enhanced cholesterol response to reduced saturated fat intake (Griffin et al., 2018). Based on the framework of Grimaldi et al. (2017) this would be classed as an intermediate interaction, since other processes will influence LDL cholesterol levels. Large observational case-control studies have demonstrated that a high saturated fat intake is associated with an increased risk of CHD and myocardial infarction in E4 carriers; however, the evidence in E2 carriers is contradictory (Corella, Portolés, et al., 2011; Yang et al., 2007). Dietary intervention studies suggest that E4 carriers are more responsive to dietary fat manipulation although this is not demonstrated in all studies; also, the response varies depending on what is used to replace saturated fat in the diet. Although this is not consistent (Griffin et al., 2018; Masson et al., 2003; Rathnayake et al., 2019). The quality of intervention studies cannot be judged using STREGA guidelines as these were developed for observational studies. The two RCTs were well conducted (Griffin et al., 2018; Rathnayake et al., 2019); although, genotyping call rates were only reported in the study by Griffin et al. (2018) and neither study explicitly reported if genotypes were in Hardy-Weinberg equilibrium. In line with Grimaldi criteria (Grimaldi et al.,

2017), both studies measured dietary intake quantitatively (Griffin et al., 2018; Rathnayake et al., 2019). Based on this evidence assessed against the Grimaldi criteria there is probable evidence that *APOE* interacts with saturated fat intake to affect blood cholesterol.

1.4.4 Methylenetetrahydrofolate reductase

MTHFR is an enzyme involved in the metabolism of folate. MTHFR converts 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate which provides a methyl donor to convert homocysteine to methionine, a reaction which is catalysed by methionine synthase with vitamin B_{12} as a cofactor (Liew & Gupta, 2015). A common missense SNP (C667T) of the *MTHFR* gene results in substitution of alanine to valine affecting the thermostability of the enzyme at 37^{o}C. The minor allele frequency is 0.25, and heterozygotes have 65% of the enzyme activity levels of homozygotes for the wild type (CC), and homozygotes for the risk allele (TT) have 30% of the enzyme activity levels of CC carriers (Frosst et al., 1995). As a result of reduced enzyme activity, homozygotes for the TT allele have been reported to have a higher plasma concentration of homocysteine compared to CC homozygotes (Holmes et al., 2011; Wald et al., 2002). Meta-analyses of case-control studies have reported an increased risk of IHD and stroke that is associated with increased serum homocysteine concentration (Holmes et al., 2011; Wald et al., 2002, 2011). Wald et al. (2002) conducted a meta-analysis of 46 studies (12193 cases and 11945 controls) and reported an OR of 1.21 (CI 1.06-1.39) for ischaemic stroke in TT compared to CC homozygotes. The mean difference in serum homocysteine concentration between groups was 2.7 µmol/L. Based on their analysis they predicted that a 3 µmol/L reduction in serum homocysteine would translate to a 16% risk reduction for ischaemic stroke. These findings were replicated in 2011 with a larger data set (Wald et al., 2011). In a meta-analysis of 75 case-control studies (22068 cases and 23618 controls) investigating the association between *MTFHR* genotype and IHD in 75 case-control studies (22068 cases and 23618 controls), Wald et al. (2011) reported a significantly higher risk of IHD (OR 1.16; CI 1.04-1.29) in TT compared to CC homozygotes. Holmes et al. (2011) carried out a meta-analysis of 79 case-control studies to determine the effect of *MTHFR* genotype on risk of stroke. They reported an OR for stroke of 1.37 (CI 1.25 – 1.50) in TT compared to CC participants. These studies show that increased serum homocysteine, as a

consequence of *MTHFR* genotype, is associated with an increased risk of IHD and stroke. Due to the role of folate in homocysteine metabolism, Holmes et al. (2011) compared studies based on geographical region. Asia is identified as a region with a low intake of folate whereas other regions including the US, Australia and New Zealand have mandatory fortification of flour with folate (Looi, 2023). Indeed, when they compared serum homocysteine concentration between CC and TT homozygotes in studies on Asian populations they found a 3.12 µmol/L higher concentration in TT homozygotes, whereas in studies from fortified regions the homocysteine concentration in TT homozygotes was only 0.13 µmol/l higher. Huang et al. (2018) carried out a retrospective analysis of data from the China Stroke Primary Prevention Trial of 16413 hypertensive adults aged 45-75 years. Participants were randomised to receive either Enalapril (control) or Enalapril plus 0.8 mg of folic acid per day. Plasma homocysteine levels were measured at the start of the trial and an average of 4.5 years later, change in plasma homocysteine levels were compared between *MTHFR* genotypes. At the end of the trial plasma homocysteine levels were significantly lower in the group that received folic acid compared to the control group. Reduction in plasma homocysteine levels was significantly greater in TT participants (−2.95 µmol/L; CI −3.71 to −2.18) compared to CT (−1.30 µmol/L; CI −1.50 to −1.10) and CC (−1.02 µmol/L; CI, −1.26 to −0.78). Furthermore, there was a significant genotype-diet interaction, the effect of *MTHFR* genotype on plasma homocysteine levels was negated when serum folate levels reached 15 ng/mL. However, approximately 30% of TT participants did not reach the target serum folate of 15 ng/mL suggesting that TT participants may require a higher dose of folic acid to reach the target and reduce homocysteine levels.

Consequently, RCTs have been carried out to determine the effect of Vitamin B supplementation on homocysteine levels and importantly incidence of CVD, these studies did not include genetics. Holmes et al. (2011) analysed 13 RCTs involving 45549 participants, and found that folic acid supplementation reduced mean plasma homocysteine concentration by 3.33 µmol/L; however, the RR of stroke was 0.94 (CI 0.85-1.04). Similarly, Wald et al. (2011) reported in a meta-analysis of 14 RCTs involving 39597 participants a significant reduction in plasma homocysteine (3.3 µmol/l) following folic acid supplementation but no effect on relative risk of IHD (RR 1.00; CI 0.93-

1.08). Therefore, the findings of case-control studies do not equate to a reduction of CVD risk following folic acid supplementation in RCTs. Some researchers have suggested that the increased OR reported in case-control studies of *MTHFR* is a result of publication bias (Clarke et al., 2012); however, Wald et al. (2011) suggest that it may be a result of the high use of anti-platelet therapy of trial participants. Wald et al. (2011) reported that when they compared trials with high (91%) v. low (60%) participant anti-platelet therapy use, RR was significantly lower in the trials with lower use. Anti-platelet therapy may negate the effect of reduced plasma homocysteine since increased plasma homocysteine has been associated with increased platelet activation, thromboxane production, and platelet aggregation, suggesting a greater role for folate supplementation in prevention rather than treatment of CVD (Wald et al., 2011). Furthermore, the folate status of populations is greatly affected by voluntary and mandatory fortification; TT carriers have 20% greater homocysteine levels than CC carriers when folate fortification is not mandatory, such as in parts of Europe and Asia (Clarke et al., 2012). Holmes et al. (2011) reported that the majority of participants (91%) in RCTs in their meta-analysis were from countries with high folate intake.

In summary, *MTHFR* genotype has a causative effect on the MTHFR enzyme and as a result, individuals with the TT genotype have increased serum homocysteine concentrations (Holmes et al., 2011; Wald et al., 2002). Meta-analyses of case-control studies report an increased risk of IHD and stroke in participants with the *MTHFR* risk genotype (Holmes et al., 2011; Wald et al., 2002, 2011). Furthermore, studies in populations with a low folate intake have demonstrated a greater difference in serum homocysteine concentrations between TT and CC genotypes compared to populations with higher folate intakes (Holmes et al., 2011). A large RCT of folic acid supplementation demonstrated a significant genotype-diet interaction between folic acid supplementation and *MTHFR* genotype, which suggests TT individuals have a greater reduction in plasma homocysteine levels following supplementation but require a larger dose to achieve target serum folic acid concentrations in order to reduce plasma homocysteine levels (Huang et al., 2018). However, although RCTs of folic acid supplementation result in a decrease in serum homocysteine levels this does not translate into a reduced risk of IHD or stroke (Holmes et al., 2011; Wald et al., 2011). Based on the above evidence assessed against the Grimaldi criteria,

there is probable evidence of an interaction between *MTHFR* genotype and folate on the risk of IHD and stroke. Table 1.3 summarises the evidence for each SNP with reference to the Grimaldi criteria (Grimaldi et al., 2017).

Table 1.3. Summary of evidence for provision of genotype-based personalised advice for SNPs in the *FTO, APOE* and *MTHFR* genes with reference to the Grimaldi criteria (Grimaldi et al., 2017).

Gene SNP	Gene - diet interaction	Biological plausibility	Assessment and advice
FTO rs9939609	**Saturated fat: Indirect** Case-control studies: significantly increased BMI in homozygous risk individuals when saturated fat intake high (Corella, Arnett, et al., 2011; Phillips et al., 2012). **Physical activity: Indirect** Meta-analysis: being physically active attenuates the effect of the risk genotype on BMI by ≈ 30% (Graff et al., 2017; Kilpeläinen et al., 2011)	**Unknown:** FTO protein is a nucleic acid demethylase. Potential roles: amino acid sensor, other nearby genes such as RPGRIP1L and IRX3 (De Caterina et al., 2020; Speakman, 2015; Yeo, 2014). Mechanism by which FTO affects body weight is still not clear (Loos, 2018).	**Probable evidence**: *FTO* SNP rs9939609 interacts with saturated fat intake and physical activity level to affect BMI. **Genotype-based personalised advice:** Personalised advice to individuals identified to have a risk-genotype for *FTO* would include to meet saturated fat recommendations and maintain or increase their level of physical activity to meet moderate recommended levels.
APOE rs429358 rs7412	**Saturated fat: intermediate** Case-control studies: diet high in saturated fat was associated with an increased OR of MI (Yang et al., 2007) and CHD in E4 carriers (Corella, Portolés, et al., 2011). RCTs: E4 carriers compared to E3/E3 had a greater reduction in TC when saturated fat replaced with low GI carbohydrate as part of a low-fat diet (Griffin et al., 2018) and decreased TAG concentrations when saturated fat replaced by MUFA (Rathnayake et al., 2019).	**Causative:** Apo E protein is involved in the regulation of plasma lipid levels. APOE4: preferential binding to VLDL and reduced binding ability to HDL, reduced lipolysis of VLDL and reduced HDL formation (Phillips, 2014). VLDL to compete with LDL in uptake by LDL receptor, more LDL remains in circulation (Griffin et al., 2018). TAG-rich lipoproteins of E4 participants on high saturated fat diet reduce LDL cholesterol uptake by LDL receptors (Calabuig-Navarro et al., 2017).	**Probable evidence**: *APOE* interacts with saturated fat intake to affect blood cholesterol. **Genotype-based personalised advice:** Personalised advice to individuals identified to have a risk-genotype for *APOE* would be to ensure they are meeting recommended intakes of saturated fat in order to maintain a healthy level of LDL cholesterol.

MTHFR rs1801133	**Folate: intermediate** Case-control studies: Increased homocysteine levels in TT v CC homozygotes in studies conducted in countries with low folate intake, not observed in countries with folate fortification (Holmes et al., 2011). Large RCT of folic acid supplementation significant genotype-diet interaction between folic acid supplementation and *MTHFR* genotype, TT individuals have a greater reduction in plasma homocysteine levels following supplementation but require a larger dose to achieve target serum folic acid concentrations in order to reduce plasma homocysteine levels (Huang et al., 2018) Meta-analysis: RCTs of folate supplementation significant reduction in plasma homocysteine following folic acid supplementation but no effect on RR of stroke or IHD (Holmes et al., 2011; Wald et al., 2011).	**Causative:** MTHFR is an enzyme involved in the metabolism of folate. TT homozygotes: missense SNP 30% enzyme activity levels of CC homozygotes. As a consequence, homozygotes for the TT allele have higher plasma concentration of homocysteine compared to CC homozygotes (Holmes et al., 2011; Wald et al., 2002). Increased risk of IHD and stroke associated with serum homocysteine concentration (Holmes et al., 2011; Wald et al., 2002, 2011).	**Probable evidence:** *MTHFR* interacts with folate to reduce the risk of IHD and stroke. **Genotype-based personalised advice:** Personalised advice to individuals identified to have a risk-genotype for *MTHFR* would be to ensure they are meeting recommended intakes of dietary folate.

BMI: body mass index; FTO: fat mass and obesity associated gene; SNP: single nucleotide polymorphism; OR: odds ratio; MI: myocardial infarction; CHD: coronary heart disease; RCT: randomised controlled trial; TC: total cholesterol; TAG: triglyceride; MUFA: monounsaturated fatty acid; VLDL: very low-density lipoprotein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; RR: relative risk; IHD: ischaemic heart disease.

1.5 Behaviour change

1.5.1 Behaviour change theories

More than 80 theories of behaviour change were identified in a systematic review by Davis and colleagues (2015). The ones most commonly cited in the literature are the Social Cognitive Theory (Bandura, 1986), the TPB (Ajzen, 1991) and the Transtheoretical (Stages of Change) Model (Prochaska & Velicer, 1997). In their Guidance for Behaviour Change, NICE (2007) do not support a particular model or theory of behaviour change but recommend the incorporation of a number of concepts drawn from the psychological literature and are presented in Table 1.4.

Table 1.4. Behaviour change concepts to structure and inform interventions (NICE, 2007).

Concept	Definition
Outcome expectancies	Helping people to develop accurate knowledge about the health consequences of their behaviours
Personal relevance	Emphasises the personal salience of health behaviours
Positive attitude	Promotes positive feelings towards the outcomes of behaviour change
Self-efficacy	Enhances the belief of people in their ability to change
Descriptive norms	Promotes the visibility of positive health behaviours in the groups with which people compare themselves
Subjective norms	Enhances social approval for positive health behaviours in significant others and reference groups
Personal and moral norms	Promotes personal and moral commitment to behaviour change
Intention formation and concrete plans	Helps people to form plans and goals for changing behaviours over time and in specific contexts
Behavioural contracts	Asks people to share their plans and goals with others
Relapse prevention	Helps people develop skills to cope with difficult situations and conflicting goals

There is a consensus that interventions designed to change health-related behaviours are more likely to be successful when theoretical links between the intervention and the behaviour have been considered in the design of the intervention (Davis et al., 2015; Horne et al., 2017; NICE, 2007; Timlin et al., 2020). One factor that has been suggested to explain the lack of response in public health campaigns to encourage healthy behaviours is 'optimistic bias': the phenomenon by which an individual underestimates their risk of developing a disease, such as CVD, compared

to others (Shepherd, 1999). The personal salience of lifestyle recommendations to reduce the risk of disease may be increased when coupled with information about an individual's genetic risk of the disease. Changes in lifestyle behaviours, as discussed above, can be used for improvement of all modifiable risk factors, in this context genetics seem to be a non-modifiable factor; however, the effect of some genetic variations may be attenuated by lifestyle adjustments (Khera et al., 2016).

1.5.2 Gene-based personalised advice to change diet and physical activity behaviour.

The objective of personalised nutrition is to maintain health using genetic, phenotypic, clinical, dietary, and other information to provide more precise and effective personalised healthy eating advice (Grimaldi et al., 2017). For the three SNPs detailed above, there is good evidence to support the provision of personalised healthy eating advice based on an individual's genotype. For example, an individual with a risk genotype for *FTO* should be advised to maintain or increase their physical activity levels and ensure they are meeting the recommended saturated fat intake. To provide this advice meaningfully, knowledge of the current diet and physical activity of the individual is also required. The second objective of personalised nutrition is to motivate appropriate behaviour change (Grimaldi et al., 2017). Research has been carried out to determine the efficacy of genotype-based personalised advice on motivation and behaviour change, with mixed findings.

1.5.3 Analogue studies

Experimental analogue (vignette) study designs have been utilised to determine the effect of disclosure of an increased genetic risk of obesity on affective outcome measures including motivation to change behaviour (Ahn & Lebowitz, 2018; Frosch et al., 2005; Meisel, Walker, et al., 2012; Sanderson et al., 2010). Experimental analogue studies provide participants with a hypothetical scenario, and they are asked to respond to determine the effect of the hypothetical scenario on, for example, their motivation to change behaviour. Studies suggest that participants informed of an increased risk of obesity are more motivated to make healthy changes to lifestyle behaviours in comparison to those informed of a low risk (Ahn & Lebowitz, 2018; Frosch et al., 2005; Meisel, Walker, et al., 2012; Sanderson et al., 2010). This effect has been observed in a

student population (Frosch et al., 2005; Meisel, Walker, et al., 2012), the general population (Ahn & Lebowitz, 2018; Sanderson et al., 2010), and in participants with weight concerns (Meisel, Walker, et al., 2012). The hypothetical nature of these types of studies limits the ability to generalise findings to the 'real world'. Furthermore, they rely on proxy outcome measures of behaviour such as intention or motivation to change. As such, intervention studies have been carried out to investigate the real effect of genotype-based personalised nutrition advice on dietary behaviour.

1.5.4 Randomised controlled trials

Several studies have reported favourable effects of genotype-based personalised nutrition on dietary and physical activity behaviour. Compared to a control group, participants informed of a risk-associated genotype significantly improved the fat quality of their diet (Hietaranta-Luoma et al., 2014), reduced their sodium intake (Nielsen & El-Sohemy, 2014), were more likely to maintain weight loss (Arkadianos et al., 2007; Vranceanu et al., 2020), and were more likely to make health behaviour changes to reduce Alzheimer's disease (AD) risk (Chao et al., 2008). Conversely, compared to a control group, knowledge of diabetes genetic risk (Grant et al., 2013), or a nutrigenetic guided weight loss programme (Frankwich et al., 2015) did not result in greater weight loss. The Food4Me study was a multi-centred European study investigating the effect of varying levels of personalised nutrition advice on eating patterns and health outcomes, compared to general dietary advice (Celis-Morales, Livingstone, et al., 2015). Using a four arm design three levels of personalisation were compared to a control group: level 1 provided personalised advice based on participants reported dietary behaviour; level 2 advice was personalised based on dietary behaviour in addition to phenotypic markers; finally level 3 advice included all aspects of level 1 and 2 with the addition of genetics (Celis-Morales, Livingstone, et al., 2015). Genotype-based personalised advice resulted in significantly greater improvements in adherence to a Mediterranean diet compared to other levels of personalised advice (Livingstone et al., 2016); moreover, any level of personalised nutrition advice (including genotype-based) reduced saturated fat intake compared to a control group (Fallaize et al., 2016). In contrast, genotype-based personalised nutrition advice had no effect on folate intake (O'Donovan et al.,

2016) or physical activity (Marsaux et al., 2016b). Most recently, a study that incorporated genotype-based dietary advice into a population-based weight management programme reported a greater reduction in reported intake of fat and greater adherence to dietary guidelines for fat intake compared to participants following the weight management programme without genotype-based dietary advice (Horne, Gilliland, O'Connor, et al., 2020).

1.5.5 Systematic reviews and meta-analyses

Several systematic reviews and meta-analyses have been conducted to investigate the effect of personalised communication of disease risk on changes in lifestyle behaviours (Hollands et al., 2016; Horne et al., 2018; Jinnette et al., 2020; Li et al., 2016; Marteau et al., 2010). For the purposes of this literature review, the focus will be on genotype-based personalised advice related to diet and physical activity as lifestyle behaviours. The first was a Cochrane review by Marteau et al. (2010), which included both clinical trials and analogue studies that provided participants with genetic risk estimates of disease that could plausibly be reduced through behaviour change. The two studies they identified that included diet as an outcome suggested a significant beneficial effect (OR 2.24; CI: 1.17-4.27); however, two studies that looked at physical activity as an outcome did not support an effect (OR 1.03; CI 0.59 - 1.80). As more studies have been published, this has enabled further systematic reviews and meta-analysis with more focused research questions. The Cochrane review by Marteau et al. (2010) was updated by Hollands et al. (2016). In their meta-analysis of RCTs investigating the impact of genotype-based disease risk advice on risk-reducing behaviours, they analysed dietary data from seven clinical studies and reported no significant benefit of genotype-based risk advice on dietary behaviour change, with a standardised mean difference (SMD) of 0.12 (CI: 0.00-0.24). Furthermore, in the six studies investigating the effect of genotype-based risk advice on physical activity behaviour change, no effect was observed (SMD: -0.03; -0.13-0.08). The authors concluded that there was a small effect of genetic risk communication on dietary behaviours, but their findings did not support the use of genotype-based risk communication to motivate dietary or physical activity behaviour change. Li et al. (2016) investigated studies providing genetic risk testing and communication of the same in relation to obesity, T2D and CVD. They included analogue studies

to investigate effects on perceived motivation to engage in lifestyle modification to reduce risk and RCTs to determine the effect on actual motivation, lifestyle modification, and clinical outcomes. They also concluded that, compared to controls, there was no benefit of personalisation of advice related to genetic risk on lifestyle modification or clinical outcomes. More recently two systematic reviews have been published; Horne et al. (2018) failed to identify a cause-effect relationship between genotype-based interventions and health behaviour change. Although, Horne et al. (2018) surmised that nutrition was the most promising area of behaviour change. Jinnette et al. (2020) evaluated the effect of personalised nutrition interventions on changes in dietary intake. They concluded that compared to other forms of personalisation there was no evidence for the addition of genotype-based advice being more effective for improving dietary behaviour. To summarise, the findings from the systematic reviews and meta-analysis suggest that there may be a small effect of genotype-based dietary advice on behaviour change, but it is not convincing. Furthermore, genotype-based advice to affect changes in physical activity does not appear to be effective.

1.5.6 Limitations of previous studies

There are limitations with the studies on which the systematic reviews and meta-analysis have been conducted. Many of the authors have commented on a high risk of bias in the included studies (Hollands et al., 2016; Li et al., 2016; Marteau et al., 2010). The contradictory findings reported in individual studies and systematic reviews reflect the heterogeneous study designs used; for example, the delivery of the genotype-based personalised advice intervention has varied between studies from remote delivery of information via email (Celis-Morales, Livingstone, et al., 2015), to delivery as part of an established intervention programme (Grant et al., 2013; Horne, Gilliland, O'Connor, et al., 2020). Moreover, studies have been carried out in the context of different chronic diseases and related genes, some studies have used a single SNP to provide specific diet intervention advice based on the gene-diet or lifestyle interaction (Celis-Morales, Livingstone, et al., 2015; Chao et al., 2008; Nielsen & El-Sohemy, 2014). Others have provided a genetic risk score based on a number of genetic variants associated with the disease (Grant et al., 2013; Vranceanu et al., 2020). Both types of genotype-based advice have

advantages and disadvantages; specific dietary advice based on one SNP may be easier to follow, whereas a genetic risk score will provide an individual with a clearer idea of their overall risk of a disease but is less clear in terms of what lifestyle behaviour to modify in response. However, different approaches may influence the participant response to advice (Jinnette et al., 2020). Dietary behaviour and physical activity have been measured in different ways (food frequency questionnaires (FFQs), dietary recall, questionnaires). The subjective nature of these measurements, particularly habitual dietary intake, is a major challenge in all nutrition research that requires participants to self-report their intake (Goldberg et al., 1991). Therefore, dietary outcome measures may not accurately reflect behaviour. Clinical outcomes such as body weight or fasting plasma glucose are more reliable than subjective reports of dietary intake but are influenced by more than one variable (diet and physical activity for example) and to see a change in body weight requires studies of a longer duration than to see a change in dietary behaviour. The duration of studies and the follow-up time is highly variable ranging from 8 weeks to more than five years after the intervention (Godino et al., 2016; Hietaranta-Luoma et al., 2018). Health behaviour change requires both initiation and maintenance of change. Acquiring the motivation to change behaviour is an important step in the initiation of behaviour change (Ryan et al., 2008). Short-term studies assess the use of genotype-based personalised nutrition advice to motivate the initiation of short-term dietary changes; however, it is not possible to determine if these changes were maintained. Studies have demonstrated significant dietary behaviour change 12 months after genotype-based personalised recommendations (Horne, Gilliland, O'Connor, et al., 2020; Nielsen & El-Sohemy, 2014) and in the longest follow-up to date that these changes were observed five and a half years after the intervention (Hietaranta-Luoma et al., 2018). Study participants have ranged from interested volunteers (Celis-Morales, Livingstone, et al., 2015) to those with a family history of a disease (Chao et al., 2008). Participants in most studies had a high level of education and grade of employment (Jinnette et al., 2020). Furthermore, by volunteering to take part in these studies they demonstrated an interest in their health and genotype-based personalised nutrition. Often these populations are already relatively healthy and not necessarily those that need to change their lifestyle to prevent associated diseases.

1.5.7 The Theory of Planned Behaviour

A consistent criticism of previous studies investigating the effect of genotype-based health advice on behaviour change is the lack of integration of behaviour change theory (French et al., 2017; Horne et al., 2018; Jinnette et al., 2020). Horne et al. (2017) have suggested how the incorporation of personalisation to public health behaviour change research can be incorporated into the TPB. The TPB is commonly utilised in the context of health behaviours and is presented in Figure 1 (Ajzen, 1991; Davis et al., 2015).

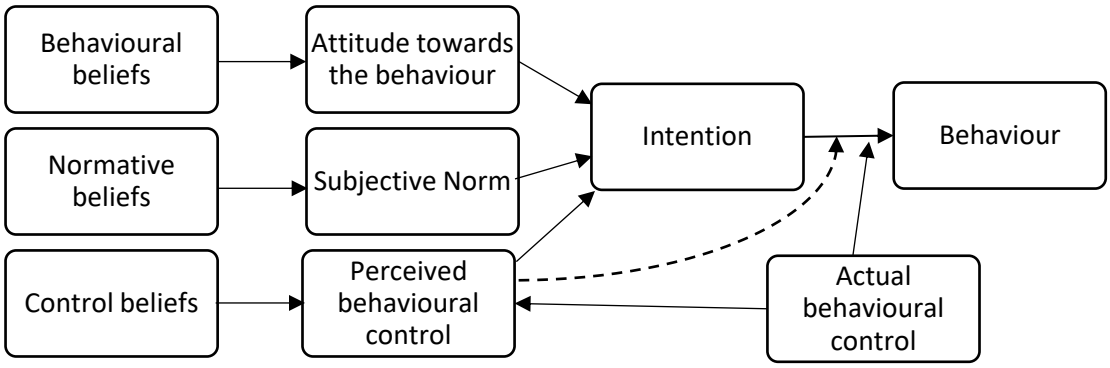

Figure 1.1 The Theory of Planned Behaviour (Ajzen, 2019).

Solid arrows indicate a direct relationship. Dashed arrows indicate a potential direct relationship.

The theory states that 'intention' or motivation to perform a behaviour can be predicted from three independent factors; 'attitudes towards the behaviour' which represents the extent to which an individual has a favourable appraisal of that behaviour, 'subjective norms' which refers to the perceived social pressure to perform or not perform the behaviour and 'perceived behavioural control (PBC)' which refers to the perception of how easy or difficult it is to perform the behaviour. Belief composites (behavioural beliefs, normative beliefs and control beliefs) affect the antecedents of intention (attitude, subjective norm and PBC). 'Attitude towards the behaviour' is affected by 'behavioural beliefs', the subjective probability that the behaviour will produce a given outcome or experience. 'Subjective norms' are affected by 'normative beliefs', which represents the perceived behavioural expectations of important referent individuals or

groups, such as a spouse or a health professional. 'PBC' is affected by 'control beliefs', the perceived presence of factors that may facilitate or impede the performance of a behaviour. 'Intention' and 'PBC' have been demonstrated to account for a large amount of variation in the behaviour, multiple correlations ranging from 0.20 to 0.78 (Ajzen, 1991). Horne et al. (2017) suggest that personalisation of behaviour change advice will affect 'behavioural beliefs' which will create a more favourable 'attitude towards the behaviour'. Also, personalisation will affect 'normative beliefs' which will have a positive effect on 'subjective norms', as shown in Figure 1.2.

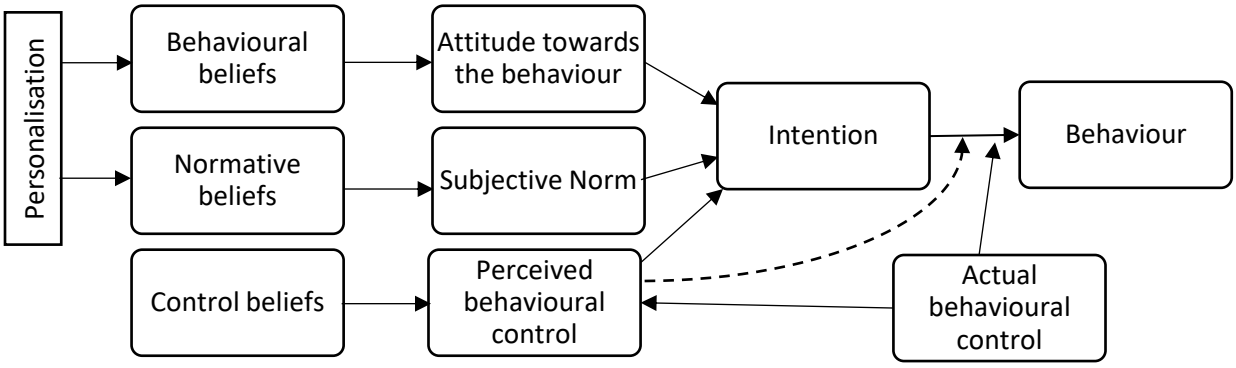

Figure 1.2. Personalisation: a proposed expansion of the 'Theory of Planned Behaviour' (Horne et al., 2017).

1.5.8 Disclosure of risk v non-risk genotype

The aim of disclosure of a high-genetic risk as a component of personalised advice is to motivate behaviour change in these individuals; however, it is also important to consider the effect of disclosure of a non-risk genotype which may increase optimistic bias and reduce compliance to health behaviours (Hunter et al., 2008; Lovegrove & Gitau, 2008). To understand the response to genotype-based advice in both risk and non-risk groups comparisons have been made between participants informed of a risk-associated genotype and those informed of a non-risk-associated genotype. Compared to participants informed of a non-risk genotype, participants informed

of an *APOE* risk-associated genotype were reported to have made greater changes to saturated fat intake (Fallaize et al., 2016) and made and maintained moderate changes to dietary behaviour which resulted in slight improvements in clinical CVD markers (Hietaranta-Luoma et al., 2018). However, there was no significant difference in folate intake between participants informed of a *MTHFR* risk-associated genotype and those informed of a non-risk-associated genotype, following a recommendation to increase their folate intake (O'Donovan et al., 2016). In reality, individuals seeking advice from nutrigenetic testing companies will receive information about a panel of genes, some of which are likely to be risk conferring and others protective. Therefore, the communication of behaviour change advice will be primarily targeted to those behaviours that confer an effect linked to an individual's risk-associated genes.

1.6 Awareness, willingness and intention towards genotype-based personalised advice

Assuming that genotype-based personalised nutrition is an effective way of preventing NCDs such as obesity, T2D and CVD; then in order for it to be used as a public health intervention, the general population needs to be aware that it exists, willing to engage with it as a service and intend to follow genotype-based personalised advice. The following section will review literature that has investigated public awareness, willingness and intention towards genotype-based personalised advice. Finally, how factors such as age, health and perceived risks and benefits may affect intention to use genotype-based personalised advice.

1.6.1 Awareness, willingness and intention

Several studies have been carried out to assess public awareness of geneotype-based personalised testing and to gauge willingness to undergo testing (Bayer et al., 2021; Cherkas et al., 2010; Fallaize et al., 2015; Poínhos et al., 2014; Stewart-Knox et al., 2009; Vallée Marcotte et al., 2018). A survey of 4050 participants sampled from the UK-based TwinsUK register was published in 2010, which reported that 13% of participants were aware of personalised genomic testing (Cherkas et al., 2010). A more recent survey of 1357 participants in Germany suggests that public awareness specifically related to genotype-based dietary advice was higher, with 19% of their participants saying they had heard of the term: 'genotype-based dietary

recommendation' (Bayer et al., 2021). Furthermore, in the same study 16% of participants reported that they had received a genotype-based diet recommendation (Bayer et al., 2021). The reported willingness of participants to undergo genetic testing is variable between studies. The variation in willingness may reflect how recently the study was conducted, characteristics of the population sampled, cultural differences, and the way in which questions were phrased (Fallaize et al., 2013). A study carried out on 5967 participants from eight European countries (UK, Spain, the Netherlands, Poland, Portugal, Ireland, Greece and Germany) in 2005 reported that 39% of participants were willing to undergo genetic testing for general interest and that 28% would follow a genotype-based diet tailored to their needs (Stewart-Knox et al., 2009). The UK sample (n = 1011) of the study were more willing to follow a genotype-based diet (39%) than the average of all participants. Since then, public use of genetic testing has increased (Regalado, 2017), with a 2015 study reporting that 91% of their sample of French Canadians (n = 1425) were willing to follow a diet based on nutrigenetic testing (Vallée Marcotte et al., 2018). The willingness to undertake genetic testing has been reported to vary between sub-groups of the population. The effect of age on willingness is not consistent between studies (Fallaize et al., 2013). Stewart-Knox et al. (2009) reported the highest percentage of participants willing follow a genotype-based diet were over the age of 65. Conversely, Bayer et al. (2021) reported that the percentage of participants that could conceive to make use of a genotype-based dietary recommendation was lowest in adults over the age of 65. However, studies have consistently reported that participants with a personal or family history of disease are more willing to undergo genetic testing (Bayer et al., 2021; Stewart-Knox et al., 2009; Vallée Marcotte et al., 2018). These studies suggest that large groups within the population are aware of and willing to follow a genotype-based diet. Willingness and intention are similar constructs, both of which can predict subsequent behaviour, researchers have suggested that willingness to perform a behaviour is more reactive and reflects a conducive environment for the behaviour, compared to intention to perform a behaviour which is more reasoned and goal oriented (Pomery et al., 2009). In the TPB intention is the proximal antecedent to actual behaviour, and represents the motivation to perform the behaviour (Ajzen, 2019). To change behaviour an understanding of what factors influence intention to perform that behaviour is required so that interventions can be designed appropriately. The following section

will discuss factors that have been identified to affect intention to use genotype-based personalised advice.

1.6.2 Factors influencing intention to use genotype-based personalised advice.

1.6.2.1 Psychological factors

As mentioned in section 1.5.1, one way in which genotype-based advice has been proposed to encourage behaviour change is by challenging an individual's optimistic bias, the phenomenon by which an individual underestimates their own risk of developing a disease, such as CVD, compared to others (Shepherd, 1999). Individuals with high levels of optimistic bias, such as young adults may not believe they need to change their behaviour as they perceive that they are at a lower risk of developing a disease (Stewart-Knox et al., 2013). 'Fear arousal', making an individual fearful of developing a health condition such as CVD has been suggested as technique to challenge optimistic bias and motivate behaviour change (Wilson, 2007). Previous research has suggested that this technique was successful at motivating behaviour change in the context of genetic risk of AD (Chao et al., 2008). Conversely, Marteau and Weinman (2006) suggest that genotype-based advice may not motivate behaviour change due to a fatalistic attitude towards the disease in those that are informed of a risk-associated genotype. When informed of a phenotypic risk factor such as a high cholesterol level, individuals relate this to their lifestyle (a high intake of saturated fat) and consequently reduce their saturated fat intake. They are less able to draw such links between their genes and cholesterol level and consequently are less motivated to make behaviour changes, as they perceive them to be less effective to counteract their genetic predisposition (Marteau & Weinman, 2006). An additional concern is that those individuals that are informed of a non-risk associated genotype may experience an increase in their optimistic bias; also termed a genetic invincibility affect. As a consequence, individuals may inaccurately conceive that they are unaffected by poor lifestyle behaviours that increase risk of obesity, the so-called genetic invincibility effect (Ahn & Lebowitz, 2018). Consequently, it is equally important that genotype-based advice does not enhance poor lifestyle behaviours in those informed of a higher genetic risk due to genetic fatalism (Ehrlinger et al., 2017; Marteau &

Weinman, 2006) or, in those informed of lower genetic risk, by increasing their optimistic bias (Hunter et al., 2008).

Poínhos et al. (2014) developed a model of psychological factors to predict intention to adopt personalised nutrition advice. Psychological factors assessed were perceived risk and benefit of personalised nutrition, perceived nutrition self-efficacy (reflects perceived ability to perform the task), internal health locus of control (HLC) (reflects perceived control over own health) and health commitment (reflects perception that health is due to chance or under control of others – reverse scored). The model was based on responses of 9381 participants from nine EU countries. In line with the TPB, attitude was incorporated into the model as an antecedent to intention, analysis was conducted to determine which psychological factors predicted attitude and intention to adopt personalised nutrition advice (Ajzen, 2020; Poínhos et al., 2014). They reported that the greater the perceived benefits of personalised nutrition, the more positive the attitude towards personalised nutrition was and the greater the intention to adopt personalised nutrition advice. Higher nutrition self-efficacy was also associated with a more positive attitude and greater intention to adopt personalised nutrition advice. A more positive perception of the efficacy of regulatory control to protect consumers, higher self-reported internal HLC, and higher health commitment all also had a positive impact on attitudes towards personalised nutrition advice. A higher perceived risk of personalised nutrition advice had a negative relationship with attitude towards personalised nutrition advice, and as expected, perceived benefit of personalised nutrition advice. However, the influence of perceived risk was less influential than perceived benefit of personalised nutrition advice on attitude towards personalised nutrition advice and intention to adopt personalised nutrition.

1.5.2.2 Food choice motives

Rankin et al. (2018) analysed data from the same participants but investigated the relationship between food choice motives on attitude towards and intention to adopt personalised nutrition advice. Food choice motives are measured using the Food Choice Questionnaire which provide an understanding of the importance of nine factors (health, mood, convenience, sensory appeal, natural content, price, weight control, familiarity, and ethical concern) governing food choice

(Steptoe et al., 1995). Rankin et al. (2018) reported that food choice motives of weight control, mood, and ethical concern (environmental and political considerations) were all positively associated with both attitude towards and intention to adopt personalised nutrition advice. Price on the other hand was negatively associated with attitude and intention to adopt personalised nutrition advice. The food choice motive of health was positively associated, and familiarity of food was negatively associated with attitude towards personalised nutrition, but neither were associated with intention to adopt personalised nutrition advice. Finally, the motive of sensory appeal of food was negatively associated with intention to adopt personalised nutrition advice. The reports of Poínhos et al. (2014) and Rankin et al. (2018) have identified a number of psychological factors and food choice motives that influence attitude and intention to adopt personalised nutrition advice. However, the other constructs of the TPB: subjective norms and PBC, need to also be considered. A greater understanding of how factors influence attitudes towards personalised nutrition and intention to adopt personalised nutrition advice can help inform the design and framing of advice delivered to individuals to increase the chance of changing behaviour.

1.5.2.3 Health

The primary motivating factor for taking a personalised genetic test is to improve health (Fallaize et al., 2013; Stewart-Knox et al., 2009). As mentioned previously, individuals with a personal or family history of chronic disease are reported to be more interested in genotype-based advice (Bayer et al., 2021; Stewart-Knox et al., 2009; Vallée Marcotte et al., 2018). Since these individuals are at higher risk of developing chronic diseases such as CVD, T2D and obesity, behaviour change to prevent disease development is imperative. It is important to understand how genotype-based advice is perceived by those individuals who are already identified as being 'at risk', based on phenotypic or biochemical markers, and to determine how disclosure of genetic risk influences behaviour. Genotype-based personalised advice can be used for the treatment of conditions such as obesity ,T2D and CVD, and has been shown to be effective in some studies (Arkadianos et al., 2007; Vranceanu et al., 2020). However, the best scenario in terms of NCDs is prevention. Young people are an important population to target since early

intervention can encourage the development of healthy behaviours; particularly since health-damaging behaviours are difficult to change once they have developed (NICE, 2007). Transition points in life, such as leaving school in young people and retirement in older adults, have been identified as good times to initiate behaviour change (NICE, 2007).

1.5.2.4 Cost

The most prohibitive factor for taking a personalised genetic test is cost (Fallaize et al., 2013; Stewart-Knox et al., 2009). Cherkas et al. (2010) reported that 5% of their participants would be interested in taking a personalised genomic test for £250 whereas 50% would be interested if it was free. The UK population have a public health service (NHS) that is free at the point of service. Compared to an Irish population, UK participants reported an expectation that delivery of personalised nutrition by the NHS would be free (Fallaize et al., 2015). Participants in their qualitative study reported that paying for a service would likely make them more committed and motivated to follow the advice. The results of the study suggest that by asking for payment for the delivery of personalised nutrition service, users will be more motivated to adhere to advice; however, by making the service free, uptake of the service will likely increase, but motivation will be lower (Fallaize et al., 2015).

1.5.2.5 Method of delivery

Studies have also investigated the preferred method of delivery of personalised nutrition advice. Delivery of genotype-based personalised advice currently ranges from a raw output of uninterpreted genetic data to clinical genetics service such as the NHS (Horton et al., 2019). Trust and preference for genotype-based personalised nutrition service providers has been demonstrated to significantly predict the intention to adopt the service (Poínhos et al., 2017). Concern regarding the security of genetic data and how it could be used by employers or insurance companies had been highlighted as a potential barrier to genotype-based personalised advice. Therefore, to gain the trust of consumers, and consequently their acceptance of the use of genetics to make lifestyle recommendations, various ethical, legal, and social issues need to be addressed (Kohlmeier et al., 2016). Consumers should be prepared for the social

consequences of adhering to recommendations they may receive in terms of their lifestyle factors following the test (Hurlimann et al., 2017; Kohlmeier et al., 2016). Ethical issues exist around ensuring there is a full understanding by the consumer regarding what information the test will reveal; in effect, consumers should be fully appraised by the provider of the benefits and the risks of the test beforehand (Hurlimann et al., 2017). Questions have been raised regarding the promises made by direct-to-consumer (DTC) companies, regarding what their tests will deliver and the subsequent disclaimers provided with the results (Ahlgren et al., 2013). Consumers need to be assured that their personal information is safe, that genetic tests are valid and carried out by secure accredited laboratories, and that the advice they receive is based on strong scientific evidence provided by health professionals with appropriate qualifications (Horne, Gilliland, Madill, et al., 2020).

In many countries, including the UK, genetic testing guidelines are still in development. A UK parliamentary inquiry into DTC genomic testing was published in June 2021. Currently in the UK, regulations that apply to genomic tests sold to consumers include: The 1987 Consumer Protection Act and Consumer Rights Act 2015, which ensures that products and services sold are fit for purpose and meet minimum standards for quality and safety; The Human Tissue Act 2004, which bans DNA analysis without appropriate consent; Advertising Codes, which ban misleading, harmful, offensive, or irresponsible adverts; and The Medical Devices Regulation 2002, which ensures the safety and performance of commercial tests with a medical purpose (although many nutrigenetic tests may be defined as 'wellness' tests rather than tests with a 'health-related purpose'). Collection, storage, and use of data is covered by the UK General Data Protection Regulation and currently all members of the Association of British Insurers are signed up to a voluntary code (reviewed every three years). The voluntary code commits insurance companies to treat applicants fairly, and to not require or pressure any applicant to undertake a predictive or diagnostic genetic test, nor ask for, or take into account the result of a predictive genetic test, except when the life insurance is over £500,000 and the applicant has had a predictive genetic test for Huntington's Disease and not ask for, or take into account, the result of any predictive genetic test obtained through scientific research (HM Government, 2018). Recommendations made to the Government following the UK Parliamentary inquiry included the setting of

requirements for clinical and analytical performance of DTC tests, the external validation of evidence to justify tests, medical supervision or genetic counselling for tests of certain conditions, external reviews of information provided to the consumer, consideration of the potential impact on the NHS of consumers seeking medical guidance following the receipt of test results, and the development of a specific timeframe for introducing new regulations for genomic tests provided directly to consumers (UK Parliament, 2021).

Security of genetic data and how it could be used by insurance companies or employers was not identified as a prominent issue in a large European population (Stewart-Knox et al., 2009). However, UK participants reported that they would have greater trust in personalised nutrition delivery if the service was provided by the NHS (Fallaize et al., 2015). The importance of remote delivery of health interventions was highlighted during the COVID-19 pandemic and acceptability of this mode of delivery may increase (Martin et al., 2020). The reported preference is for face-to-face delivery of personalised (including genotype-based) nutrition by a health care professional (Bayer et al., 2021; Fallaize et al., 2015).

1.6. Summary and aims.

NCDs are the leading cause of mortality worldwide (GBD 2017 Risk Factors Collaborators, 2018), of which CVD is the most common, causing an estimated 17.9 million deaths in 2019 (World Health Organisation, 2021). In the UK CVD is the second most common cause of death after cancer, causing approximately 168,000 deaths in 2017 (British Heart Foundation, 2019). The conditions of obesity, T2D and CVD are inextricably linked; obesity increases the risk of developing T2D and both obesity and T2D increase the risk of CVD (de Gonzalez et al., 2010; Singh et al., 2013). An individual's phenotype is a product of their genes and their environment (including their behaviour). As such, it has been estimated that positive changes in behaviour could considerably reduce the prevalence of NCDs (Ezzati et al., 2003). Findings from the NDNS of the UK population and HSE suggests that current dietary and physical activity advice is not being met by a significant proportion of the population (Health Survey for England, 2017; Roberts et al., 2018). Public health interventions appear to raise population awareness but fail to translate

into modification of behaviour (Croker et al., 2012). Gene variants that increase the risk of developing obesity, T2D and CVD interact with diet and physical activity behaviours, therefore an individual can attenuate the effect of some gene variants and reduce the risk of developing these diseases by making favourable changes in their dietary and physical activity behaviours (Corella, Arnett, et al., 2011; Graff et al., 2017; Griffin et al., 2018; Huang et al., 2018; Kilpeläinen et al., 2011; Phillips et al., 2012; Rathnayake et al., 2019). Personalisation based on genetics enables the personal salience of dietary and physical activity advice to be highlighted to those with a risk-associated genotype, which may reduce 'optimistic bias' and motivate behaviour change. In contrast to current public health dietary recommendations, which use a 'one size fits all' approach, it has been suggested that a genotype-based personalised approach to dietary recommendations may motivate individuals to make positive changes in their dietary behaviour (Celis-Morales, Lara, et al., 2015). Research suggests that populations are increasingly aware and willing to receive lifestyle advice based on their genetics (Bayer et al., 2021; Stewart-Knox et al., 2009; Vallée Marcotte et al., 2018). However, reports are conflicting with regards to the effect of genotype-based personalised advice on motivation and actual behaviour change (Hollands et al., 2016; Horne et al., 2018; Jinnette et al., 2020; Li et al., 2016; Marteau et al., 2010). Previous research has identified several factors that influence intention to adopt genotype-based advice, including psychological factors, food choice motives, health and mode of delivery (Bayer et al., 2021; Fallaize et al., 2013; Poínhos et al., 2014; Rankin et al., 2018). A greater understanding of these factors will enable researchers and health care practitioners delivering genotype-based advice to tailor interventions appropriately to the target audience. Populations that are at increased risk of developing disease are reportedly more willing to engage with genotype-based advice, but whether this translates to a change in behaviour is not clear (Bayer et al., 2021; Stewart-Knox et al., 2009; Vallée Marcotte et al., 2018). Since prevention of NCDs such as obesity, T2D and CVD is more effective than treatment the young adult population are particularly important group to target. Finally, development of interventions designed to change behaviour should be based on theoretical underpinnings. The TPB has been suggested as a model to understand and develop behaviour change interventions using genotype-based diet and physical activity advice (Horne et al., 2017). Therefore, the aim of the current programme of work was to

determine the efficacy of genotype-based personalised advice to motivate and promote dietary and physical activity behaviour change, in the context of reducing the risk of obesity, T2D, and CVD.

The overall aim was broken down into the following specific aims for each study:

Aim 1: Determine the effect of personalised nutrition advice on dietary intake in participants informed of a high-risk genotype compared to those informed of non-risk genotype (Chapter 2: Study 1).

Aim 2: Determine the efficacy of genotype-based personalised dietary and physical activity advice on healthy-eating motivation in young adults (Chapter 3: Study 2).

Aim 3: Evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2D or obesity in the general population and individuals that are at-risk of CVD or T2D (Chapter 4: Study 3).

Aim 4: Investigate the factors that influence the intention to adopt genotype-based personalised advice for diet and physical activity in young adults that perceive themselves to be a healthy weight versus those that perceive themselves to be overweight or obese. (Chapter 5: Study 4)

Ethics:

Ethical approval for Study 1 (SMEC_2016-17_143), Study 2 (SMEC_2018-19_052) and Study 4 (SMEC_2022-23_027) was provided by St Mary's University Research Ethics Sub-Committee (Appendix 1).

Chapter 2: Does personalised nutrition advice based on apolipoprotein E and methylenetetrahydrofolate reductase genotype affect dietary behaviour?

This chapter presents the findings of the first study of my PhD. In terms of the overall research question of the thesis, this study investigates the effectiveness of genotype-based advice to change dietary behaviours to reduce the risk of CVD. Importantly, it compares the response of individuals informed of a risk-associated genotype with those informed of a non-risk-associated genotype. This study was published in Nutrition and Health in November 2021.

2.1. Background

CVD is the most common cause of death worldwide, causing an estimated 17.9 million deaths globally (Wang et al., 2016). In the UK CVD is the second most common cause of death after cancer, causing approximately 168,000 deaths in 2017 (British Heart Foundation, 2019). CVD is a preventable cause of premature death and dietary intake is linked to numerous modifiable risk factors of CVD (NICE, 2010). A recent survey of the UK population suggests that current dietary advice to reduce the risk of CVD is not being met (Bates et al., 2020; British Heart Foundation, 2017). In contrast to current public health dietary recommendations which use a 'one size fits all' approach, it has been suggested that a genotype-based personalised approach to dietary recommendations may motivate individuals to make positive changes to their dietary behaviour (Celis-Morales, Lara, et al., 2015).

There is evidence to suggest that SNPs in the *APOE* gene rs7412 (E2) rs429358 (E4) and in the *MTHFR* gene rs1801133 (C/T) are associated with CVD risk; this evidence can be used to provide more effective dietary advice at the individual or genetic subgroup level (Grimaldi et al., 2017). A comprehensive overview of the evidence for the use of *APOE* and *MTHFR* for genotype-based dietary advice is provided in section 1.4.4 and 1.4.5 of the literature review and summarised in Table 1.4. Briefly, a positive dose response has been reported between *APOE* genotype and LDL cholesterol, with lowest concentrations in E2/E2 carriers and highest concentrations in E4/E4 (Khan et al., 2013). Consequently, reduced saturated fat intake has been suggested as a means of reducing CVD risk in individuals with an E4 genotype (Minihane et al., 2007). A common missense SNP of the *MTHFR* gene affects the thermostability of the corresponding enzyme

(Frosst et al., 1995). Hyperhomocysteinaemia has been identified as a risk factor for CVD. Reduced *MTHFR* activity results in increased plasma homocysteine levels and reduced plasma folate levels in TT homozygotes (Liew & Gupta, 2015). Therefore, it is particularly important for T allele carriers to meet folate recommendations to reduce homocysteine levels (Huang et al., 2018).

To date, studies investigating the effect of genotype-based personalised nutrition advice on dietary behaviour have reported mixed findings. Compared to a control group, participants with a risk-associated genotype significantly improved fat quality of their diet (Hietaranta-Luoma et al., 2014), reduced sodium (Nielsen & El-Sohemy, 2014), fat (Horne, Gilliland, O'Connor, et al., 2020), and saturated fat intake (Fallaize et al., 2016), improved their adherence to a Mediterranean diet (Livingstone et al., 2016), were more likely to maintain weight loss (Arkadianos et al., 2007; Vranceanu et al., 2020), and were more likely to make health behaviour changes to reduce AD risk (Chao et al., 2008). In contrast, there was no significant difference compared to a control group in associated behaviours following advice to increase folate intake (O'Donovan et al., 2016), advice related to diabetes risk (Grant et al., 2013) or in response to a weight loss programme (Frankwich et al., 2015). Moreover, Hollands et al. (2016) analysed seven RCTs and reported no significant evidence of a benefit of DNA based risk communication on dietary behaviour change, with a SMD of 0.12 (CI: 0.00-0.24).

Comparisons have also been made between participants informed of a risk-associated genotype and those informed of a non-risk-associated genotype. Participants informed of an *APOE* risk-associated genotype have been reported to make greater changes to saturated fat intake (Fallaize et al., 2016) and made and maintained moderate changes to dietary behaviour which resulted in slight improvements in clinical CVD markers 5.5-6.5 years after disclosure, (Hietaranta-Luoma et al., 2018) compared to participants informed of a non-risk genotype. However, there was no significant difference in folate intake between participants informed of a *MTHFR* risk-associated genotype and those informed of a non-risk-associated genotype, following a recommendation to increase their folate intake (O'Donovan et al., 2016). The aim of disclosure of genetic risk is to motivate behaviour change in these individuals; however, it is also

important to consider the effect of disclosure of a non-risk genotype which has the potential to reduce compliance to health behaviours (Lovegrove & Gitau, 2008).

Unanswered questions remain regarding the efficacy of genotype-based personalised nutrition advice as an intervention for positive dietary behaviour change. Furthermore, the effect of disclosure of a non-risk as well as a risk-associated genotype on dietary behaviour warrants further investigation to ensure there is not a negative impact on dietary behaviour in this group. The present study therefore used behaviour change techniques (BCT) in the context of two SNPs with probable evidence of an interaction with dietary behaviours that affect CVD risk, to motivate positive changes in related dietary behaviours. The aim of the present study was to determine the effect of personalised nutrition advice, based on *APOE* and *MTHFR* genotype, on dietary intake of saturated fat and folate in participants informed of a high-risk genotype compared to those informed of non-risk genotype.

2.2. Methods

2.2.1 Study population

Men and women (aged $\geq$ 18 years) without a current diagnosis of CHD (including angina or heart attack) or stroke/transient ischaemic attack were recruited to take part in the study. Participants were recruited through advertisements and internet postings. Baseline data were collected from 114 participants; 99 participants completed the study.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Institutional Ethical Committee. Written informed consent was obtained from all participants (Appendix 2 and 3). All data were collected and stored according to the Data Protection Act 1998 and the Human Tissue Authority.

2.2.2 Study design

Baseline measures were collected in person and included participants' height, weight, blood pressure, blood lipids, dietary intake, and 10-year cardiovascular risk. A saliva sample was obtained for genotyping. Following genotyping, participants were provided with genotype-based

personalised nutrition advice via email and 10 days after receiving this advice they were asked to complete a second 24-hour dietary recall (figure 2.1).

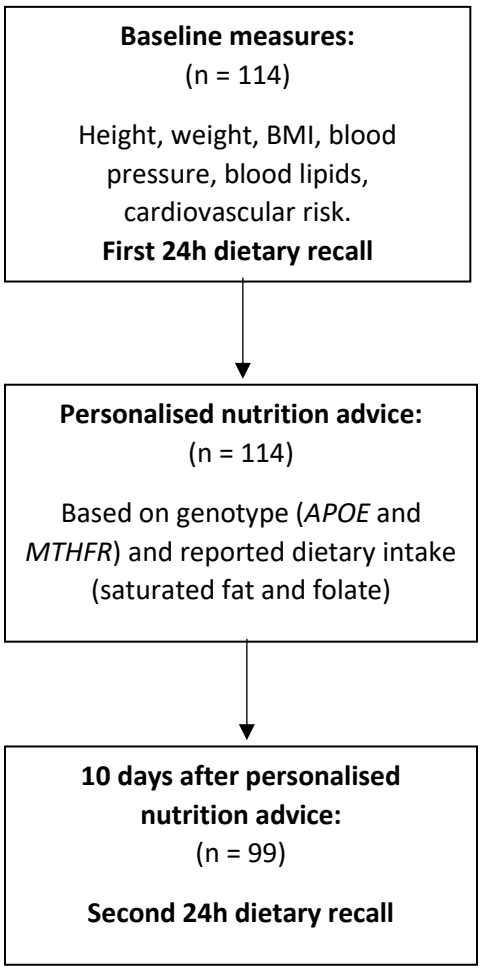

Figure 2.1. Study design flow chart. BMI, body mass index; *APOE*, apolipoprotein E; *MTHFR*, methylenetetrahydrofolate reductase.

2.2.3 Baseline measures

Height was measured without shoes using a free-standing height measure (Seca UK, Birmingham, UK). Weight was measured clothed without shoes or overgarments using a portable scale (MPMS-230 Marsden Weighing Group, Oxfordshire UK). BMI was calculated by dividing participants' weight (kg) by their height (m) squared. Systolic blood pressure (SBP) was measured for each participant using a digital sphygmomanometer (OMRON i-C10, OMRON Healthcare Europe B.V. Hoofddorp, Netherlands). Total cholesterol (TC), HDL, and TAG were measured from

a 35-40 µL capillary blood sample using a point-of-care test system (The CardioChek® Professional Analyser, Polymer Technology Systems Inc., Indianapolis, USA), in accordance with the manufacturers' protocol. Cardiovascular risk was estimated using the QRISK®2-2017 CVD risk calculator.

2.2.4 Dietary intake

Habitual dietary intake was estimated from a 24-hour recall, administered as an online survey, using the multiple-pass approach (Moshfegh et al., 2008) (Appendix 4). Reported dietary intake data (including dietary supplements) were analysed using nutrition analysis software (Nutritics; Nutritics Ltd, Swords, Ireland), to determine energy, saturated fat, and folate intake.

2.2.5 Genotype-based personalised nutrition advice

Participants were provided with personalised nutrition advice based on their *APOE* genotype and *MTHFR* genotype by email (Appendix 5). For *APOE,* a risk-associated genotype was defined as presence of an E4 allele (E3/E4 and E4/E4) and, for *MTHFR,* a risk-associated genotype was defined as presence of a T allele (CT and TT). To improve the reporting, implementation, and evaluation of behaviour change interventions, Michie et al. (2011) developed a taxonomy of BCT for physical activity and healthy eating behaviours, four of which lend themselves to a genotype-based personalised nutrition intervention delivered via email. Firstly, participants were informed for both genotypes whether they had a risk-associated genotype. The framing of this information was designed to promote '*fear arousal*' (BCT 1), for example, for *MTHFR,* those with a risk-associated genotype were informed "You have a genetic variation in the *MTHFR* gene that is associated with a higher cardiovascular disease risk; consequently, it is beneficial for you to keep a healthy intake of folate." This also highlights the '*consequences of their dietary behaviour to them as an individual*' (BCT 2). Conversely, participants with a non-risk genotype were advised to follow healthy eating guidelines as recommended in the Eatwell Guide. Participants were informed of their dietary intake of folate and saturated fat and whether they were meeting current UK recommendations (folate > 200 µg per day; saturated fat < 11% TEI) (Department of Health, 1991). Therefore, participants were encouraged to make a behavioural resolution ('*goal setting*'; BCT 3) to change their dietary behaviour in order to meet dietary recommendations.

Finally, participants were provided with advice on how they could increase their folate intake and reduce their saturated fat intake ('*how to perform the behaviour*'; BCT 4).

2.2.6 DNA isolation and genotyping

Genotyping was performed according to a method described elsewhere (Pilic & Mavrommatis, 2018). In brief, genotyping for *APOE* genotype rs7412 (E2) rs429358 (E4) and *MTHFR* genotype C677T rs1801133 was carried out using the TaqMan® method using qPCR (StepOnePlus Real-time, LifeSciences, Applied Biosystems, CA, USA) with two technical replicates for each sample. The primers and the probes were pre-designed by Applied Biosystems with the following codes; C_904973_10; C_3084793_20; C_1202883_20. The polymerase chain reaction amplification was performed under the conditions specified by the manufacturer. Genotypes were inferred by Thermofisher Connect™ platform. Call rates for all SNPs were above 95%. Genotype frequencies were within Hardy Weinberg Equilibrium for rs1801133 in the *MTHFR* gene (p = 0.904) and for rs7412 in the *APOE* gene (p = 0.760) but not for rs429358 in the *APOE* gene (p = 0.037). However, haplotype frequencies (ε2, 6%; ε3, 82%; ε4, 12%) and participant profiles were similar to previous studies (Fallaize et al., 2016; Schiele et al., 2000).

2.2.7 Statistical analysis

A sample size of 110 was calculated based on a decrease in saturated fat intake by 2% of TEI in the *APOE* risk group (expected ratio of no-risk to risk of 7:3, 1-β=0.8, α=0.05 and standard deviation (SD) = 3.4 g/day). The sample size calculation was conducted using the statistical power analyses software G*Power version 3.1.9.2 (Faul et al., 2007). Statistical analysis was carried out using IBM SPSS Statistics 24 for Windows (IBM Corp, New York, USA). The hypotheses were specified before the data were collected. The analytic plan was pre-specified and any data-driven analyses are clearly identified and discussed appropriately. Saturated fat intake was analysed as a percentage of TEI and folate as µg per 10 MJ. Measures of centrality and spread are presented as means ± SD. Normality of data was assessed using the Shapiro-Wilk test and if data were not normally distributed, where appropriate, it was transformed to enable parametric statistical analysis. A three-way mixed ANOVA was carried out to assess differences between genotypes (non-risk v. risk), meeting recommendations (met v. not met at baseline) and time (pre v. post

advice) on reported dietary intake of saturated fat and folate. Interactions between all independent variables were also investigated. *Post hoc* pairwise comparisons were performed with Bonferroni corrections as appropriate. One sample *t*-tests were carried out to compare actual with recommended saturated fat intakes (Department of Health, 1991). All tests were two tailed and considered statistically significant when $p < 0.05$.

2.3. Results

2.3.1 Participant characteristics

Baseline data including participant characteristics (age, height, weight, BMI) and intermediate CVD risk factors (SBP, TC, HDL, TC:HDL and QRISK) were determined for 117 participants; two participants subsequently withdrew from the study and the single *APOE* E2/E4 participant was removed from analysis because of their low population frequency. The study population was predominantly Caucasian (76%; n=87). Baseline characteristics are presented in Table 2.1 for males and females, and Table 2.2 for genotype; there were no statistically significant differences in baseline characteristics of participants with a risk-associated genotype compared to those with a non-risk genotype.

Table 2.1. Baseline characteristics of male and female participants.

	All (n=114)	Male (n=35)	Female (n=79)
Age (years)	36 ± 11	36 ± 10	36 ± 12
Height (m)	1.69 ± 0.10	1.80 ± 0.08*	1.65 ± 0.06
Weight (kg)	71 ± 15	85 ± 12*	65 ± 12
BMI (kg/m^2)	24.7 ± 4.0	26.3 ± 3.5*	24.0 ± 4.0
SBP (mmHg)	118 ± 16	128 ± 14*	113 ± 15
TC (mmol/L)	4.52 ± 0.95	4.27 ± 1.08	4.63 ± 0.87
HDL (mmol/L)	1.71 ± 0.54	1.36 ± 0.46*	1.87 ± 0.51
TC: HDL	2.90 ± 1.19	3.49 ± 1.61*	2.64 ± 0.83
Qrisk (%)	1.70 ± 3.02	2.99 ± 4.73*	1.12 ± 1.57

Values presented as means ± standard deviations. For non-normally distributed variables analysis conducted on log-transformed values. Independent t-test used to compare between males and females *denotes a significant difference ($p < 0.05$). BMI: body mass index; SBP: systolic blood pressure; TC: total cholesterol; HDL: high-density lipoprotein cholesterol.

Table 2.2. Baseline characteristics of participants for genotype.

	All (n=114)	*APOE* risk (E4+) (n = 23)	*APOE* non-risk (E4-) (n = 91)	*MTHFR* risk (CT/TT) (n = 53)	*MTHFR* non-risk (CC) (n = 61)
Gender (M/F)	35/59	6/17	29/62	14/39	21/40
Age (years)	36 ± 11	33 ± 12	37 ± 11	36 ± 11	37 ± 12
Height (m)	1.69 ± 0.10	1.70 ± 0.09	1.69 ± 0.10	1.69 ± 0.09	1.70 ± 0.10
Weight (kg)	71 ± 15	71 ± 16	71 ± 16	69 ± 13	73 ± 16
BMI (kg/m^2)	24.7 ± 4.0	24.5 ± 3.4	24.7 ± 4.2	24.2 ± 3.7	25.1 ± 4.2
SBP (mmHg)	118 ± 16	116 ± 18	118 ± 16	116 ± 17	119 ± 15
TC (mmol/L)	4.52 ± 0.95	4.52 ± 0.96	4.52 ± 0.96	4.50 ± 0.98	4.54 ± 0.94
HDL (mmol/L)	1.71 ± 0.54	1.79 ± 0.58	1.69 ± 0.54	1.80 ± 0.57	1.64 ± 0.52
TCHDL	2.90 ± 1.19	2.76 ± 1.00	2.94 ± 1.24	2.69 ± 0.87	3.08 ± 1.39
Qrisk (%)	1.70 ± 3.02	0.95 ± 1.27	1.88 ± 3.31	1.33 ± 2.22	2.00 ± 3.58

Values presented as means ± standard deviations. For non-normally distributed variables analysis conducted on log-transformed values. Independent t-test used to compare between risk and non-risk groups, except for gender where chi-square analysis was used. There were no significant differences between groups. BMI: body mass index; SBP: systolic blood pressure; TC: total cholesterol; HDL: high-density lipoprotein cholesterol; *APOE:* apolipoprotein E; *MTHFR*: methylenetetrahydrofolate reductase.

2.3.2 Effects of genotype-based personalised advice on dietary intake of saturated fat

Personalised genotype-based advice did not affect saturated fat intake in participants with a risk genotype who were meeting the saturated fat intake recommendation (n=12) (p = 0.126). However, risk participants who were not meeting the saturated fat recommendation (n=9) reduced their reported saturated fat intake following genotype-based personalised nutrition advice (p = 0.012).

Participants with a non-risk genotype who were meeting the saturated fat intake recommendation (n=38) at baseline increased their saturated fat intake following personalised nutrition advice (p = 0.007), whereas participants with a non-risk-associated genotype who were not meeting the recommendation (n=40) reduced their reported saturated fat intake (p = 0.001).

2.3.3 Effects of personalised advice on meeting the recommendation for saturated fat

In the group of participants who did not meet the saturated fat recommendation, both genotype sub-groups were above the recommended level at baseline (p = 0.001 for risk-associated (n=11) and p < 0.001 for non-risk-associated (n=46)). After the intervention, participants who did not

meet the saturated fat recommendation at baseline and had a risk-associated genotype (n=9), reduced their saturated fat intake to meet the recommendation (mean = 11.9 %TEI; p = 0.409); however, saturated fat intakes of those without a risk-associated genotype (n=40) remained significantly above the recommendation (mean = 12.9 %TEI; p = 0.007). Both genotype groups that met the recommended intake of saturated fat before the intervention continued to meet the recommendation post- intervention Figure 2.2).

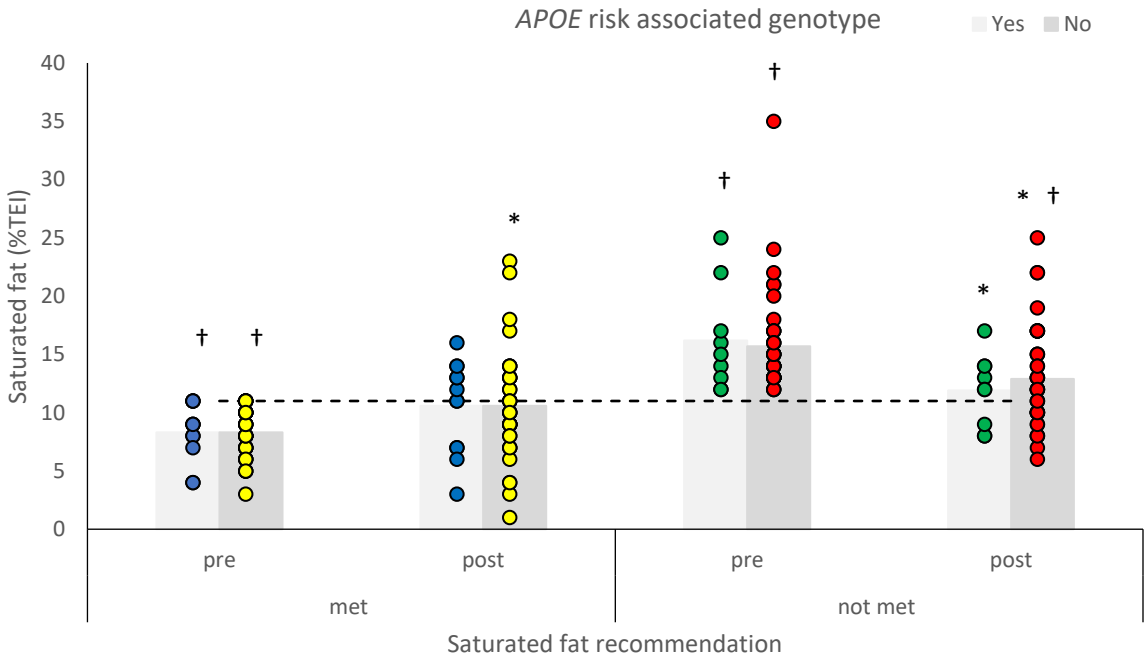

Figure 2.2. Mean reported saturated fat intake (%TEI) of participants with a risk-associated or non-risk-associated genotype for *APOE*, who were meeting or not meeting the saturated fat intake recommendation, before and after personalised nutrition advice. * Significantly different to pre-intake (p<0.05), † significantly different to saturated fat recommendation (p<0.05). Horizontal line indicates recommended intake (Department of Health, 1991). *APOE:* apolipoprotein E.

2.3.4 Effects of genotype-based personalised advice on dietary intake of folate

Participants with a risk-associated genotype who were meeting the folate intake recommendation (n=35) did not significantly change their folate intake following personalised nutrition advice (p = 0.127). In contrast, those who were not meeting the recommendation (n=9) significantly increased their reported folate intake following personalised nutrition advice (p = 0.009).

For participants with a non-risk genotype, those who were meeting the folate intake recommendation (n=39) did not significantly change their folate intake following personalised nutrition advice (p = 0.203), whereas those who were not meeting the recommendation (n=16) significantly increased their reported folate intake following personalised nutrition advice (p = 0.010) (Figure 2.3).

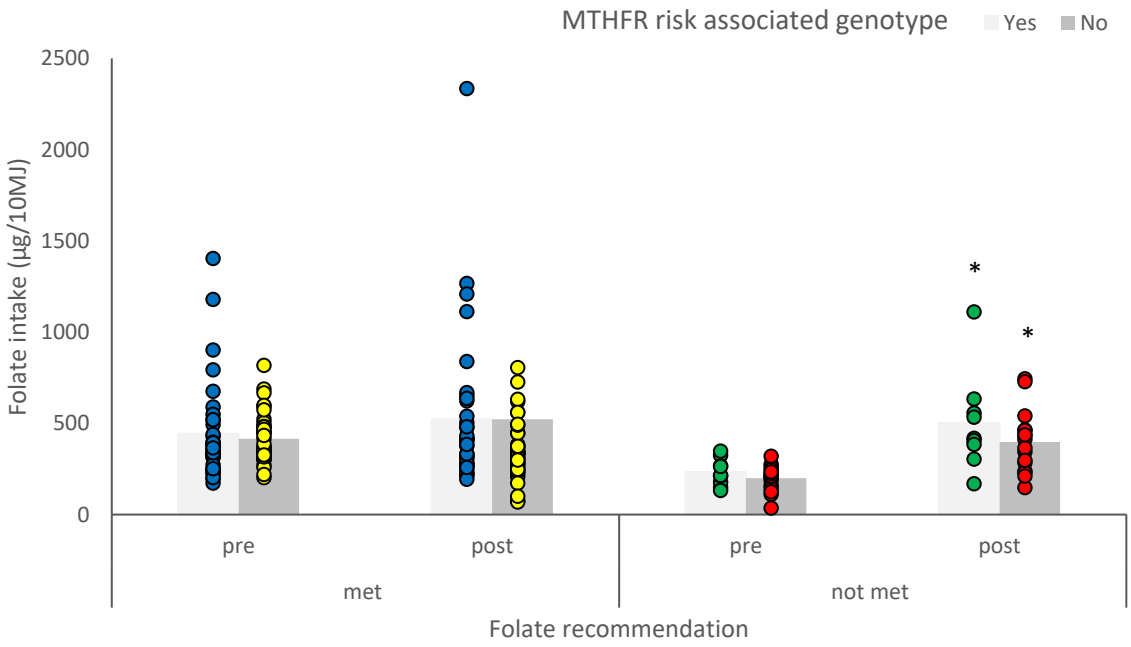

Figure 2.3. Mean reported folate intake (µg /10MJ) of participants with a risk or non-risk-associated genotype for *MTHFR*, who were meeting or not meeting the folate intake recommendation, before and after personalised nutrition advice. * Significantly different to pre-intake (p<0.05). *MTHFR*: methylenetetrahydrofolate reductase.

2.4. Discussion

The aim of the present study was to determine the effect of personalised nutrition advice based on *APOE* and *MTHFR* genotype on dietary intake of saturated fat and folate in participants informed of a risk genotype compared to those informed of a non-risk genotype.

2.4.1 Effects of genotype-based personalised advice on dietary intake

The main findings were that in participants that exceeded the recommended intake for saturated fat, only the group informed of genetic risk decreased their mean intake to the recommended level. The group of participants with intakes that exceeded the recommendation but were informed of non-risk genotype decreased their intake, but mean intake remained above the recommended level. Furthermore, individuals whose baseline saturated fat intakes met the recommendation, increased their saturated fat intake; although this was only significant in the non-risk group and is likely due to lower participant numbers in the risk group. Importantly, both genotype groups maintained a saturated fat intake that met the recommendation. These findings suggest that providing personalised nutrition advice based on *APOE* genotype (incorporating BCT), promotes positive changes in dietary saturated fat intake for groups not meeting the recommendation and that the magnitude of the effect is increased in those informed of a genetic risk. Participants who were not meeting the folate recommendation at baseline and were advised of a genetic risk subsequently increased their intake, as did participants who were informed that they did not have a risk-associated genotype. Similarly, participants who were meeting the folate recommendation did not change their folate intake, irrespective of their genetic risk.

APOE and *MTHFR* genotype were two of five genes for which 1607 participants received genotype-based personalised nutrition advice in the Food4Me project (Celis-Morales, Livingstone, et al., 2015; Fallaize et al., 2016; O'Donovan et al., 2016). Reported responses of genotype-based personalised nutrition advice on dietary behaviour varied depending on the gene and dietary response analysed. As in the present study, intakes of saturated fat were significantly decreased in participants informed of a risk *APOE* genotype compared to the control group, although this was also observed for participants without a risk-associated genotype

(Fallaize et al., 2016). However, in the present study only the participants informed of a risk-associated genotype reduced their saturated fat intake to meet the recommended intake. Similarly, findings for *MTHFR* genotype in the present study showed that folate intake increased in participants informed that they were not meeting the recommendation irrespective of genotype. However, O'Donnovan et al., (2016), reported no significant difference in folate intake after six months between control and risk *MTHFR* genotype group advised to increase their folate intake. Since participants in the Food4Me project received information regarding five different genotypes, the effect of receiving a risk diagnosis for one genotype may have been minimised by the effect of non-risk advice for another, making it more difficult to make comparisons within each genotype and corresponding health behaviour (Meisel, Beeken, et al., 2012). Overall dietary behaviour in the Food4Me participants was assessed by adherence to the Mediterranean diet (MedDiet score). All levels of personalisation of advice resulted in significantly greater improvements in MedDiet score compared to the control group. Furthermore, the greatest improvements were observed in participants receiving genotype-based personalised nutrition advice (Livingstone et al., 2016).

This inconsistent pattern in the effect of genotype-based personalised nutrition advice on behaviour is evident in other research (Frankwich et al., 2015; Grant et al., 2013; O'Donovan et al., 2016). A meta-analysis of seven studies investigating the effect of DNA-based risk estimates on dietary behaviour change reported an SMD of 0.12 (CI: 0.00-0.24) (Hollands et al., 2016). Therefore, the findings of the present study add to the mixed findings reported in previous studies investigating the effect of genotype-based advice on dietary behaviour. The contradictory findings reported may be the result of the heterogeneous study designs used; the delivery of the genotype-based personalised nutrition intervention has varied between studies from remote delivery of information via email (Celis-Morales, Livingstone, et al., 2015) to delivery as part of a 12-week intervention programme (Grant et al., 2013). Studies have been carried out in the context of different chronic diseases and related genes, dietary behaviour has been measured using different outcomes, in different ways with variable durations of follow up and the study participants have ranged from interested volunteers (Celis-Morales, Livingstone, et al., 2015) to those with a family history of a disease (Chao et al., 2008). Participants of the present study were

generally in good health with baseline blood pressure, cholesterol and QRISK2 scores of the study participants suggesting that they were on average at low risk of CVD (NICE, 2014a). Also, by volunteering to take part in the study they demonstrated an interest in their health and genotype-based personalised nutrition, therefore may not be reflective of the general population.

The incorporation of behaviour change theory in genotype-based lifestyle behaviour interventions has been suggested as a way to improve efficacy (Horne et al., 2018; NICE, 2007). In the present study the framing of genetic information to the participant was designed to promote 'fear arousal', to make the participant fearful of the risk of developing CVD to motivate behaviour change (Wilson, 2007). This BCT was not incorporated in the Food4Me project and was suggested as an explanation for not observing a significant difference in dietary behaviour between participants with an *APOE* risk genotype compared to those with a non-risk genotype (Fallaize et al., 2016). The framing of the message to participants in the REVEAL study, as in the present study, was designed to promote 'fear arousal' and they reported, participants with a risk-associated genotype were more likely to make AD related health behaviour changes than those without a risk-associated genotype or control (Chao et al., 2008). Therefore, our findings suggest 'fear arousal' may be an effective BCT to utilise in interventions using genotype-based dietary advice to change behaviour.

2.4.2 Public health application

In line with our findings, previous studies have reported significant positive changes in health behaviour in participants informed of a high *APOE* genetic risk in the context of CVD or AD (Chao et al., 2008; Fanshawe et al., 2008; Hietaranta-Luoma et al., 2014, 2018; Vernarelli et al., 2010). A significant effect of genotype-based personalised nutrition advice has also been reported for other genes related to other dietary outcomes such as, sodium intake (Nielsen & El-Sohemy, 2014) and weight loss (Arkadianos et al., 2007; Vranceanu et al., 2020). Dietary recommendations in the UK are not being met, with mean intakes of saturated fat exceeding recommendations in all age groups studied (Roberts et al., 2018). Public health interventions appear to raise population awareness but fail to translate into modification of behaviour (Croker et al., 2012).

One factor that has been suggested to explain the lack of response to public health campaigns to encourage healthy behaviours is 'optimistic bias'; the phenomenon by which an individual underestimates their own risk of developing a disease, such as CVD, compared to others (Shepherd, 1999). Genotype-based personalised dietary advice enables the personal salience of dietary advice to be highlighted to those with a risk-associated genotype. Personal salience of health advice is more difficult to achieve with a 'one size fits all' approach and has been identified as a key concept in the delivery of behaviour change interventions (NICE, 2007).

Making dietary information personally salient to participants with a risk-associated genotype, could increase optimistic bias for participants with a non-risk-associated genotype (Hunter et al., 2008). The findings of the present study suggest that the pattern of dietary change is similar for participants with a risk and non-risk genotype. This is in accordance with findings of previous studies, non-risk participants not meeting recommendations still make positive dietary behaviour changes, although they may be smaller than those in participants without knowledge of their genotype (Fallaize et al., 2016; Nielsen & El-Sohemy, 2014), which highlights the importance of how nutrigenetic advice is disclosed to participants (Nielsen & El-Sohemy, 2014). Individuals seeking advice from nutrigenetic testing companies will receive information about a panel of genes, some of which are likely to be risk conferring and others protective. Therefore, the receipt of this information alongside dietary advice is likely to be received in a balanced way.

2.4.3 Strengths and limitations

A strength of the present study was the successful collection of dietary information and delivery of health advice via email. The importance of remote delivery of health interventions has been highlighted during the COVID-19 pandemic and acceptability of this mode of delivery may increase (Martin et al., 2020). A further strength was that dietary intake was quantitatively measured rather than participants reporting if they had changed their behaviour (Chao et al., 2008; Fanshawe et al., 2008; Vernarelli et al., 2010) or their intention to change their behaviour (Grant et al., 2013). However, the measurement of habitual dietary intake is a major challenge in all nutrition research that requires participants to self-report their intake. Nevertheless, validity of a multiple pass recall has been demonstrated in comparison to other subjective measures of

dietary intake data (Moshfegh et al., 2008). A control group was not included in the present study; therefore, dietary change was compared pre- and post-intervention, within and between participants with a risk and non-risk-associated genotype. Inclusion of a control group would have enabled the effect of genotype-based dietary advice compared to general dietary advice to be discerned. However, this comparison was not the aim of the current study. The recommendation for saturated fat intake was mistakenly expressed as <11% of TEI, this should have been <10% of TEI or <11% of food energy (Department of Health, 1991). It is unlikely that this technical discrepancy will have significantly altered results. Participant numbers were low; particularly in the *APOE* risk group and those that were not meeting folate recommendations at baseline. Low participant numbers increase the risk of a type II error and may explain why a significant difference was not found in dietary change between risk and non-risk *MTHFR* participants who were not meeting folate recommendations. As in the Food4Me study (Fallaize et al., 2016), the rs*429358* SNP in the *APOE* gene was not in Hardy Weinberg equilibrium. However, haplotype frequencies in the present study (ε2, 6%; ε3, 82%; ε4, 12%) and participant profiles were similar to previous studies (Fallaize et al., 2016; Schiele et al., 2000). Health behaviour change is tasked with both initiation and maintenance of change. Acquiring the motivation to change behaviour is an important step in the initiation of behaviour change (Ryan et al., 2008). The present study assessed the use of genotype-based personalised nutrition advice to motivate the initiation of short-term dietary changes; therefore, maintenance of changes were not evaluated. Considering the attrition rate observed after 10 days, it is likely that the study would have been under powered if the follow-up was extended. Previous studies have demonstrated significant dietary behaviour change 12 months after genotype-based personalised recommendations (Horne, Gilliland, O'Connor, et al., 2020; Nielsen & El-Sohemy, 2014) and, in the longest follow-up to date, those changes were observed more than five years after the intervention (Hietaranta-Luoma et al., 2018). The aim of the present study was to use genotyping to promote adherence to associated general dietary recommendations. Participants were advised of their current intake and how it compared to the general UK recommendation for saturated fat and folate and their genotype and how that may interact with their diet to affect their risk of CVD. Previous studies have used personalised nutrition to provide individualised recommendations based on genotype

that have for example resulted in enhanced weight loss (Arkadianos et al., 2007; Vranceanu et al., 2020). This type of advice is currently being provided by numerous commercial companies (De et al., 2019). Providing more accurate individualised advice which over time provides individuals with greater success because of changes in dietary behaviour may result in greater maintenance of those behaviours. This would be an interesting area for future research in personalised nutrition to promote behaviour change.

2.4.4 Conclusion

In conclusion, genotype-based personalised nutrition advice led to favourable dietary changes in participants who were not meeting dietary recommendations, irrespective of risk or non-risk genotype. In participants not meeting dietary recommendations, only those with a risk *APOE* genotype met saturated fat recommendations following personalised nutrition advice. Therefore, incorporation of genotype-based personalised nutrition advice in a diet behaviour intervention may initiate favourable changes in dietary behaviour. Since, maintenance of positive dietary behaviours is essential to observe health benefits, further research is required to determine the long-term effect of genotype-based personalised dietary advice on dietary behaviour and associated markers of health.

Chapter 3: The effect of genotype-based personalised diet and physical activity advice on healthy-eating motivation in young adults.

This chapter presents the second study of my PhD research which builds on the findings of my first study. In the first study I used a pre-post-test design to compare the effect of genotype-based advice between participants with a risk genotype with those with a non-risk genotype. To enable the effect of genotype-based personalised advice to be isolated from other types of personalised advice this study included a control group as well as a group receiving personalised diet and physical activity advice without the addition of genetics. In terms of the overall research question of the thesis, this study examined the effectiveness of genotype-based dietary and physical activity advice compared to other types of personalised advice, or no advice to affect healthy-eating motivation.

3.1 Background:

Obesity is associated with an increased risk of chronic disease and subsequent burden to both the health of the population and the economy (Bloom et al., 2012; NCD Risk Factor Collaboration, 2016; Saeedi et al., 2019). The prevalence of obesity has risen sharply since the 1990s as a consequence of environmental factors, such as reduced physical activity and increased availability of highly palatable energy dense foods (Speakman, 2007). However, overfeeding studies in twins suggests that there is a genetic component to the risk of obesity (Bouchard et al., 1990). It is likely that genetic and environmental risk factors interact, resulting in an increased likelihood of individuals developing obesity based on their genetics if they have unfavourable lifestyle behaviours (van der Klaauw & Farooqi, 2015). A SNP in the first intron of the *FTO* gene was the first common variant identified that could affect the risk of obesity in the general population and *FTO* is consistently identified in GWAS to explain the largest proportion of inter-individual genetic variation in BMI (Yeo, 2014). There is strong evidence from large well conducted trials and meta-analyses that the risk-associated with *FTO* rs9939609 can be moderated by modification of both saturated fat intake (Corella, Arnett, et al., 2011; Phillips et al., 2012; Sonestedt et al., 2009) and physical activity (Celis-Morales et al., 2016; Kilpeläinen et al., 2011) to affect BMI. A comprehensive overview of the evidence for the use of *FTO* for

genotype-based dietary advice is provided in section 1.4.3 of the literature review and summarised in Table 1.4.

Since 80-90% of individuals that successfully lose weight return to their previous weight, prevention rather than treatment of obesity is a more favourable approach (Rosenbaum & Leibel, 2010). The prevalence of obesity increases with age; in England, 36% of adults aged 65-74 years are obese compared to 13% of those aged 16–24 years (Moody, 2020). Therefore, young adults are an important population to target to prevent this trend from continuing. The transition to higher education and subsequent years at university is a period of risk for weight gain (Deforche et al., 2015; Fedewa et al., 2014), and transition points, such as leaving school in young people, have been demonstrated as a good time to initiate behaviour change (NICE, 2007).

Dietary intake and physical activity have long been identified as modifiable risk factors that can reduce the risk of becoming obese, yet recommendations are not met and worldwide the prevalence of obesity continues to increase (Health Survey for England, 2017; Roberts et al., 2018; The GBD 2015 Obesity Collaborators, 2017). Current public health interventions appear to raise population awareness but fail to translate into modification of behaviour (Croker et al., 2012). Interventions designed to change health-related behaviours are more likely to be successful when theoretical links between the intervention and the behaviour have been considered in the design (Davis et al., 2015; Horne et al., 2017; NICE, 2007; Timlin et al., 2020).

One of the most frequently cited behaviour change theories incorporated in health-related interventions is the TPB (Ajzen, 1991; Davis et al., 2015). The theory states that motivation to perform a behaviour (intention) can be predicted from three independent factors: 1. The extent to which an individual has a favourable appraisal of that behaviour (attitude towards the behaviour), 2. An individual's perceived social pressure to perform or not perform the behaviour (subjective norm) and 3. An individual's perception of how easy or difficult it is to perform the behaviour (PBC). 'Attitude towards the behaviour' is affected by an individual's 'behavioural beliefs', the subjective probability that the behaviour will produce a given outcome or experience. 'Subjective norms' are affected by 'normative beliefs', the perceived behavioural expectations of important referent individuals or groups. 'PBC' is affected by 'control beliefs', the

perceived presence of factors that may facilitate or impede performance of a behaviour (Figure 3.1). The 'intention' and 'PBC' have been demonstrated to account for a large amount of variation in the behaviour, multiple correlations ranging from 0.20 to 0.78 (Ajzen, 1991). Therefore, to elicit behaviour change, an intervention should aim to address one or more of these factors to increase an individual's motivation to perform the behaviour.

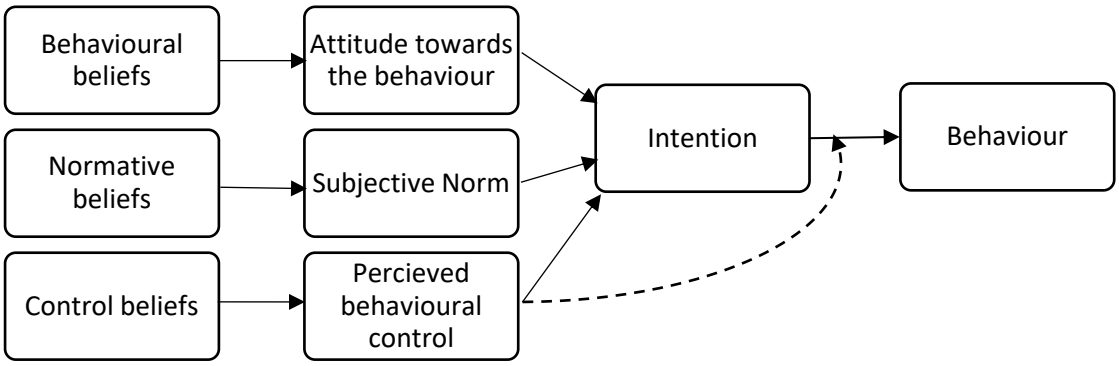

Figure 3.1 The 'Theory of Planned Behaviour' (Ajzen, 1991).

A genotype-based personalised approach to dietary recommendations has been proposed as a means to motivate individuals to make positive changes in their dietary and physical activity behaviour (Celis-Morales, Lara, et al., 2015). Genotype-based advice is delivered in combination with other levels of personalisation (phenotypic, clinical, dietary), with the aim to provide more precise and effective advice as well as to encourage behaviour change (Grimaldi et al., 2017). In the context of the TPB, personalisation of behaviour change advice will affect 'behavioural beliefs' which will create a more favourable 'attitude towards the behaviour'. The provision of this advice from a health care provider may affect 'normative beliefs' which will have a positive effect on 'subjective norms' (Horne et al., 2017). 'Control beliefs' may be affected if instructions are provided on how to meet the advice, which will increase 'PBC' (Ajzen, 1991). Each of these factors should then increase motivation or 'intention' to perform the behaviour and subsequently the actual behaviour.

Experimental analogue (vignette) study designs have been utilised to determine the effect of disclosure of an increased genetic risk of obesity on affective outcome measures including motivation to change behaviour. Analogue studies aim to simulate real world situations by asking participants to imagine given scenarios, in these studies participants were asked to anticipate their response to being informed of genetic risk results. Analogue studies suggest that participants informed of an increased risk of obesity are more motivated to make healthy changes to lifestyle behaviours in comparison to when informed of an average risk (Ahn & Lebowitz, 2018; Frosch et al., 2005; Meisel et al., 2012; Sanderson et al., 2010). This effect was observed in a student population (Frosch et al., 2005; Meisel et al., 2012), the general population (Ahn & Lebowitz, 2018; Sanderson et al., 2010) as well as participants with weight concerns (Meisel et al., 2012).

However, studies that have measured motivation following actual genotype-based advice have not shown such an effect. In the context of risk related to T2D, three studies have demonstrated that communication of genetic risk did not significantly increase intention or motivation to make changes to diet or physical activity behaviour (Godino et al., 2016; Grant et al., 2013), or affect stages of change (Grant et al., 2013; Knowles et al., 2017). One exception was the disclosure of lower genetic risk, which resulted in a smaller percentage of participants increasing their stages of change compared to a control group (Grant et al., 2013). Since these studies have not been carried out in the context of obesity prevention and only one of them was in a healthy population, further research is required to determine whether the findings from analogue studies can be replicated in a study where actual genetic risk of obesity is communicated to a young adult population. Therefore, the aim of the present study was to determine the efficacy of genotype-based personalised dietary and physical activity advice on healthy-eating motivation in a young adult population.

3.2. Methods:

3.2.1. Study population

Undergraduate students aged 18-25 years enrolled at St Mary's University in September 2019 were recruited to participate in the study. Students aged above 25 years, those that were pregnant, lactating, had a chronic disease, had a history of disordered eating, or were following a restricted diet were excluded. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee (SMEC_2018-19_052). Written informed consent was obtained from all participants (Appendix 6). All data were collected and stored according to the Data Protection Act 1998 and the Human Tissue Authority. This study is registered with ClinicalTrials.gov: NCT04096404.

3.2.2. Study design

Baseline measures were collected in person and included participants' height, weight, body fat percentage and WC. A saliva sample was obtained for genotyping for the *FTO* rs9939609 genotype. Participants were asked to complete an online questionnaire to measure physical activity and healthy-eating motivation. Following baseline measures, participants were randomly allocated (stratified by genotype) to one of three groups: 1. Genotype-based personalised advice; 2. Non-genotype-based personalised advice; 3. Control: no advice. Following allocation to groups, participants in groups 1 and 2 received appropriate dietary and physical activity advice via email and one week later all participants were asked to complete the healthy-eating motivation questionnaire for a second time (Figure 3.2).

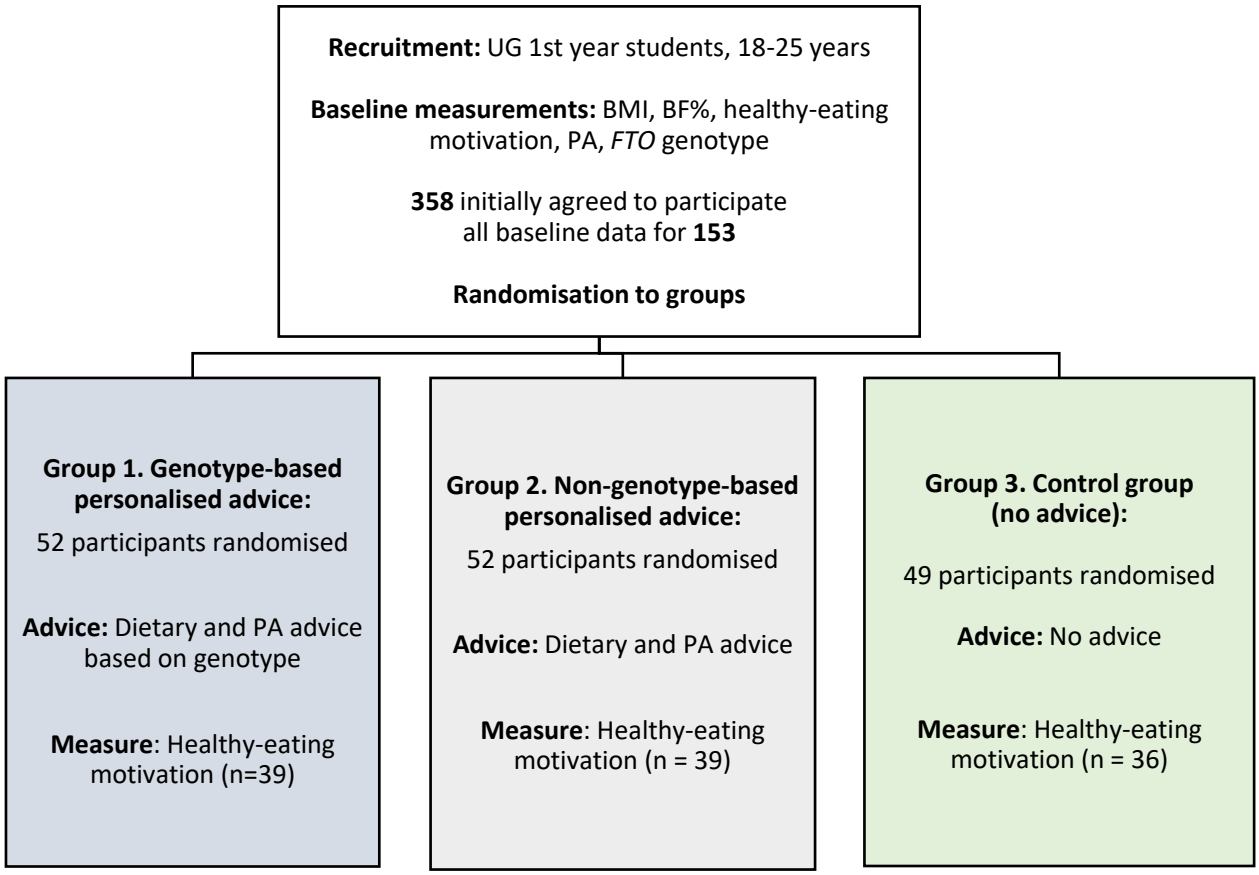

Figure 3.2. Study design flow chart. UG: undergraduate; BMI: body mass index; BF%: body fat percentage; PA: physical activity.

3.2.3 Measures

3.2.3.1 Participant characteristics and adiposity indices

Participants were asked to report their age, ethnicity, programme of study, who they live with, and smoking status. Height was measured to the nearest cm using a free-standing height measure (Seca UK, Birmingham); participants were asked to stand erect without shoes. Weight was measured to the nearest 0.1 kg and body fat percentage to the nearest 0.1% using a bioelectrical impedance analysis system and scales (Tanita BC-418 Foot-to-FootMPMS-230, Tanita Corporation of America, Inc., IL, USA). Participants' weight was measured clothed without shoes or overgarments. BMI was calculated by dividing participants weight (kg) by their height (m) squared. Participants with a BMI in the overweight or obese category (> 25 kg/m^2) were considered to not meet the BMI recommendation (World Health Organisation, 2000).

Recommendations for body fat percentage are not provided by the World Health Organisation or NICE and cut-offs provided by different research papers (Flegal et al., 2009; Gallagher et al., 2000) and manufacturers (MARSDEN; TANITA) vary. In this study, male participants with a body fat percentage > 18% and female participants with a body fat percentage > 31% were considered to not be meeting the recommendation for body fat percentage, these values have been reported to correspond to a BMI of 25 kg/m^2 (WHO Expert Consultation, 2004).

3.2.3.2 DNA isolation and genotyping

Genotyping was performed according to a method described elsewhere (Pilic & Mavrommatis, 2018). In brief, genotyping for *FTO* genotype rs9939609 was carried out using the TaqMan® method using qPCR (StepOnePlus Real-time, LifeSciences, Applied Biosystems, CA, USA) with two technical replicates for each sample. The polymerase chain reaction amplification was performed under the conditions specified by the manufacturer. Genotypes were inferred by Thermofisher Connect™ platform. Call rate for rs9939609 was above 95%. Genotype frequencies for *FTO* genotype rs9939609 were within Hardy Weinberg Equilibrium (p = 0.998). Individuals with an A allele (A+) were considered the 'risk-associated' genotype, those without (A-) were considered the 'non-risk-associated' genotype.

3.2.3.3 Physical activity

Physical activity was measured using the EPIC Physical Activity Questionnaire (EPAQ2) (Wareham et al., 2002) (Appendix 7). The self-reported questionnaire measured participants' physical activity in the previous year. Closed questions were arranged in three sections to estimate duration, intensity, and frequency of physical activity at home, at work, and for recreation. Energy expenditure was estimated by multiplying the time spent on each moderate or vigorous intensity activity (min/week) by the metabolic equivalent (MET) for that activity. Current guidelines for physical activity in the UK are to accumulate at least 150 minutes of moderate intensity activity and/or 75 minutes of vigorous intensity activity each week (Department of Health and Social Care, 2019), which equates to 500 MET minutes/week (Kaminsky & Montoye,

2014). Participants reporting < 500 MET minutes/week of moderate or vigorous intensity physical activity were considered to not meet the recommendation for physical activity.

3.2.3.4 Healthy-eating motivation

Participants' motivation to eat healthily was measured using the Healthy Eating Motivation Score (Naughton et al., 2015) (Appendix 8). The healthy-eating motivation score was calculated by recording the mean score from participants seven items (Table 3.1). Items five and six were reverse scored for analysis. Cronbach's alpha (α) for the healthy-eating motivation score items was 0.82; this value is similar to the alpha score of 0.81 reported by Naughton et al. (2015). A α > 0.7 has been suggested to indicate adequate internal consistency (Tavakol & Dennick, 2011).

Table 3.1. Healthy-eating motivation items.

Items
1. It is important that the food I eat contains vitamins and minerals
2. It is important that the food I eat keeps me healthy
3. It is important that the food I eat is nutritious
4. I always follow a healthy and balanced diet
5. I eat what I like and I do not worry about healthiness of food **R**
6. The healthiness of food has little impact on my food choices **R**
7. It is important that the food I eat helps me control my weight

R Items reverse scored for analysis.

3.2.4 Personalised advice

BCT were utilised in the design and implementation of advice provided to group 1 and 2 to align with constructs of the TPB, and are indicated in Table 3.2. Incorporated BCTs included: 'fear arousal', 'consequences of their behaviour to them as an individual', 'goal setting', and 'how to perform the behaviour' (Michie et al., 2013). With reference to the TPB, 'fear arousal' and 'consequences of their behaviour to them as an individual' were incorporated to target their 'behavioural beliefs'. 'Goal setting' and 'how to perform the behaviour' were both incorporated to target 'control beliefs'. The provision of this advice by a university lecturer and registered nutritionist was aimed to target their 'normative beliefs'.

Participants in group 1 and 2 were informed of their current BMI, body fat percentage, and physical activity status, of the recommendation for each measure and if they were meeting the recommendation. Participants in group 1 were also provided with personalised advice based on their *FTO* genotype. Both groups were provided with information about what to do to reduce their risk of weight gain, which included practical tips on the basics of physical activity and healthy-eating to help make healthier choices (Appendix 9). Participants in group 3 were not provided with any advice (Table 3.2).

Table 3.2. Personalised advice provided to participants in group 1, 2 and 3; behaviour change techniques utilised are indicated.

Advice	**Group 1:** Genotype-based (Risk)	**Group 1:** Genotype-based (Non-risk)	**Group 2:** Non-genotype-based	**Group 3**
Importance	"Obesity is a risk factor for numerous chronic diseases including diabetes, cardiovascular disease and cancer. The risk of individuals to develop obesity is highly variable. Some of this variation may be explained by the interaction between an individual's DNA variation (genotype) and their diet and physical activity. You can reduce your risk of becoming obese by adhering to the diet and physical activity advice below" **BCT**: fear arousal; consequences of their behaviour to them as an individual.		"Obesity is a risk factor for numerous chronic diseases including diabetes, cardiovascular disease and cancer. You can reduce your risk of becoming obese by adhering to the diet and physical activity advice below" **BCT**: fear arousal; consequences of their behaviour to them as an individual.	No advice
BMI	Informed of their current BMI, recommendation and if they were meeting the recommendation; **BCT**: goal setting.			No advice
Body fat percentage	Informed of their current BF%, recommendation and if they were meeting the recommendation; **BCT**: goal setting.			No advice
Physical activity	Informed of their current physical activity, recommendation and if they were meeting the recommendation; **BCT**: goal setting.			No advice
Genotype-based	"You have a genetic variation in the *FTO* gene that is associated with a higher risk of obesity; consequently, it is important for you to meet recommendations for physical activity and dietary intake of energy, saturated fat and sugar." "Research suggests that individuals with your genotype are more likely to become obese. Obesity is linked to numerous chronic diseases such as cardiovascular disease, diabetes and cancer. Individuals with your genotype that are more physically active are less likely to become obese. Individuals with your genotype that eat less saturated fat are less likely to become obese." **BCT**: fear arousal; consequences of their behaviour to them as an individual.	"You do not have a genetic variation in the *FTO* gene that is associated with a higher risk of obesity; you should follow healthy eating and physical activity guidelines."	No advice	No advice
Practical	Provided with information about what to do to reduce their risk of weight gain which included practical tips on the basics of physical activity and healthy eating to help make healthier choices. **BCT**: goal setting and how to perform the behaviour.			No advice

BCT: behaviour change technique; BF%: body fat percentage; BMI: body mass index.

3.2.4 Statistical analysis

According to a sample size calculation, to identify a medium effect size (Cohen's d = 0.5), for a two-tailed test, with a power of 0.8 and probability of 0.05, 34 participants per group were required. The power calculation was conducted using the statistical power analyses software G*Power version 3.1.9.2 (Faul et al., 2007). Statistical analysis was carried out using IBM SPSS Statistics 26 for Windows (IBM Corp, New York, USA). Internal consistency of the healthy-eating motivation score was assessed using Cronbach's α. Measures of centrality and spread are presented as means ± SD; categorical data are presented as frequencies and percentages. Normality of data was assessed using the Shapiro-Wilk test. Baseline continuous measures were compared between groups using a one-way ANOVA for normally distributed data or an Independent-Samples Kruskal-Wallis test for data that was not normally distributed. Categorical variables were compared between groups using a Chi-squared Test. Two-way mixed ANOVA was used to determine the effect of different levels of personalised advice (control, non-genotype-based advice, genotype-based advice) and time (pre v. post advice) on healthy-eating motivation scores. A three-way mixed ANOVA was carried out to assess differences between groups (control, non-genotype-based advice, genotype-based advice), compliance with recommendations (met v. not met at baseline) and time (pre v. post advice) on healthy-eating motivation score. Interactions between all independent variables were also investigated. All tests were two tailed and considered statistically significant when $p < 0.05$.

3.3. Results:

3.3.1 Baseline data

The majority of participants were female (56%), were of white ethnicity (78%) with a mean age of 19 ± 2 years. Fifty seven percent of participants were living in student accommodation, 68% were studying a science based undergraduate degree and 87% were non-smokers. The mean healthy-eating motivation score of 5.0 from a maximum of 7 suggests participants were positively oriented to healthy eating. The mean BMI of all participants was within the healthy category (23.5 ± 3.7 kg/m^2) and 25% of participants were classified as overweight or obese (BMI > 25 kg/m^2). The mean body fat percentage of both male (14.2 ± 6.1%) and female (28.2 ± 7.3%) participants was within the healthy range. Twenty-three percent of male and 27% of female participants had a body fat percentage above the recommendation for body fat percentage. Mean reported physical activity levels (6116 ± 4384 MET mins/week) were above recommended levels for physical activity and 97% of participants were meeting the recommendation for physical activity. There were no significant differences in any of the baseline characteristics between groups ($p \geq 0.05$; Table 3.3). Thirty-nine participants did not complete the study (Figure 3.2). There was no significant difference in age, BMI, body fat percentage, physical activity level, or baseline healthy-eating motivation score between participants included in analysis and those that did not complete the second healthy-eating motivation questionnaire ($p \geq 0.05$). There was no significant difference in BMI, body fat percentage, or physical activity level between *FTO* genotype groups ($p \geq 0.05$).

Table 3.3. Participant baseline characteristics (n = 153).

		n (%) or mean ± sd
Gender	*Men*	68 (44)
	Women	85 (56)
Age (years)		19 ± 2
Ethnicity	*White*	120 (78)
	Asian or Asian British	12 (8)
	Black or Black British	9 (6)
	Other ethnic group	12 (8)
Living situation	*At home with parent*	49 (32)
	Student accommodation	87 (57)
	Other	17 (11)
Undergraduate programme	*Science based*	104 (68)
	Non-science based	49 (32)
Smoking status	*Non-smoker*	133 (87)
	Light smoker	13 (9)
	Moderate	2 (1)
	Ex-smoker	5 (3)
Genotype	TT	67 (44)
	AT	60 (39)
	AA	26 (17)
BMI (kg/m^2)	*Men and women*	23.5 ± 3.7
	Meeting recommendation	115 (75)
Body fat (%)	*Men*	14.2 ± 6.1
	Meeting recommendation	52 (77)
	Women	28.2 ± 7.3
	Meeting recommendation	62 (73)
Physical activity (MET mins/week)		6116 ± 4384
	Meeting recommendation	149 (97)
Healthy-eating motivation score		5.0 ± 1.0

BMI: body mass index; MET: metabolic equivalent.

3.3.2 The effect of levels of advice on healthy-eating motivation

3.3.2.1 All participants

A two-way ANOVA was used to assess the effect of level of advice provided on healthy-eating motivation before and after the intervention. There was no significant effect of time (F = 0.025, p = 0.875), group (F = 0.176, p = 0.839), or time group interaction on healthy-eating motivation score (F = 0.881, p = 0.417) (Figure 3.3).

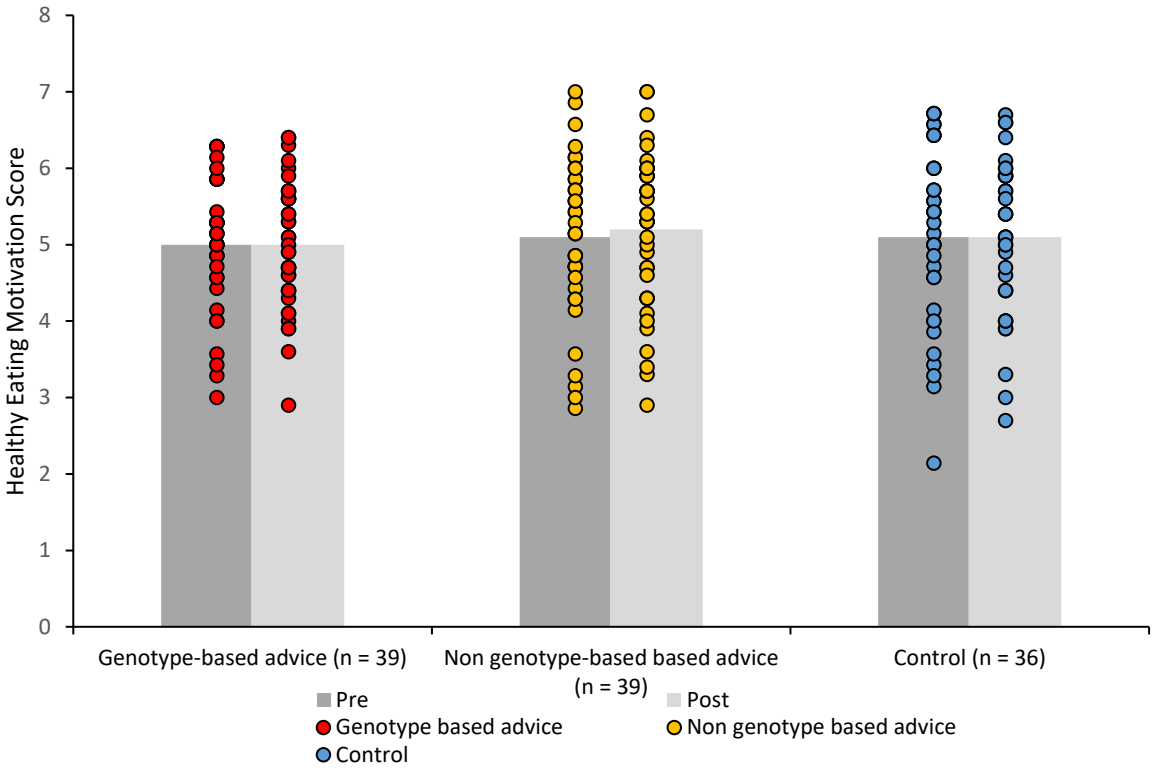

Figure 3.3 Mean healthy-eating motivation score pre and post advice for participants provided with genotype-based personalised advice, non-genotype-based personal advice and no advice.

3.3.2.2 Participants informed of a risk v non-risk-associated genotype

Within the genotype-based personalised advice group, a two-way ANOVA was used to assess the effect of being informed of a risk v. a non-risk-associated genotype on healthy-eating motivation before and after the intervention. There was a significant effect of risk on healthy-eating motivation score (F = 4.955, p = 0.032). Participants with a risk-associated genotype had a significantly higher healthy-eating motivation score than participants with a non-risk-associated genotype. However, there was no significant effect of time (F = 0.054, p = 0.818), or time risk interaction on healthy-eating motivation score (F = 1.383, p = 0.287). Therefore, healthy-eating motivation score was unchanged in either group following disclosure of genotype-based advice (Figure 3.4).

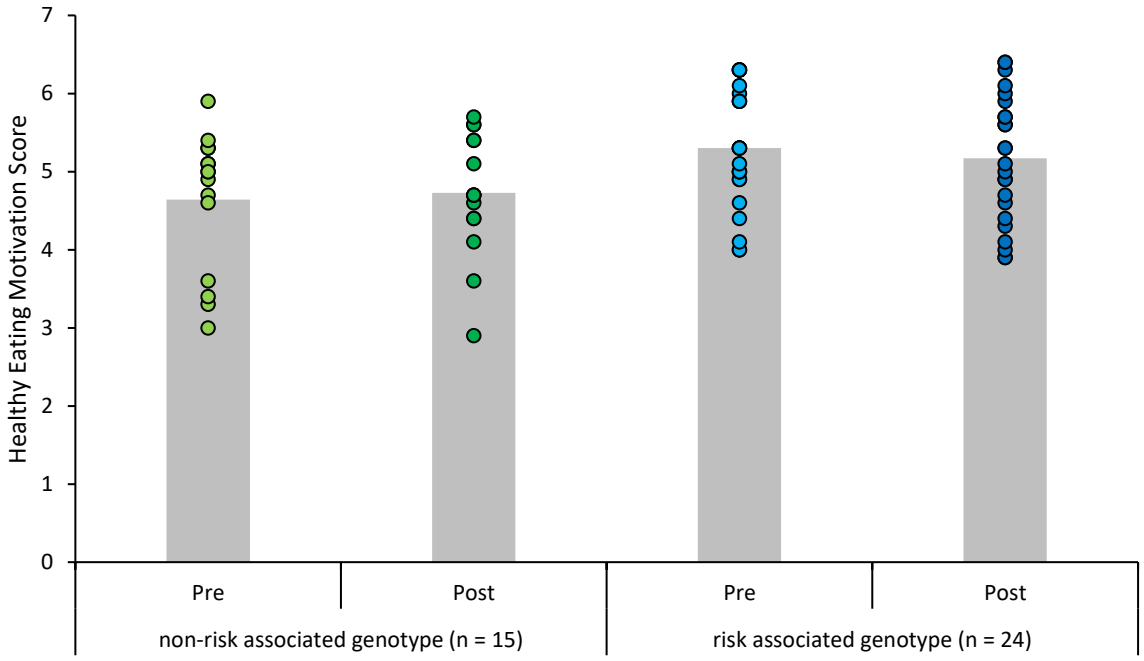

Figure 3.4 Mean healthy-eating motivation score pre and post advice for participants within the genotype-based personalised advice group, informed of a risk-associated genotype or a non-risk-associated genotype.

3.3.3 BMI recommendation

Healthy-eating motivation score was compared before and after advice, between participants meeting or not meeting the BMI recommendation and also between groups. There was no significant time × compliance × group interaction on healthy-eating motivation (F = 1.101, p = 0.336). There were no significant two-way interactions ($p \geq 0.05$) or main effects of time, compliance, or group ($p \geq 0.05$) (Figure 3.5).

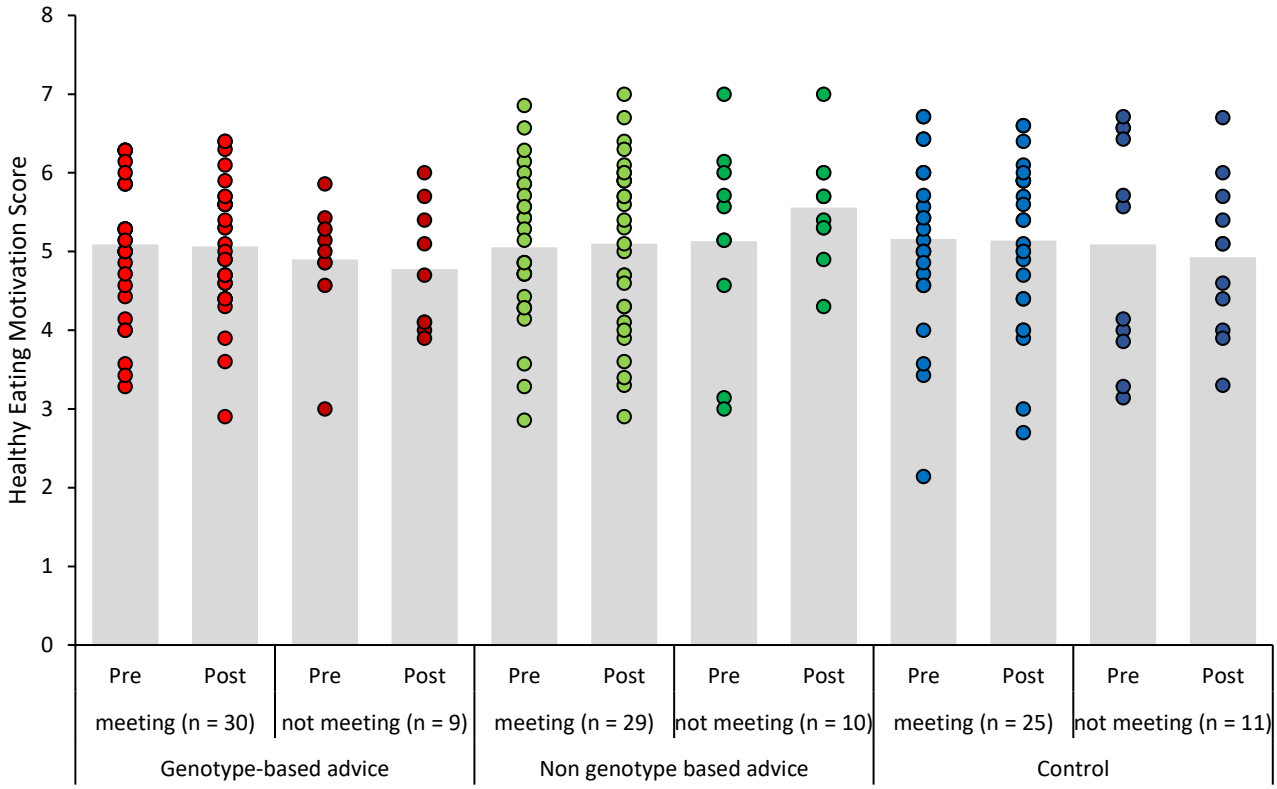

Figure 3.5. Mean healthy-eating motivation score pre and post advice for participants meeting and not meeting BMI recommendation (>25 kg/m^2), provided with genotype based personalised advice, non-genotype-based personal advice and no advice.

3.3.4 Body fat percentage recommendation

Healthy-eating motivation score was compared before and after advice, between participants meeting or not meeting the body fat percentage recommendation, and between groups. There was no significant interaction between time, compliance and group (F = 0.958, p = 0.387). There were no significant two-way interactions ($p \geq 0.05$) or main effects of time, compliance or group ($p \geq 0.05$) (Figure 3.6).

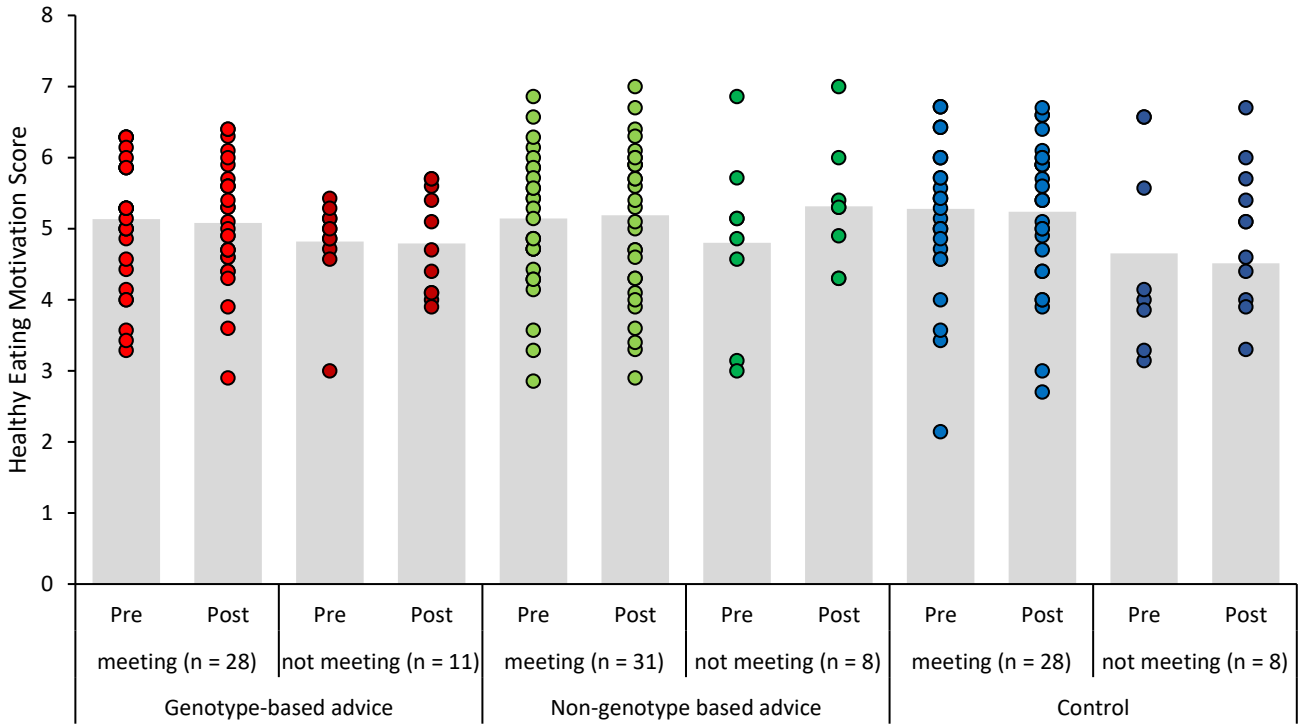

Figure 3.6. Mean healthy-eating motivation score pre and post advice for participants meeting and not meeting body fat recommendation (men: >18%; women: >31%), provided with genotype based personalised advice, non-genotype-based personal advice and no advice.

3.4. Discussion:

3.4.1 Aim and summary of findings

The aim of the present study was to determine the efficacy of genotype-based personalised dietary and physical activity advice on healthy-eating motivation in young adults. The findings suggest that genotype-based personalised dietary advice did not affect healthy-eating motivation: when participants were analysed as a whole, when analysed in those informed of a risk or non-risk-associated genotype, or when analysed in those meeting or not meeting the BMI or body fat percentage recommendation. Healthy-eating motivation was also unaffected by non-genotype-based personalised advice or no advice.

3.4.2 Genotype-based personalised advice to motivate healthy eating

The null findings of this study are in agreement with previous studies that have measured motivation or intention to eat a healthy diet following actual genotype-based advice (Godino

et al., 2016; Grant et al., 2013; Knowles et al., 2017). Although these studies were carried out in the context of T2D rather than obesity, the lifestyle behaviours they were aiming to motivate were comparable. It was hypothesised that the inclusion of genetic risk within personalised dietary advice would increase the personal salience of recommendations, positively influencing behavioural beliefs and subsequently motivate healthy eating behaviour (Horne et al., 2017). Previously, vignette studies which had asked participants to imagine they had received results of genetic testing for obesity, suggested that their motivation to eat healthily would increase following a high genetic risk result (Ahn & Lebowitz, 2018; Frosch et al., 2005; Meisel, Walker, et al., 2012; Sanderson et al., 2010). However, in the present study, although healthy-eating motivation score was significantly higher in participants with a risk associated genotype compared to those with a non-risk-associated genotype, healthy-eating motivation did not change significantly in either group following genotype-based advice. The significant difference in healthy-eating motivation score between the risk-associated genotype group and the non-risk associated genotype group was apparent prior to disclosure of genotype-based advice. This difference is likely a chance finding since these participants were not aware of their genotype at this time point, furthermore there was no significant difference in healthy-eating motivation between the risk and non-risk-associated genotype participants within group 2 or 3.

The personalised advice provided to both the genotype-based and non-genotype-based groups was delivered using BCT to target constructs of the TPB that could subsequently increase participants' intention or motivation to eat a healthy diet (Ajzen, 1991; Horne et al., 2017; Michie et al., 2013). There are several possible explanations why genotype-based advice did not translate to increased healthy-eating motivation. Vignette studies overestimate predicted behaviours in response to genetic testing scenarios (Lerman et al., 2002; Persky et al., 2007). This may explain the contradictory findings between vignette and actual studies of participants' intentions following disclosure of genotype-based advice. Additionally, participants may have viewed genetic-risk as deterministic and consequently developed a fatalistic attitude in response to disclosure of a high genetic risk for obesity (Ehrlinger et al., 2017). Compared to phenotypic health outcomes, such as high blood cholesterol that can be changed through lifestyle modification, genes are not modifiable and therefore changes in behaviours to address outcomes linked to genetics may be inaccurately

assessed by participants to be beyond their control (Marteau & Weinman, 2006). In the current study the wording of advice was provided carefully to avoid this inaccurate interpretation. Participants were clearly told that genes can interact with lifestyle behaviours '*Individuals with your genotype that eat less saturated fat are less likely to become* obese'; therefore, it should be unlikely that this would explain the lack of an effect on healthy-eating motivation. Most participants in the present study were meeting recommendations for BMI, body fat percentage, and physical activity; furthermore, based on their baseline healthy-eating motivation score they were positively oriented to healthy eating (Naughton et al., 2015). The study population of young adults was deliberately targeted with a view to prevent rather than treat overweight and obesity. Therefore, in this young, physically active and relatively healthy population, with a baseline positive orientation towards motivation for healthy eating, maintenance of their current behaviour was what was required. As a consequence an unchanged motivation score in response to disclosure of a risk-associated genotype should be considered a positive outcome. Furthermore, the response of individuals informed of a non-risk-associated genotype should be considered; these individuals may inaccurately conceive that they are unaffected by poor lifestyle behaviours that increase risk of obesity, the so-called genetic invincibility effect (Ahn & Lebowitz, 2018). Previous research reported that participants that received imagined feedback of a non-risk-associated genotype reported reduced worth of the importance of diet and exercise and an increased likelihood to select unhealthy food (Ahn & Lebowitz, 2018). In the present study participants informed of a non-risk-associated genotype were also advised of the influence diet and physical activity behaviours have with risk of obesity. Actual disclosure of a non-risk-associated genotype in the present study did not affect healthy-eating motivation score, which is in line with other studies that disclosed actual genetic risk (Grant et al., 2013).

3.4.3 Strengths and limitations

The provision of actual rather than imagined genotype-based advice was provided to participants in the present study; therefore, the subsequently reported motivation of participants to eat a healthy diet provides stronger evidence than that reported from vignette studies (Lerman et al., 2002; Persky et al., 2007). The present study adds to a small number of previous studies that have investigated the response to genotype-based personalised

advice on healthy-eating motivation. A limitation of these studies is that healthy-eating motivation, intention or stages of change were secondary outcomes (Godino et al., 2016; Grant et al., 2013; Knowles et al., 2017). The present study was designed to measure change in body weight as the primary outcome; however, due to issues with data collection during the COVID-19 pandemic, healthy-eating motivation score was the only planned outcome that could be utilised. It is a limitation of the study that within the group that received genotype-based advice there was a significant difference in baseline healthy-eating motivation score between participants with a risk v. a non-risk-associated genotype. As, discussed above this is likely a chance finding since there was no significant difference in healthy-eating motivation score between risk and non-risk-associated genotype participants in groups 2 and 3. The present study measured motivation to eat healthily; although the TPB has demonstrated that intention to perform a behaviour is strongly linked to the actual behaviour (Ajzen, 1991), it was not possible to measure participants' eating behaviour in response to the advice.

3.4.4 Recommendations for further research

Although, in the present study we did not observe an effect of BMI or body fat percentage on motivation to eat a healthy diet. Previous research suggests that compared to normal weight, overweight individuals are more interested in genotype-based advice (Bayer et al., 2021; Stewart-Knox et al., 2009; Vallée Marcotte et al., 2018) and more motivated to eat a healthy diet following disclosure of a high genetic risk (Frosch et al., 2005). Further research should be conducted to determine the effect of genotype-based personalised advice in populations that are healthy compared to those that are already 'at-risk' of developing NCD such as T2D and CVD.

The findings from this study suggest that healthy-eating motivation in relatively healthy young adults was not influenced by genotype-based personalised advice. However, genotype-based personalisation of advice offers a tool to increase the personal salience of healthy lifestyle advice in preventative interventions to be delivered earlier in the lifespan. A deeper understanding of additional psychological factors that may interact with how genotype-based advice is perceived by young adults is required to target and develop interventions in this population appropriately.

3.4.5 Conclusion

In conclusion, the findings of the present study suggest that genotype-based personalised advice for the prevention of obesity does not affect healthy-eating motivation in young adults. Further research is needed to understand perceptions of genotype-based personalised nutrition in different population groups including healthy versus 'at-risk', and young adults if it is to be used within interventions for the prevention of obesity.

Chapter 4: The efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2D or obesity: a systematic review and meta-analysis.

In this chapter I present the third study of my PhD. The contradictory findings of my first two studies add to the already conflicting research to assess the effect of genotype-based diet and physical activity advice to promote increased motivation and behaviour change. In terms of the overall research question of the thesis, this chapter evaluates the efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2D or obesity in the general population and individuals that are at-risk of CVD or T2D. This study was published in Nutrition Reviews in February 2023.

4.1 Background

NCDs are the leading cause of mortality worldwide and are responsible for 75% of 'premature deaths', defined as deaths of individuals aged between 30 and 69 years (GBD 2017 Risk Factors Collaborators, 2018; World Health Organisation, 2018). The prevention of NCDs has been identified as a key focus in the promotion of health globally (UN General Assembly, 2015), the importance of which has been further highlighted since NCDs are a major risk factor for adverse outcomes in individuals with COVID-19 (Department of Health & Social Care, 2020; Kluge et al., 2020). Obesity, T2D, and CVD are inextricably linked; obesity increases the risk of developing T2D and both obesity and T2D increase the risk of CVD (de Gonzalez et al., 2010; Singh et al., 2013). Maintaining a healthy diet and being physically active have been identified as key modifiable risk factors for the prevention of obesity, T2D, and CVD (Dunkley et al., 2014; Hu et al., 2001; Yusuf et al., 2004; Zheng et al., 2017). Findings from the Global Nutrition Report 2021 suggest that most countries are not on course to meet Global NCD diet-related targets by 2025; specifically, no countries are on course to meet the target of halting the rise in adult obesity (Global Nutrition Report, 2021).

One factor that has been suggested to explain the lack of response to public health campaigns to encourage healthy behaviours is 'optimistic bias'; the phenomenon by which an individual underestimates their own risk of developing a disease, such as CVD, compared to others (Shepherd, 1999). Personal salience of health advice is more difficult to achieve with a 'one

size fits all' approach and has been identified as a key issue in the successful delivery of behaviour change interventions (NICE, 2007). Personalised nutrition has been defined by Stewart-Knox et al. (2013) as "healthy eating advice that is tailored to suit an individual based on their own personal health status, lifestyle, and/or genetics''. Dietary and physical activity advice can be personalised by providing information to an individual based on their current dietary or physical activity behaviour, phenotypic or clinical markers of health, or their genetics (Grimaldi et al., 2017). The aim of personalised health advice is to provide an individual with more precise and effective dietary or physical activity advice and to motivate behaviour change (Grimaldi et al., 2017).

Several studies have reported favourable effects of genotype-based personalised nutrition advice on dietary and physical activity behaviour. Compared to a control group, participants informed of a risk-associated genotype significantly improved fat quality of their diet (Hietaranta-Luoma et al., 2014), reduced sodium intake (Nielsen & El-Sohemy, 2014), were more likely to maintain weight loss (Arkadianos et al., 2007; Vranceanu et al., 2020), and were more likely to make health behaviour changes to reduce AD risk (Chao et al., 2008). Conversely, no significant effects on behaviour were reported in response to diabetes risk (Grant et al., 2013) and a weight loss programme (Frankwich et al., 2015). In the Food4Me study, genotype-based personalised advice led to significantly greater adherence to a Mediterranean diet compared to other levels of personalised advice (Livingstone et al., 2016). However, any level of personalised nutrition advice (including genotype) led to reduced saturated fat intake compared to a control group (Fallaize et al., 2016), but had no effect on folate intake (O'Donovan et al., 2016) or physical activity (Marsaux et al., 2015). One reason for inconsistency in findings may be related to the populations included within studies. Study participants have ranged from interested volunteers (Celis-Morales, Livingstone, et al., 2015) to those with a family history of a disease (Chao et al., 2008). Studies have consistently reported that participants with either personal or family history of disease are more willing to undergo genetic testing (Bayer et al., 2021; Stewart-Knox et al., 2009; Vallée Marcotte et al., 2018). Therefore, studies that have included an at-risk population may be more likely to observe a change in behaviour.

Several systematic reviews and meta-analyses have been carried out into the effect of personalised communication of disease risk on changes in lifestyle behaviours (Hollands et al., 2016; Horne et al., 2018; Jinnette et al., 2020; Li et al., 2016; Marteau et al., 2010). While an early Cochrane review reported a significant beneficial effect of genetic risk estimates of disease on dietary behaviour change (Marteau et al., 2010). An updated meta-analysis by Hollands et al. (2016), which analysed dietary data from seven clinical studies reported little or no significant evidence of a benefit of DNA-based risk communication on dietary behaviour change, with a standardised mean difference (SMD) of 0.12 (95% CI 0.00 to 0.24, p = 0.05). For physical activity behaviour both reviews reported no effect of DNA-based risk communication (Hollands et al., 2016; Marteau et al., 2010); the updated review pooled data from six studies investigating physical activity, with a SMD of -0.03 (95% CI -0.13 to 0.08, p = 0.62) (Hollands et al., 2016). The authors concluded that there was a small effect of genetic risk communication on dietary behaviours, but their findings did not support the use of DNA-based risk communication to motivate behaviour change. Li et al. (2016) investigated studies providing genetic risk testing and communication in relation to obesity, T2D, and CVD on dietary intake and physical activity behaviours. Due to heterogeneity in the dietary outcome measures they did not perform a meta-analysis and they concluded that there was an inconsistent impact of genetic risk on dietary behaviour. Only one study was identified that measured the impact of genetic risk communication on physical activity behaviour and the authors reported no significant effect (Li et al., 2016). More recently, two systematic reviews have been published. Horne et al. (2018) did not identify a cause-effect relationship between genetic testing and health behaviours; that review included studies investigating diet and physical activity behaviour as well as smoking. Based on their systematic review, Horne et al. (2018) reported that nutrition was the most promising area of behaviour change. Jinnette et al. (2020) evaluated the effect of personalised interventions (genotype-based and non-genotype-based) on changes in dietary intake. They concluded that compared to other forms of personalisation there was no evidence of the addition of genetic risk as being superior or more effective in improving diet.

The inconsistent findings reported in individual studies that have investigated the effect of genotype-based advice on behaviour change, inconclusive statements from previous meta-analyses and systematic reviews, plus recent publications in this research area provide a

rationale for a further systematic review and meta-analysis of the literature. Therefore, the aim of this review is to evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2D or obesity in the general population and individuals that are at-risk of CVD or T2D.

4.2 Methods

The systematic review and meta-analysis was conducted following guidance from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2022) and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021) (Appendix 10). The protocol was registered with PROSPERO (CRD42021231147).

4.2.1 Eligibility criteria

Studies were eligible RCTs or non-randomised studies on interventions (NRSIs). Participants of eligible studies were adults (aged 18 years and above) from the general population or adults at-risk of T2D or CVD (such as having a family history, overweight or meeting any of the criteria for metabolic syndrome). Studies were included if they contained a genotype-based dietary and/or physical activity advice intervention that aimed to change dietary and/or physical activity behaviour. The mode of delivery of the intervention could be in person or remote. Eligible studies needed to include a comparator group; this could be a control group which received no advice, general advice, or non-genotype-based personalised advice. In studies with multiple arms, the arm that most clearly isolated the effects of genotype-based advice was chosen as the comparator. Only articles published in English were included. Observational studies, animal studies, and studies without a control group were excluded as were studies with participants under the age of 18 years or populations diagnosed with CVD or T2D. Obesity is a risk factor for both CVD and T2D; therefore, studies with overweight or obese participants were included within the at-risk inclusion criteria (Table 4.1).

Table 4.1. PICOS criteria for the inclusion of studies.

Parameter	Inclusion Criteria	Exclusion Criteria
Participants	Adults General population or at-risk of T2D or CVD	Participants < 18 years Diagnosed with CVD or T2D
Interventions	Genotype-based dietary and/or physical activity advice intervention that aimed to change dietary and/or physical activity behaviour	Interventions that did not provide dietary and/or physical activity genotype-based advice aimed to change dietary and/or physical activity behaviour
Comparisons	Control group which received no advice, general advice or non-genotype-based personalised advice	Studies without a control or comparator group
Outcomes	Quantified measures of dietary and or physical activity behaviour change to reduce the risk of CVD, T2D or obesity	
Study Design	RCTs or NRSI	Observational studies, animal studies, reviews

CVD: cardiovascular disease, NRSI: non-randomised studies on interventions, RCT: randomised controlled trial, T2D: type 2 diabetes.

4.2.2 Information sources

The databases searched were MEDLINE, Embase, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL). Reference lists of included studies and relevant previous systematic reviews were screened for additional eligible studies. Searches were from inception to the search date of 7th January 2022. The search strategy combined relevant keywords and Emtree or MeSH terms to search the themes: 'personalised nutrition', 'obesity or type II diabetes or cardiovascular disease', and 'health behaviour'. Themes were combined using the Boolean operator 'AND'. Full search strategies for all databases are presented in (Appendix 11).

4.2.3 Selection and data collection process

Records identified by the search strategy were uploaded to Covidence systematic review management software. Duplicates were identified and removed. Title and abstract screening were carried out by two researchers independently according to the inclusion and exclusion criteria. Eligible reports were moved to full text review and were assessed independently by two researchers against inclusion and exclusion criteria. Multiple reviewers worked

independently at each stage of screening and any disagreements between reviewers were resolved by consensus. If criteria were met, studies were moved to the data extraction phase. Data extraction was carried out by two reviewers independently using Covidence systematic review management software; any disagreements between reviewers were resolved by consensus. One author entered the extracted data into Review Manager (RevMan) 5.4 software and that data was checked by another author.

4.2.4 Data items

The primary outcomes are quantified measures of dietary behaviour change and quantified measures of physical activity behaviour change to reduce the risk of CVD, T2D, or obesity. Where more than one dietary or physical activity outcome was reported, the outcome with the greatest relevance to the genotype-based advice provided and the strongest evidence of an effect on risk of CVD, T2D or obesity was selected. Where the same outcome was reported in multiple measures the least subjective measure was selected; for example, if physical activity was measured using an accelerometer and a self-reported questionnaire, the data from the accelerometer was included. Where outcomes were measured at multiple time points the longest time point was selected. Data extracted included: study identification details (sponsorship source, country, corresponding author, study registration) study population (baseline characteristics, inclusion/exclusion criteria, sample size), study design (RCT, NRIS), intervention details, and outcome measures including methods and time points.

4.2.5 Study risk of bias assessment

Risk of bias was assessed using the Risk of Bias 2 (RoB 2) tool (Higgins et al., 2022). The following domains were considered: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Overall risk of bias judgement was “low risk of bias” if all domains were deemed to have low risk of bias. If at least one domain was deemed to raise some concerns, but no domain was deemed to have a high risk of bias, the study was judged to “raise some concerns”. If at least one domain was deemed to have high risk of bias or multiple domains were deemed to raise some concerns, the study was judged to have “high risk of bias”. Risk of bias assessment was carried out by two reviewers independently using Covidence review management software. Multiple

reviewers worked independently and any disagreements between reviewers were resolved by consensus.

4.2.6 Effect measures

Effect sizes for each outcome (change in dietary behaviour or change in physical activity behaviour) were summarised as SMD. The SMD was used for both dietary and physical activity outcomes as they were assessed by studies using different scales. The SMD allows the studies to be standardised to a uniform scale so they can be combined (Higgins et al., 2022). SMD was calculated using change-from-baseline scores.

4.2.7 Synthesis methods

Studies were analysed separately for dietary behaviour change and physical activity behaviour change. Planned sub-group analysis was carried out to compare studies in the general population with studies including at-risk participants. Studies were considered to have at-risk participants if participants were recruited to the study based on a characteristic that increased their risk of T2D or CVD. Where data were presented separately for participants informed of a risk-associated genotype and non-risk-associated genotype, additional analysis was carried out to compare between risk and non-risk informed groups. Analysis was also carried out to compare these groups (risk and non-risk informed groups) separately to the comparator group (control group or group that received non-genotype-based personalised advice). Effect sizes were centred on zero, with values greater than zero favouring genotype-based advice and less than zero the comparator advice. In studies where a reduction in the outcome measure was beneficial, scores were multiplied by -1 (Higgins et al., 2022).

Authors were contacted for missing information for studies that did not report outcomes as mean change from baseline scores and standard deviations. Where authors were unable to provide missing information, mean change scores and standard deviations were imputed using the standard error, 95% confidence intervals, or probability values following methods outlined in the Cochrane handbook (Higgins et al., 2022). The correlation coefficient between the standard deviations for change as well as for baseline and post-intervention from the Food4Me study (Celis-Morales et al., 2017; Marsaux et al., 2016a) were used to impute standard deviations for changes from baseline for those studies where data was not available

from the author (Higgins et al., 2022). For one study (Voils et al., 2015), where data was reported as log values, the SMD was calculated from the log value as the author was unable to provide the untransformed data. A sensitivity analysis was carried out to compare findings on primary outcomes based on mean change-from-baseline scores compared to post intervention scores.

A meta-analysis of SMD scores was conducted using RevMan 5.4 software and a random effects model was used to pool effect sizes. The random effects model using the inverse variance method was chosen since, although all studies aimed to measure dietary or physical activity behaviour change, the specific behaviour measured, and the methods of measurement varied between studies. Therefore, rather than estimating a true-effect estimate as would be seen with a fixed effects model, the mean for a distribution of true effects was estimated (Higgins et al., 2022). Effect estimates and 95% CI for each included study and the overall effect for each comparison are presented as forest plots. Heterogeneity was assessed using χ^2 and quantified using I^2 test (Higgins et al., 2022).

4.2.8 Certainty assessment

The GRADE approach was used to assess confidence in the body of evidence. The following factors were considered to reduce the quality of evidence: limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias. Outcomes were graded as 'high' (very confident that the true effect lies close to that of the estimate of the effect), 'moderate' (moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), 'low' (confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect), or 'very low' (very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect) (Schünemann et al., 2013). Results of assessment of certainty using the GRADE approach are presented in the summary of findings tables for each outcome.

4.3 Results:

4.3.1 Study selection

Overall, 7899 records were screened for inclusion, following the removal of duplicates. A total of 7824 were removed after screening of the title and abstract leaving 75 full-text reports to be reviewed. Fourteen reports from 11 studies met the inclusion criteria (Figure 4.1). There were two reports identified from the Food4Me study that investigated the effect of genotype-based personalised advice on dietary patterns using adherence to the Healthy Eating Index (HEI) (Celis-Morales et al., 2017) or Mediterranean Diet Score (MDS) (Livingstone et al., 2016). The HEI outcome was included in the analysis as it was deemed to be a more universal approach. Mediterranean countries (Spain and Greece) were reported to have significantly higher MDS and, although HEI scores tended to be higher in Northern EU countries (UK and Netherlands), these differences were not significant (Fallaize et al., 2018).

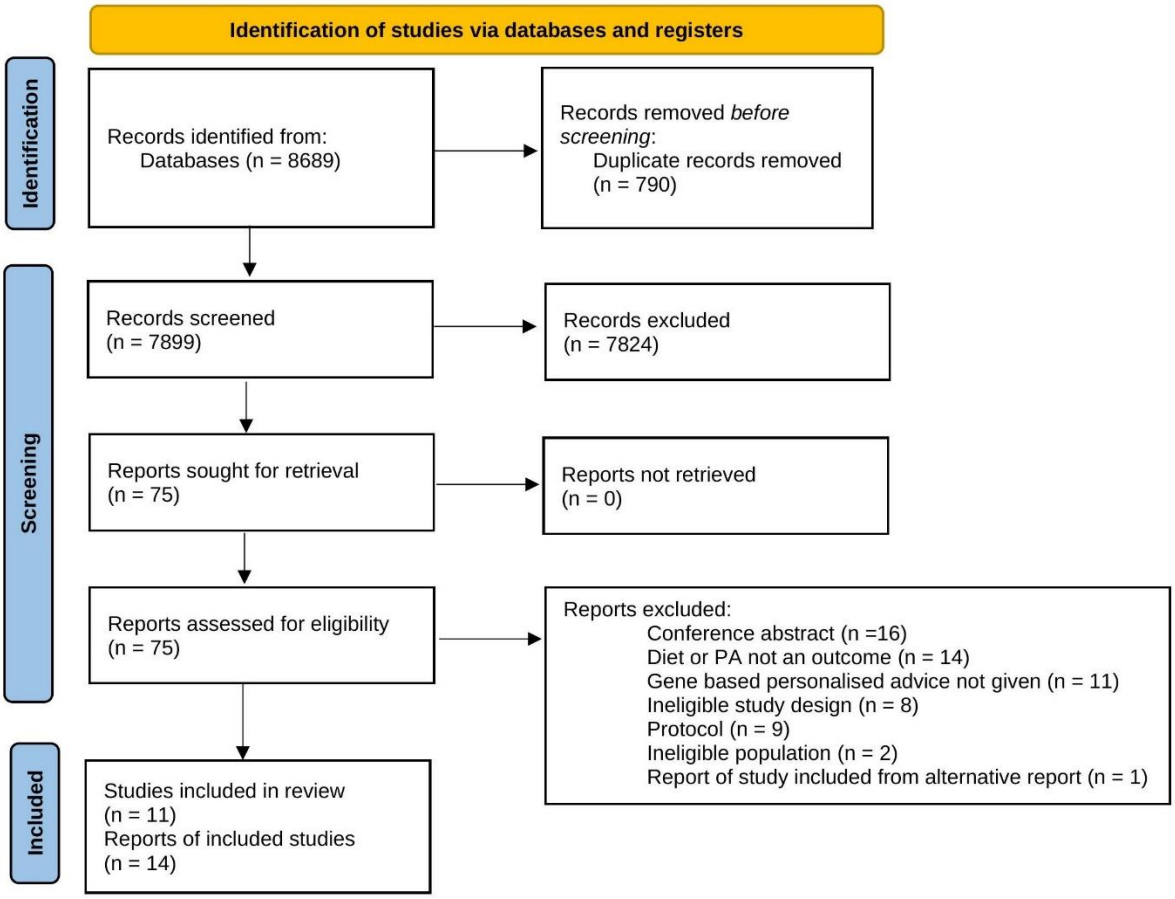

Figure 4.1: PRISMA flow diagram of reports identified and included in the meta-analysis.

4.3.2 Characteristics of included studies

Characteristics of included studies are presented in Table 4.2 (Celis-Morales et al., 2017; Fallaize et al., 2016; Godino et al., 2016; Hietaranta-Luoma et al., 2014; Horne, Gilliland, O'Connor, et al., 2020; Knowles et al., 2017; Kullo et al., 2016; Leskinen et al., 2021; Marsaux et al., 2015, 2016a; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Silarova et al., 2019; Voils et al., 2015). Sample sizes ranged from 57 participants (Roke et al., 2017) to 1488 (Celis-Morales et al., 2017); all studies included male and female participants except Roke et al., (2017) which included only female participants. Three studies were conducted in the US (Knowles et al., 2017; Kullo et al., 2016; Voils et al., 2015), three in Canada (Horne, Gilliland, O'Connor, et al., 2020; Nielsen & El-Sohemy, 2014; Roke et al., 2017), two in Finland (Hietaranta-Luoma et al., 2014; Leskinen et al., 2021), one in the UK (Godino et al., 2016), and one recruited from seven European countries (Celis-Morales et al., 2017). Seven of the included studies recruited participants from the general population (Celis-Morales et al., 2017; Godino et al., 2016; Hietaranta-Luoma et al., 2014; Leskinen et al., 2021; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Silarova et al., 2019). Four studies were carried out on an at-risk population, two studies recruited overweight participants (Horne, Gilliland, O'Connor, et al., 2020; Voils et al., 2015) and two recruited participants with an increased risk of CVD (Knowles et al., 2017; Kullo et al., 2016).

Genotype-based dietary and or physical activity advice was described as being provided remotely by six studies (Celis-Morales et al., 2017; Godino et al., 2016; Hietaranta-Luoma et al., 2014; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Silarova et al., 2019), and four studies provided advice in person (Horne, Gilliland, O'Connor, et al., 2020; Knowles et al., 2017; Kullo et al., 2016; Voils et al., 2015). For one study it was not clear how genotype had been disclosed to the participants in that, although advice was provided online, face-to-face counselling was offered on a voluntary basis (Leskinen et al., 2021). Five studies reported inclusion of behaviour change theory within their intervention. The incorporation of BCT were reported in two studies (Celis-Morales et al., 2017; Silarova et al., 2019), one study reported the incorporation of the TPB (Horne, Gilliland, O'Connor, et al., 2020), one study included the Extended Parallel Process Model (Hietaranta-Luoma et al., 2014) and, one study developed an action plan for behaviour change (Kullo et al., 2016). The remaining studies did not explicitly report the use of behaviour change theory in their interventions.

The comparator group from five studies were provided with advice based on general healthy eating or physical activity recommendations (Hietaranta-Luoma et al., 2014; Horne, Gilliland, O'Connor, et al., 2020; Leskinen et al., 2021; Nielsen & El-Sohemy, 2014; Roke et al., 2017). Six studies provided advice based on phenotypic, family history, or current lifestyle assessment (Celis-Morales et al., 2017; Godino et al., 2016; Knowles et al., 2017; Kullo et al., 2016; Silarova et al., 2019; Voils et al., 2015).

All 11 studies included a self-reported measure of dietary behaviour change. Dietary behaviour was measured using a food frequency questionnaire (Celis-Morales et al., 2017; Godino et al., 2016; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Voils et al., 2015), multiple 24 hour recalls (Horne, Gilliland, O'Connor, et al., 2020), or various brief dietary questionnaires (Hietaranta-Luoma et al., 2014; Knowles et al., 2017; Kullo et al., 2016; Leskinen et al., 2021; Silarova et al., 2019). Seven studies included a measure of physical activity behaviour; three studies included an objective measure of physical activity (Godino et al., 2016; Marsaux et al., 2015; Silarova et al., 2019), and four studies measured physical activity using a self-reported physical activity questionnaire (Hietaranta-Luoma et al., 2014; Knowles et al., 2017; Kullo et al., 2016; Voils et al., 2015). Two studies were not able to be included in the meta-analysis as physical activity was reported as the number of participants exercising 'at least two times a week' (Hietaranta-Luoma et al., 2014; Leskinen et al., 2021). Six studies provided a measure of dietary behaviour separately for risk and non-risk participants (Fallaize et al., 2016; Hietaranta-Luoma et al., 2014; Kullo et al., 2016; Leskinen et al., 2021; Nielsen & El-Sohemy, 2014; Roke et al., 2017). Two studies provided a measure of physical activity behaviour separately for risk and non-risk participants (Kullo et al., 2016; Marsaux et al., 2016a).

All included studies were RCTs, and four reports from the Food4Me study were included in the analysis (Celis-Morales et al., 2017; Fallaize et al., 2016; Marsaux et al., 2015, 2016a). Study durations ranged from 8 weeks (Godino et al., 2016) to 18 months (Leskinen et al., 2021).

Table 4.2. Study characteristics and reported results included in the meta-analysis.

Study	**Participants** Age Country Population	**Study design** Duration Inclusion of behaviour change theory	**Intervention**	**Comparison**	**Outcomes for review**	**Results**
(Celis-Morales et al., 2017) Report from Food4Me study	1488 M 618 F 870 18-79 years 7 European countries **General population**	RCT 6 months BCT	Personalised dietary advice provided via online interface on the basis of current diet and PA, phenotypic and genotypic data. Based on *FTO, MTHFR, TCF7L2, APOE, FADS1.*	Personalised dietary advice provided via online interface on the basis of current diet and PA and phenotypic data.	**Diet:** HEI based on self-reported dietary intake from FFQ.	At 6 months there was no significant difference between intervention group and comparator group for HEI. Compared to a control group HEI was significantly greater in participants that received any level of PN.
(Fallaize et al., 2016) Report from Food4Me study	1439 M 611, F 846 40 ± 0.4 years 7 European countries **General population**	RCT 6 months BCT	Personalised dietary advice to reduce SFA intake provided via online interface on the basis of current diet and PA, phenotypic and genotypic data. Based on *APOE*.	Personalised dietary advice to reduce SFA intake provided via online interface on the basis of current diet and PA, phenotypic data.	**Diet:** SFA from self-reported dietary intake from FFQ. **Subgroup-analysis participants informed of genetic risk**	No significant difference in SFA intake between E4+ and E4- participants at 6 months. SFA intake was significantly reduced in participants receiving genotype-based advice compared to a control group.
(Godino et al., 2016)	569 M 268 F 301 48.7 ± 7.3 years UK **General population**	RCT 8 weeks BC theory not reported	Standard written lifestyle advice for T2D, encouraged to maintain a healthy weight and adhere to governmental guidelines for PA and diet. Plus, genetic risk estimate (23 SNPs associated with T2D)	Standard written lifestyle advice for T2D, encouraged to maintain a healthy weight and adhere to governmental guidelines for PA and diet. Plus, phenotypic risk estimate (Cambridge Diabetes Risk Score).	**Diet**: Self-reported fruit and vegetable consumption from FFQ. **Physical activity:** Objective energy expenditure.	No significant differences between groups post intervention for physical activity energy expenditure or self-reported fruit and vegetable intake. No significant difference was observed in outcomes compared to a control group.

(Hietaranta-Luoma et al., 2014)	107 M 33, F 74 47.0 ± 12.1 years Finland **General population**	RCT 12 months EPPM	6 communication sessions (lectures on lifestyle and healthy diet, gene-diet interaction*;* health messages and information on personal *APOE* genotype provided by mail).	6 communication sessions (lectures on lifestyle and healthy diet, gene-diet interaction; common health messages on lifestyle and CVD risk provided by mail)	**Diet**: Self-reported dietary fat quality **Physical activity:** self-reported question leisure time PA. **Subgroup-analysis participants informed of genetic risk**	No significant difference between groups in dietary fat quality or physical activity at 12 months. No significant difference was observed in outcomes compared to a control group.
(Horne et al., 2020)	140 M 18, F 122 Int: 53.5 ± 13.6 years Comp: 56.4 ± 12.1 years Canada **at-risk**: BMI ≥25.0 kg/m^2	RCT 12 months TPB	12-month intervention (weekly meetings for first 3 months then once a month), specific targets derived from genetics for eight nutrients.	12-month intervention (weekly meetings for first 3 months then once a month), specific targets derived from population-based guidelines for eight nutrients.	**Diet:** Self-reported dietary intake of energy.	No significant reduction in energy intake from baseline to 12 months in either group.
(Knowles et al., 2017)	94 Int: M 30 F 19 57±10 years Comp: M 24, F 21 58 ± 8 years US **at-risk**: at least moderate risk CAD	RCT 3 months BC theory not reported	Standard care advice based on phenotypic measures and family history including diet and physical activity to reduce risk of high cholesterol plus GRS for 19 SNPs.	Standard care advice based on phenotypic measures and family history including diet and physical activity to reduce risk of high cholesterol.	**Diet:** Self-reported brief dietary questionnaire. **Physical activity**: Self-reported leisure time PA	No significant difference in diet score or physical activity between groups.
(Kullo et al., 2016)	203 M 97 F 106 59.4 years US **at-risk**: Intermediate risk of CHD	RCT 6 months Action plan for BC	Disclosure of 10-year CHD risk (based on genotype of 28 CHD susceptibility SNPs) by genetic counsellor and visit with physician for shared decision making for statin use. high GRS ≥1.1, low/average GRS ≤1.1.	Disclosure of 10-year CHD risk (based on conventional risk score) by genetic counsellor and visit with physician for shared decision making for statin use.	**Diet:** Self-reported dietary fat intake score. **Physical activity**: self-reported (TAPA) questionnaire. **Subgroup-analysis participants informed of genetic risk**	No significant differences in dietary fat intake or physical activity levels between groups at 6 months.

(Leskinen et al., 2021)	188 M 33 F 155 51 ± 6 years Finland **General population**	RCT 18 months BC theory not reported	Diet and lifestyle guidance via monthly internet-based lectures, face-to-face counselling, printed education material plus *APOE* genotype information.	Diet and lifestyle guidance via monthly internet-based lectures, face-to-face counselling, printed education material.	**Diet**: Self-reported dietary fat quality **Physical activity:** self-reported question leisure time PA. **Subgroup-analysis participants informed of genetic risk**	There was no significant difference in fat quality scores or physical activity between groups after 18 months. Fat quality scores were improved in all participants compared to baseline.
(Marsaux et al., 2015) Report from Food4Me study	1480 M 614 F 866 40 ± 13 years 7 European countries **General population**	RCT 6 months BCT	Personalised physical activity advice provided via online interface on the basis of current PAL and BMI, phenotypic (WC and TC) and genotypic data. Based on *FTO*.	Personalised physical activity advice provided via online interface on the basis of current PAL and BMI, phenotypic (WC and TC).	**Physical activity:** Objective measurement of PAL using accelerometer.	No significant difference in activity energy expenditure between groups at 6 months. Significant increase in physical activity from baseline in all groups. No significant difference compared to a control group.
(Marsaux et al., 2016) Report from Food4Me study	1279 M 536, F 743 40 ± 13 years 7 European countries **General population**	RCT 6 months BCT	Personalised physical activity advice provided via online interface on the basis of current PAL and BMI, phenotypic (WC and TC) and genotypic data. Based on *FTO*.	Personalised physical activity advice provided via online interface on the basis of current PAL and BMI, phenotypic (WC and TC).	**Physical activity:** Objective measurement of PAL using accelerometer. **Subgroup-analysis participants informed of genetic risk**	There was no difference in objectively measured physical activity in participants informed of an *FTO* risk genotype or an *FTO* non-risk genotype.
(Nielsen & El-Sohemy, 2014)	138 M 32, F 106 26.5 ± 3.0 years Canada **General population**	RCT 12 months BC theory not reported	Dietary report by email, informed of genotype for *CYP1A2; GSTT1; GTM1; TAS1R2; ACE* and corresponding DNA based recommendation, monthly reminder emailed.	Report of current general recommendations for the same nutrients as intervention with no genetic information.	**Diet:** Self-reported dietary intake of sodium. **Subgroup-analysis participants informed of genetic risk**	Participants in the risk intervention group had a significantly greater reduction in sodium intake compared to the control group at 12-months. No difference between non-risk and control group at 12-months.

(Roke et al., 2017)	57 F 57 22.0 ± 1.5 years Canada **General population**	RCT 12 weeks BC theory not reported	One-to-one information session. Written general nutritional information about omega-3 FAs and possible health effects Information about effect of *FADS1* (rs174537) SNP on omega-3 FA levels. Letter informing them of *FADS1* genotype.	One-to-one information session. Written general nutritional information about omega-3 FAs and possible health effects. Information about effect of *FADS1* (rs174537) SNP on omega-3 FA levels.	**Diet**: Self-reported omega-3 intake – FFQ. **Subgroup-analysis participants informed of genetic risk**	No significant interaction between group and time. Reported omega-3 intake increased significantly 12 weeks after the intervention in both groups.
(Silarova et al., 2019)	953 M 531, F 422 56.7 years UK **General population**	RCT 12 weeks BCT	Genetic CHD risk estimate (absolute risk of CHD in next 10 years; 'Heart Age' and comparative risk estimate). Web-based lifestyle intervention, 3 interactive sessions delivered at monthly intervals.	Phenotypic CHD risk estimate (absolute risk of CHD in next 10 years; 'Heart Age' and comparative risk estimate). Web-based lifestyle intervention, 3 interactive sessions delivered at monthly intervals.	**Diet:** Self-reported dietary intake of fruit and vegetables **Physical activity:** Objectively measured physical activity – Accelerometer 7 days.	No significant differences in mean change from baseline between groups on objectively measured physical activity. Mean change from baseline of self-reported intakes of fruit and vegetables were not significantly different between groups. No significant difference compared to a control group.
(Voils et al., 2015)	601 M 483, F 118 54.1 ± 8.7 years US **at-risk:** baseline BMI ≥ 27 kg/m^2	RCT 6 months. BC theory not reported	T2D risk counselling session (based on age, race, sex, BMI, family history and FPG) plus genetic risk counselling (based on *TCF7L2, PPARγ, KCNJ11*).	T2D risk counselling session (based on age, race, sex, BMI, family history and FPG) plus education of age-related macular degeneration.	**Physical activity:** self-reported IPAQ (moderate intensity physical activity). **Diet:** Self-reported energy intake from FFQ	No significant difference in energy intake or physical activity between groups at 6 months.

BC: behaviour change, BCT: behaviour change techniques, BMI: body mass index, CAD: coronary artery disease, CVD: cardiovascular disease, CHD: coronary heart disease, Comp: comparator group, CRS: conventional risk score, EPPM: Extended Parallel Process Model, F: female, FPG: fasting plasma glucose, FA: fatty acid, FFQ: food frequency questionnaire, GRS: genetic risk score, HEI: healthy eating index, Int: Intervention group, M: male, PA: physical activity, PAL: physical activity level, PN: personalised nutrition, RCT: randomised controlled trial, SFA: saturated fat, SNP: single nucleotide polymorphism, TC: total cholesterol, TPB: Theory of Planned Behaviour, T2D: type 2 diabetes, WC: waist circumference.

4.3.3 Risk of bias

Two reports were judged to have low risk of bias (Godino et al., 2016; Silarova et al., 2019), one report was judged to have high risk of bias due to a lack of information regarding deviations from the intended intervention (Leskinen et al., 2021). The remaining 11 reports were judged to have some concerns, many of which were due to bias in measurement of the outcome as a consequence of self-reported dietary or physical activity behaviour (Figure 4.2) (Celis-Morales et al., 2017; Fallaize et al., 2016; Godino et al., 2016; Hietaranta-Luoma et al., 2014; Horne, Gilliland, O'Connor, et al., 2020; Knowles et al., 2017; Kullo et al., 2016; Leskinen et al., 2021; Marsaux et al., 2015, 2016a; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Silarova et al., 2019; Voils et al., 2015).

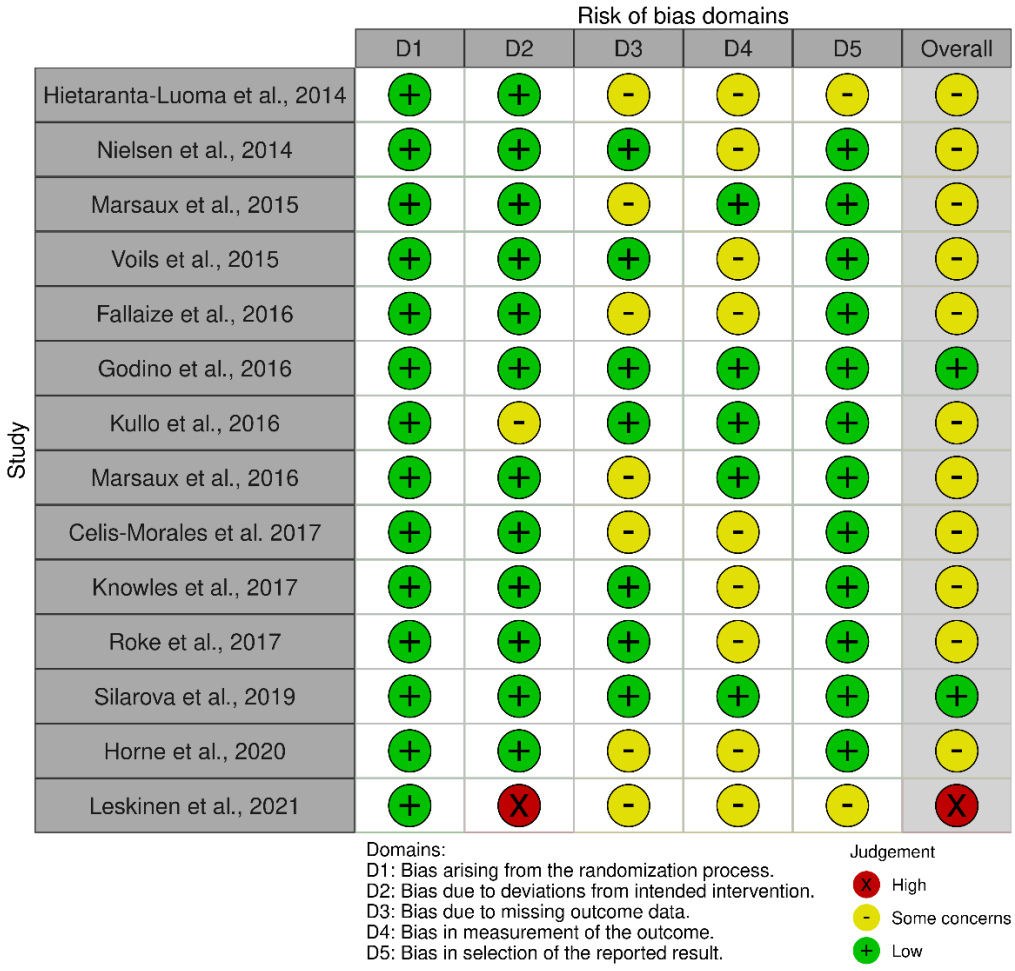

Figure 4.2. Risk of bias judgments for each included study.

4.3.4 Quality of evidence

The first domain considered was risk of bias; the majority of studies were judged to have 'some concerns', two had low risk of bias and one study had high risk of bias. The main concerns were related to the lack of blinding of participants and outcome assessors to the intervention, in addition to self-reporting of outcome measures. For the dietary behaviour outcome, quality scores were downgraded by one level due to the high risk of bias study (Leskinen et al., 2021); that study did not report physical activity behaviour, so the physical activity outcome was not downgraded for risk of bias. The second domain considered was inconsistency of results, which refers to unexplained heterogeneity (Schünemann et al., 2013). Across analysis, χ^2 was not significant and I^2 ranged from 0% (no between-study heterogeneity) to 50% suggesting moderate variation (Higgins et al., 2022). Sub-group analysis of healthy and at-risk populations did not explain between-study heterogeneity. Confidence limits of studies were mostly overlapping zero for both outcomes. Therefore, although there was some heterogeneity, quality of evidence was not downgraded within this domain. The indirectness of evidence domain considers whether the participants included in studies, the intervention delivered, and outcomes reported enable the research question to be answered (Schünemann et al., 2013). Although PICOS criteria were met, due to the variation between interventions and measurement of outcomes, certainty of evidence was downgraded by one level for both dietary behaviour outcome and physical activity for the indirectness of evidence domain. The imprecision of evidence domain is primarily assessed by considering the 95% confidence intervals of the estimate of effect (Schünemann et al., 2013). The confidence intervals of pooled SMD did not include a meaningful effect for dietary or physical activity behaviour outcomes. In addition, optimal information size, which refers to the number of participants was considered. The number of participants included in the meta-analysis was adequate for both outcomes. Finally, visual inspection of the funnel plots suggests that publication bias was not evident (Schünemann et al., 2013).

4.3.5 Dietary behaviour change

Eleven studies, including 2604 participants, assessed dietary behaviour change following genotype-based dietary or physical activity advice (Celis-Morales et al., 2017; Godino et al., 2016; Hietaranta-Luoma et al., 2014; Horne, Gilliland, O'Connor, et al., 2020; Knowles et al.,

2017; Kullo et al., 2016; Leskinen et al., 2021; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Silarova et al., 2019; Voils et al., 2015). Pooled data from these studies suggest no significant benefit of genotype-based dietary or physical activity advice compared to no advice, general advice, or personalised advice without genetics (SMD 0.00, 95% CI -0.11 to 0.11, p = 0.98). Pooled sub-group analysis of studies that recruited participants from an at-risk population (SMD 0.00, 95% CI -0.16 to 0.16, p = 0.99) or general population (SMD 0.01, 95% CI -0.14 to 0.16, p = 0.87) also suggest no significant benefit of genotype-based advice compared to no advice, general advice, or personalised advice without genetics. Findings are presented as a forest plot (Figure 4.3 (Celis-Morales et al., 2017; Godino et al., 2016; Hietaranta-Luoma et al., 2014; Horne, Gilliland, O'Connor, et al., 2020; Knowles et al., 2017; Kullo et al., 2016; Leskinen et al., 2021; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Silarova et al., 2019; Voils et al., 2015)) and in a summary of findings table (Table 4.3). Sensitivity analysis was conducted using SMD of final scores; pooled data from studies using final scores also suggest no significant benefit of genotype-based advice compared to no advice, general advice, or personalised advice without genetics.

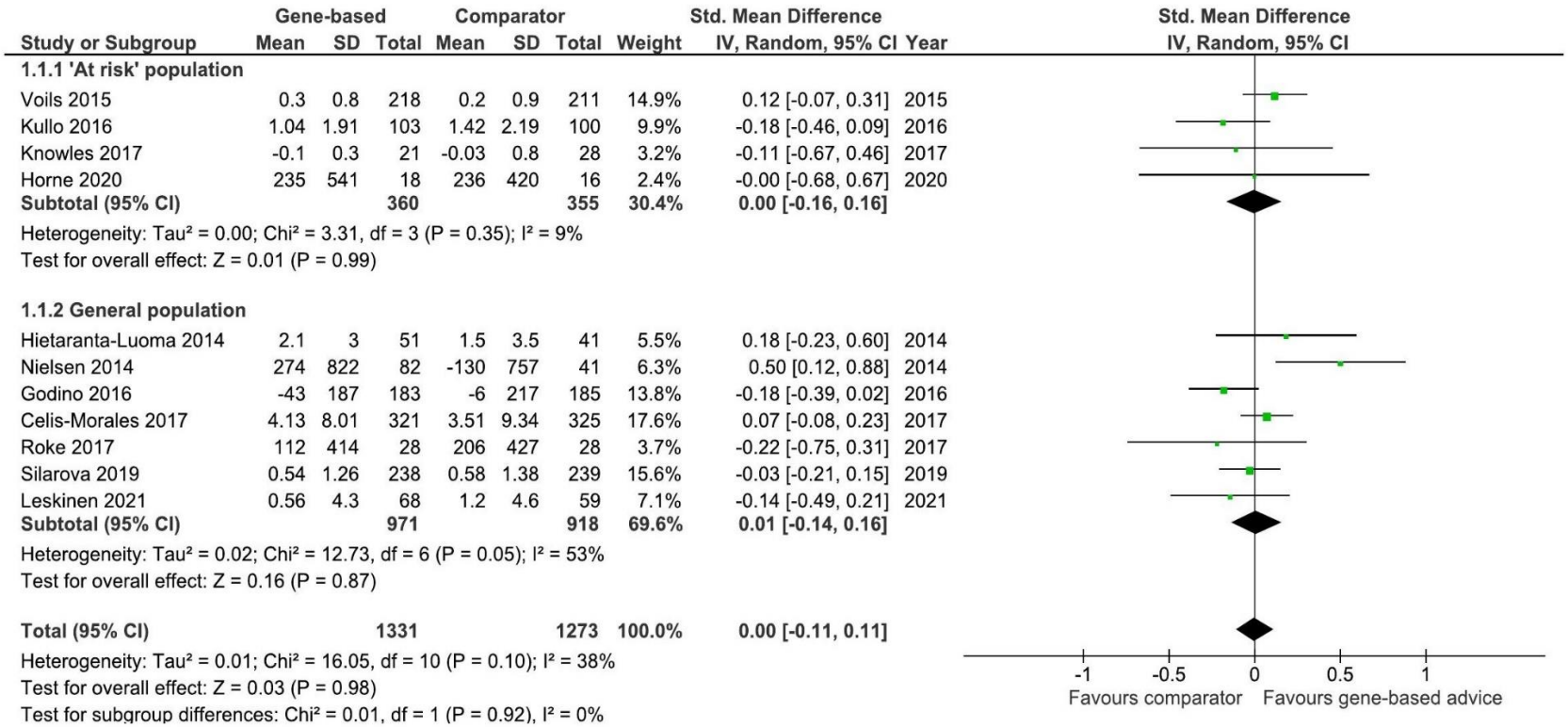

Figure 4.3: Forest plot of main comparison: Dietary behaviour change following genotype-based dietary or physical activity advice compared to no advice, general advice or personalised advice without genetics (SMD calculated from diet change from baseline).

4.3.6 Physical activity behaviour change

Six studies, including 1924 participants, assessed physical activity behaviour change following genotype-based dietary or physical activity advice (Godino et al., 2016; Knowles et al., 2017; Kullo et al., 2016; Marsaux et al., 2015; Silarova et al., 2019; Voils et al., 2015). Pooled data from these studies suggest no significant benefit of genotype-based dietary or physical activity advice compared to no advice, general advice, or personalised advice without genetics (SMD -0.01, 95% CI -0.10 to 0.08, $p = 0.88$). Pooled sub-group analysis of studies that recruited participants from an at-risk population (SMD 0.07, 95% CI -0.18 to 0.31, $p = 0.59$) or general population (SMD -0.02, 95% CI -0.13 to 0.10, $p = 0.77$) also suggest no significant benefit of genotype-based advice compared to no advice, general advice, or personalised advice without genetics. Findings are presented as a forest plot (Figure 4.4 (Godino et al., 2016; Knowles et al., 2017; Kullo et al., 2016; Marsaux et al., 2016a; Silarova et al., 2019; Voils et al., 2015)) and in a summary of findings table (Table 4.3). Sensitivity analysis was conducted using SMD of final scores; pooled data also suggest no significant benefit of genotype-based advice compared to no advice, general advice, or personalised advice without genetics. There were two additional studies included in the systematic review that measured physical activity behaviour change but, due to the way the outcome was reported, they were not able to be included in the meta-analysis. Both studies reported no significant effect (Hietaranta-Luoma et al., 2014; Leskinen et al., 2021).

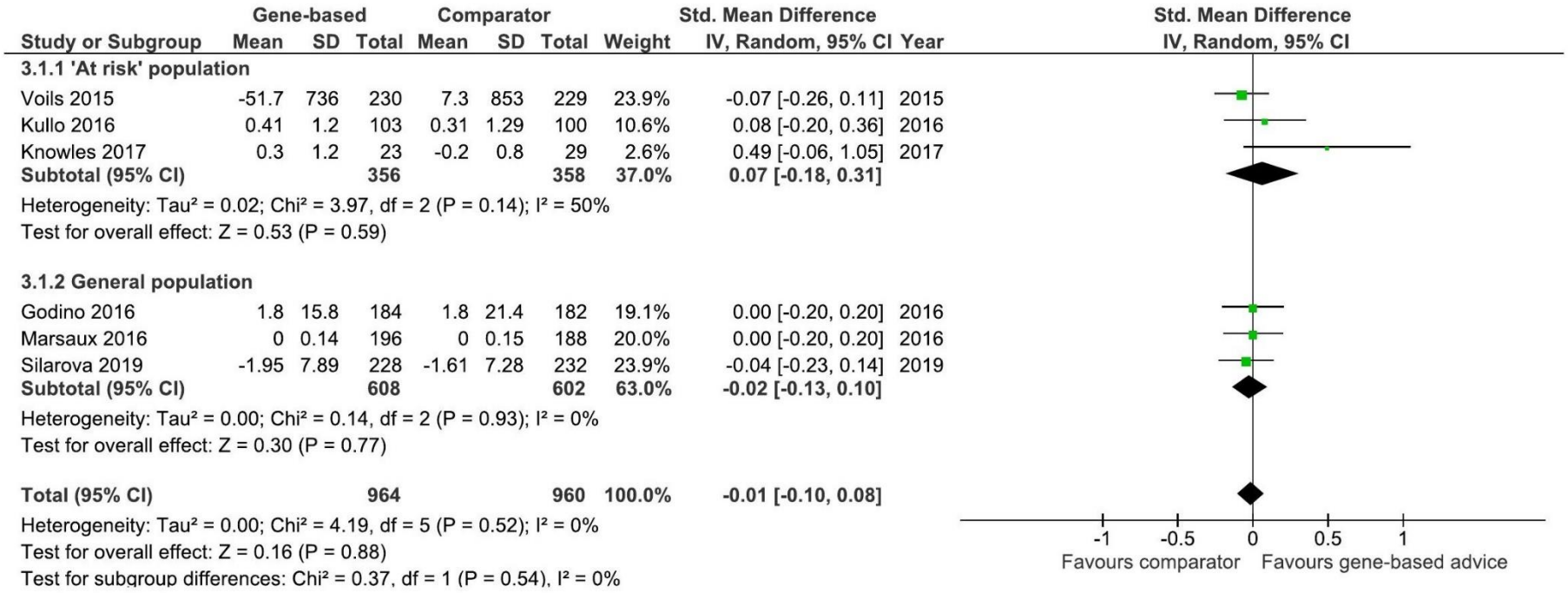

Figure 4.4: Forest plot of main comparison: Physical activity behaviour change following genotype-based dietary or physical activity advice compared to no advice, general advice or personalised advice without genetics (SMD calculated from diet change from baseline).

Table 4.3. Summary of findings for the main comparison: Dietary and physical activity behaviour change following genotype-based dietary or physical activity advice compared to no advice, general advice, or personalised advice without genetics.

Population: **Adults (general population or at-risk of cardiometabolic disease)** Setting: **Face-to-face or online** Intervention: **genotype-based dietary and/or physical activity advice intervention to change dietary and/or physical activity behaviour** Comparison: **No advice, general advice, or personalised advice without genetics.**			
Outcomes	**Impact:** SMD (95% CI)	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
Dietary behaviour change: **Self-reported dietary behaviour (24-hour recall, FFQ, other dietary questionnaires)**	No effect of genotype-based dietary or physical activity advice on dietary behaviour for all studies SMD 0.00 (-0.11 – 0.11) or when analysed by sub-group; at-risk SMD 0.00 (-0.16-0.16); general population SMD 0.01 (-0.14 – 0.16).	2604 (11 RCTs)	⨁⨁⨀⨀ Low [a, b]
Physical activity behaviour change: **Objectively measured (accelerometer) Self-reported physical activity (various questionnaires)**	No effect of genotype-based dietary or physical activity advice on physical activity behaviour for all studies SMD - 0.01 (-0.10 – 0.08) or when analysed by sub-group; at-risk SMD 0.07 (-0.18-0.31); general population SMD -0.02 (-0.13 – 0.10).	1924 (6 RCTs)	⨁⨁⨁⨀ Moderate [b]

SMD: standardised mean difference; CI: confidence interval; RCT: randomised controlled trial; FFQ: food frequency questionnaire

[a] Downgraded by one level for high risk of bias: one trial

[b] Downgraded by one level for indirectness: variation between interventions and measurement outcomes

4.3.7 Risk v non-risk genotype

Six studies including 444 participants reported change in dietary behaviour separately for participants informed of a risk-associated genotype compared to a non-risk-associated genotype (Fallaize et al., 2016; Hietaranta-Luoma et al., 2014; Knowles et al., 2017; Kullo et al., 2016; Leskinen et al., 2021; Roke et al., 2017). Pooled data from these studies suggest no effect of being informed of a risk-associated genotype compared to a non-risk-associated genotype in addition to genotype-based dietary or physical activity advice on dietary behaviour (SMD 0.14, 95% CI -0.06 to 0.33, p = 0.16) (Table 4.4, Figure 4.5 (Fallaize et al., 2016; Hietaranta-Luoma et al., 2014; Kullo et al., 2016; Leskinen et al., 2021; Nielsen & El-Sohemy, 2014; Roke et al., 2017)).

Two studies including 298 participants reported change in physical activity behaviour separately for participants informed of a risk-associated genotype compared to a non-risk-associated genotype (Kullo et al., 2016; Marsaux et al., 2016a). Pooled data from these studies suggest no effect of being informed of a risk-associated genotype compared to a non-risk-associated genotype in addition to genotype-based dietary or physical activity advice on physical activity behaviour (SMD 0.01, 95% CI -0.24 to 0.25, p = 0.96) (Table 4.4).

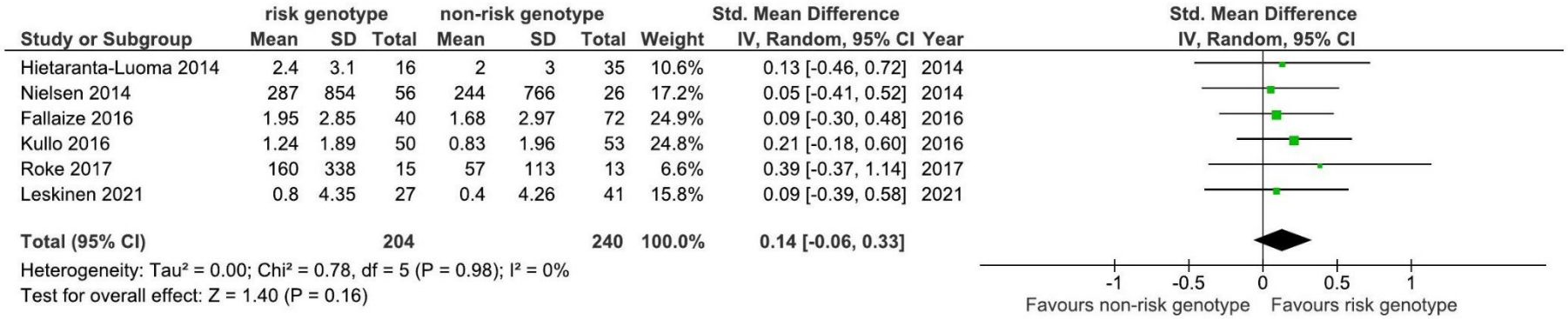

Figure 4.5: Forest plot of dietary behaviour change following genotype-based dietary or physical activity advice, participants informed of a risk-associated genotype compared to participants informed of a non-risk-associated genotype (SMD calculated from diet change from baseline).

Table 4.4. Summary of findings: Dietary and physical activity behaviour change following genotype-based dietary or physical activity advice, participants informed of a risk-associated genotype compared to participants informed of a non-risk-associated genotype.

Population: **Adults (general population or at-risk of cardiometabolic disease)** Setting: **Face-to-face or online** Intervention: **Genotype-based dietary and/or physical activity advice, participants informed of a risk-associated genotype** Comparison: **Genotype-based dietary and/or physical activity advice, participants informed of a non-risk-associated genotype**			
Outcomes	**Impact:** SMD (95% CI)	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
Dietary behaviour change: **Self-reported dietary behaviour (FFQ, other dietary questionnaires)**	No effect of being informed of a risk-associated genotype compared to a non-risk-associated genotype in addition to genotype-based dietary or physical activity advice on dietary behaviour SMD 0.14 (-0.06 – 0.33).	444 (6 RCTs)	⨁⨁⨀⨀ Low [a, b]
Physical activity behaviour change: **Objectively measured (accelerometer)** **Self-reported physical activity (various questionnaires)**	No effect of being informed of a risk-associated genotype compared to a non-risk-associated genotype in addition to genotype-based dietary or physical activity advice on physical activity behaviour SMD 0.01 (-0.24 – 0.25).	298 (2 RCTs)	⨁⨁⨁⨀ Moderate [b]

SMD: standardised mean difference; CI: confidence interval; RCT: randomised controlled trial; FFQ: food frequency questionnaire.

[a] Downgraded by one level for high risk of bias: one trial

[b] Downgraded by one level for indirectness: variation between interventions and measurement outcomes

4.4 Discussion

4.4.1 Summary of main results

The aim of this systematic review was to evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2D, or obesity in the general population and individuals that are at risk of CVD or T2D. A meta-analysis of pooled data suggests that genotype-based advice does not affect dietary or physical activity behaviour more than general advice or advice based on lifestyle or phenotypic measures. This finding was consistent in studies that had recruited participants from the general population as well as studies that had recruited participants from populations at-risk of CVD or T2D.

4.4.2 Quality of the evidence

The outcome measures of dietary and physical activity behaviour were judged to be of 'low' and 'moderate' quality of evidence respectively, due to concerns with risk of bias and indirectness of evidence domains (Schünemann et al., 2013). For risk of bias, the main concerns were related to the lack of blinding of participants and outcome assessors to the intervention, in addition to self-reporting of outcome measures. Blinding participants to the intervention is often not feasible in a lifestyle intervention (Mirmiran et al., 2021). Only one study attempted to blind the participants to the intervention by providing the control group with information about risk of age-related macular degeneration (Voils et al., 2015). Furthermore, due to the subjective nature of measuring dietary intake and physical activity, in the majority of studies, outcome assessors were the participants themselves. Objective measures of dietary intake are available for few aspects of the diet; furthermore, biochemical measures of nutritional status may not reflect dietary intake and therefore behaviour (Laville et al., 2017; Margetts & Nelson, 1997). Finally, concerns have been raised that the RoB 2 tool results in lower ratings of overall risk of bias compared to the previous Cochrane tool for assessing risk of bias in randomised trials (RoB tool). Consequently, this should be considered when comparing risk of bias assessments from this study to assessments of risk of bias in earlier systematic reviews (Sterne et al., 2019).

The indirectness of evidence domain considers whether the participants included in studies, the intervention delivered, and outcomes reported enable the research question to be answered (Schünemann et al., 2013). Participants of included studies met the inclusion

criteria. All studies included an intervention which incorporated the delivery of genotype-based dietary or physical activity advice. However, the way in which advice was delivered varied considerably between studies. Some delivered advice remotely (Celis-Morales et al., 2017; Godino et al., 2016; Hietaranta-Luoma et al., 2014; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Silarova et al., 2019) and some in person (Horne, Gilliland, O'Connor, et al., 2020; Knowles et al., 2017; Kullo et al., 2016; Voils et al., 2015); moreover, the extent of advice varied between studies from written advice to counselling sessions. The way in which genotype-based advice is delivered may influence understanding and engagement (Haga, Barry, et al., 2014; Haga, Mills, et al., 2014). Health literacy, genetic literacy, and e-health literacy have all been suggested to influence understanding (Haga, Mills, et al., 2014). Furthermore, understanding of genetic risk was significantly greater when delivered in person compared to remote delivery (Haga, Barry, et al., 2014). Outcome measures, particularly for diet, also varied between studies. These variations in study design could affect both the effectiveness of the intervention and whether the outcome measure could detect a change in behaviour.

Based on GRADE assessments when interpreting the findings of this meta-analysis it should be acknowledged that the true effect of genotype-based dietary and physical activity advice on dietary behaviour change might be markedly different from the estimated effect. However, for physical activity behaviour the true effect is probably close to the estimated effect.

4.4.3 Genotype-based advice for behaviour change

The findings of this meta-analysis supersede the findings from two previous meta-analyses of genotype-based advice on dietary and physical activity behaviour change. Marteau et al. (2010) reported a significant benefit of genotype-based advice on dietary behaviour from two studies (OR 2.24, 95% CI 1.17 to 4.27) but no significant effect from two studies of physical activity behaviour (OR 1.03, 95% CI 0.59 to 1.80). Hollands et al. (2016) reported that analysis of seven studies suggested little or no benefit of genotype-based advice on dietary behaviour (SMD 0.12, 95% CI 0.00 to 0.24) and no benefit from six studies of physical activity behaviour (SMD -0.03, 95% CI -0.14 to 0.07). The present meta-analysis focused on dietary and physical activity behaviour change to reduce the risk of obesity, T2D and CVD. Therefore, there are some studies included in the previous meta-analyses that were not included in the present

meta-analysis as they were focused on reducing the risk of other diseases such as AD (Chao et al., 2008). In the context of reducing the risk of obesity, T2D and CVD, the present meta-analysis provides evidence for no beneficial effect of genotype-based advice from 11 studies of dietary behaviour (SMD 0.00, 95% CI -0.11 to 0.11) and six studies of physical activity behaviour (SMD -0.01, 95% CI -0.10 to 0.08).

In addition to these meta-analysis, three recent systematic reviews have carried out thematic analysis of the effect of genotype-based advice on dietary (Jinnette et al., 2020) and physical activity behaviour (Horne et al., 2018; Li et al., 2016). Of the lifestyle factors reviewed by Horne et al., (2018) dietary behaviour change was suggested to be the most promising in response to genotype-based advice. Both Li et al. (2016) and Jinnette et al. (2020) suggest there are benefits to personalisation of advice, but these can be seen with the addition of lifestyle and or phenotypic measures and the addition of genetics does not appear to provide further benefit. Whilst only one study in the present meta-analysis reported a significant difference in dietary behaviour following genotype-based advice, the comparator group for this study was provided with general healthy eating advice (Nielsen & El-Sohemy, 2014). Two additional studies that reported no significant difference between the genotype-based group compared to a group provided with phenotypic or lifestyle-based advice reported that compared to a control group there was a significant improvement in dietary behaviour (Celis-Morales et al., 2017; Fallaize et al., 2016). Furthermore, two studies that also reported no significant difference in behaviour between groups reported that behaviour significantly improved from baseline measures in both the intervention and comparator groups (Leskinen et al., 2021; Roke et al., 2017). These findings are in agreement with those of Li et al. (2016) and Jinnette et al. (2020) that personalisation of advice can increase positive behaviour change, but also highlight the importance of the comparator group chosen for the determination of the benefit of genotype-based dietary and physical activity advice on behaviour change. Comparator groups varied between included studies. Some studies compared to a group that received general healthy eating or physical activity advice, (Hietaranta-Luoma et al., 2014; Horne, Gilliland, O'Connor, et al., 2020; Leskinen et al., 2021; Nielsen & El-Sohemy, 2014; Roke et al., 2017) whereas others more clearly isolated the genotype-based component of personalised advice from other levels of personalisation and the comparator group received advice based on phenotypic, family history or current lifestyle

assessment (Celis-Morales et al., 2017; Godino et al., 2016; Knowles et al., 2017; Kullo et al., 2016; Silarova et al., 2019; Voils et al., 2015). It is important to be able to distinguish between different levels of personalisation; dietary and physical activity advice based on current behaviour and phenotypic measures has been provided by health professionals for a long time to motivate healthy behaviour change. Whether the addition of genetic risk of disease to this advice can enhance motivation and maintenance of behaviour change is what this meta-analysis aimed to find out. The findings of this meta-analysis and previous reviews would suggest that benefits beyond other levels of personalisation are not observed. However, it is also important to consider that three studies included in the meta-analysis reported no significant difference in behaviour following genotype-based advice but more importantly they did not report any significant difference in the comparative or control group either (Godino et al., 2016; Hietaranta-Luoma et al., 2014; Silarova et al., 2019). Therefore, it is unclear if this lack of an effect on behaviour was due to the genotype-based advice. The heterogeneity of interventions delivered, populations and disease context of the included studies may explain the contradictory findings and are discussed below.

Marteau & Weinman (2006) suggest that one reason why genotype-based advice may not motivate behaviour change is due to a fatalistic attitude towards the disease in those that are informed of a risk-associated genotype. When informed of a phenotypic risk factor such as a high cholesterol level, individuals relate this to their lifestyle (a high intake of saturated fat) and consequently reduce their saturated fat intake. They are less able to draw such links between their genes and cholesterol level and consequently are less motivated to make behaviour changes, as they perceive them to be less effective to counteract their genetic predisposition (Marteau & Weinman, 2006). To avoid this inaccurate interpretation, interventions should choose genetic predispositions that respond to lifestyle modifications, highlighting how the specific genetic predisposition can be moderated by actionable advice. It is not possible to determine precisely how genotype-based advice was delivered in the included studies or indeed how this was perceived by participants; however, this could be a potential source of bias in determining the effectiveness of genotype-based advice.

It is important to note that the findings from this meta-analysis suggest that genotype-based advice does not cause negative changes in dietary or physical activity behaviour. Those informed of their genotype-based risk have a similar response to those in the comparator

group. Moreover, within the intervention group there were a proportion of participants informed of a risk-associated genotype and a group that were informed of a non-risk-associated genotype. It is also important to consider how these two groups may respond differently to dietary and physical activity advice. One way in which genotype-based advice has been proposed to encourage behaviour change is by challenging an individual's optimistic bias, the phenomenon by which an individual underestimates their own risk of developing a disease, such as CVD, compared to others (Shepherd, 1999). The disease context of the studies included in this meta-analysis are all polygenic diseases and risk is determined by both genetics and lifestyle behaviours (De Caterina et al., 2020; Hu et al., 2001; Yusuf et al., 2004; Zheng et al., 2017). Studies have demonstrated how those with a low-risk genotype, but an unfavourable lifestyle, can be at a comparable risk of disease outcomes than those with a high-genetic risk but a favourable lifestyle (Khera et al., 2016). Consequently, it is equally important that genotype-based advice does not enhance poor lifestyle behaviours in those informed of a higher genetic risk due to genetic fatalism (Ehrlinger et al., 2017; Marteau & Weinman, 2006) or, in those informed of lower genetic risk, by increasing their optimistic bias (Hunter et al., 2008). To determine the effects of disclosure of a risk-associated or non-risk-associated genotype, behaviour change between risk and non-risk informed groups for both dietary and physical activity behaviour was compared. In all six studies that compared dietary behaviour between participants informed of a risk compared to non-risk genotype there was a SMD that favoured the risk informed group; however, this was not statistically significant. In the two studies that reported on physical activity behaviour there was no effect. Similar findings were reported by Hollands et al. (2016).

There is considerable heterogeneity between studies researching the effect of genotype-based advice on dietary and physical activity behaviour and this has been noted in previous systematic reviews (Horne et al., 2018; Jinnette et al., 2020; Li et al., 2016). Variations in interventions of the included studies have already been discussed; however, an additional consideration in any intervention designed to change behaviour is the incorporation of behaviour change theory in the design. A consistent criticism of previous studies investigating genotype-based behaviour change is the lack of integration of behaviour change theory (French et al., 2017; Horne et al., 2018; Jinnette et al., 2020). Five studies included in the present meta-analysis mentioned behaviour change to some extent in the delivery of their

intervention (Celis-Morales et al., 2017; Hietaranta-Luoma et al., 2014; Horne, Gilliland, O'Connor, et al., 2020; Kullo et al., 2016; Silarova et al., 2019). The remaining studies did not explicitly report the use of behaviour change theory in their interventions; although, it is likely that BCT were incorporated to some extent even if they were not identified. For this reason, sub-group analysis was not carried out to compare studies that reported the use of behaviour change theory to those that did not. Incorporation of behaviour change theory in genetic-based lifestyle behaviour interventions has been suggested as a way of improving efficacy (Horne et al., 2018; NICE, 2007). Therefore, any studies wishing to change behaviour should incorporate behaviour change theory within their intervention design.

To determine the effect of an intervention, the assessment of an appropriate outcome to represent the behaviour addressed by the intervention is required. The variation in methods and measures of dietary and physical activity behaviour have already been discussed. However, it should be acknowledged also that the assessment of dietary and physical activity outcomes are a considerable challenge (Goldberg et al., 1991; Mirmiran et al., 2021). It is not clear whether such outcomes can be measured with the necessary degree of accuracy to identify behaviour change as a consequence of the intervention (Laville et al., 2017; Mirmiran et al., 2021). One previous systematic review included physiological and clinical measures such as body weight and blood pressure as outcomes, which can be assessed objectively (Li et al., 2016). The problem with physiological and clinical measures is that it is not possible to determine whether the change in outcome is a consequence of participants changing their behaviour or if the genotype-based advice has been more effective due to the gene-diet interaction. Consequently, for dietary behaviour outcomes it is difficult to address issues related to self-reporting. A number of studies did measure physical activity behaviour objectively (Godino et al., 2016; Marsaux et al., 2015; Silarova et al., 2019) and subsequent research to assess physical activity behaviour should utilise objective measures.

The aim of personalised health advice is to provide an individual with more precise and effective dietary or physical activity advice and to motivate behaviour change (Grimaldi et al., 2017). This and previous meta-analyses suggest that the addition of genetics to personalised advice may not motivate behaviour change beyond that observed at levels of personalisation based on current behaviour or phenotypic measures (Hollands et al., 2016; Jinnette et al., 2020; Li et al., 2016). However, in younger populations where unhealthy lifestyle behaviours

are yet to develop and phenotypic measures are within the healthy range, personalisation based on genetics may enable the prevention of the development of these behaviours and subsequent phenotypic outcomes. As such, further research in the use of genotype-based personalisation of advice in younger populations is warranted.

4.4.4 Strengths and limitations

Strengths of the present meta-analysis are that guidance from the Cochrane handbook and PRISMA were followed to comprehensively address the study aim. It updates the understanding of the use of genotype-based dietary and physical activity advice for behaviour change and included findings from 11 studies. As discussed, the main limitation of the review is the between-study heterogeneity in the delivery of the intervention, the comparator group, and assessment of the outcome. The impact of these limitations is discussed above. Where studies had numerous outcomes and follow up times, decisions were made by consensus with regards to inclusion. Alternative outcomes showed a different effect in response to advice in some studies; however, outcomes were chosen based on the context of the genotype-based advice and disease prevention. Study duration varied widely, from eight weeks (Godino et al., 2016) to 18 months (Leskinen et al., 2021), with some studies having multiple follow up points. Health behaviour change requires both initiation and maintenance of change; acquiring the motivation to change behaviour is an important step in the initiation of behaviour change (Ryan et al., 2008). The longest time point was selected for inclusion in the meta-analysis. Some studies demonstrated significant differences between the intervention and comparator group at earlier time points that were not maintained subsequently; however, for this meta-analysis an estimate of maintenance of behaviour change was preferred. Therefore, if investigating different dietary outcomes or the initiation of behaviour change, findings may have differed.

4.4.5 Conclusion

The findings from this meta-analysis suggest that the use of genotype-based advice to promote dietary or physical activity behaviour is no more effective than general advice or advice based on lifestyle or phenotypic measures. This finding was consistent in studies that had recruited participants from the general population as well as studies that had recruited participants from populations at-risk of CVD or T2D. Future studies of genotype-based advice

for changing behaviour should incorporate behaviour change theory explicitly in their design and where possible behaviour outcomes should be measured objectively.

Chapter 5: Factors that influence intention to adopt genotype-based personalised advice on diet and physical activity in young adults that perceive themselves to be a healthy weight versus overweight or obese.

This chapter presents the findings of my final study, the rationale for which was developed based on the findings of the first three studies. Previous findings suggest that personalisation of dietary and physical activity advice promotes behaviour change, although the addition of genetics to other levels of personalisation may not be warranted. Genotype-based personalisation of advice can be delivered earlier in the lifespan and therefore has the potential to prevent the development of unhealthy lifestyle behaviours. In study two, healthy-eating motivation in young adults was unaffected by any level of personalised advice. Therefore, in terms of the overall research question of the thesis, the final study investigated the factors that influence the intention to adopt genotype-based personalised advice on diet and physical activity in young adults that perceive themselves to be a healthy weight versus those that perceive themselves to be overweight or obese.

5.1 Background

The prevalence of obesity and associated NCD continue to rise (NCD Risk Factor Collaboration, 2016; Saeedi et al., 2019). Modification of lifestyle behaviours, including diet and physical activity can considerably reduce the prevalence of NCD, reducing the burden of disease for both the individual and society (Bloom et al., 2012; Dunkley et al., 2014; Ezzati et al., 2003; Hu et al., 2001; Knowler et al., 2002; Public Health England, 2017; Timmis et al., 2020; Tuomilehto et al., 2001; Yusuf et al., 2004). However, generic public health advice to address dietary and physical activity behaviours is not adhered to (Health Survey for England, 2017; Roberts et al., 2018). Compared to this 'one size fits all' approach to dietary and physical activity advice, researchers have hypothesised that personalisation of advice based on an individual's genes could motivate greater adherence to guidance (Celis-Morales, Lara, et al., 2015).

Genotype-based personalised advice is delivered in combination with other levels of personalisation (phenotypic, clinical, dietary), with the aim to provide more precise and effective advice as well as to encourage behaviour change (Grimaldi et al., 2017). Studies that have investigated the effect of provision of genotype-based dietary advice on behaviour change have reported contradictory findings, both within and between studies (Celis-Morales

et al., 2017; Horne, Gilliland, O'Connor, et al., 2020; King et al., 2022; Nielsen & El-Sohemy, 2014). Study three, a systematic review and meta-analysis of genotype-based personalised advice for dietary and physical activity behaviour change, suggested that genotype-based advice does not affect dietary or physical activity behaviour more than general advice or advice based on lifestyle or phenotypic measures (King et al., 2023). This is in agreement with a systematic review by Jinnette at al. (2020) who concluded that although personalisation of dietary advice promotes positive changes in dietary behaviour, the addition of genetics to other levels of personalisation of advice may not be warranted to motivate and initiate behaviour change.

However, one benefit of genotype-based personalisation of advice over other levels of personalisation is that it can be delivered earlier in the lifespan. Personalisation of advice based on genotype can be delivered to young adults before unhealthy lifestyle behaviours or metabolic and physiological conditions have developed. Informing a young adult of their genotype-based risk and providing appropriate advice has the potential to prevent the development of unhealthy lifestyle behaviours that can lead to metabolic and physiological conditions (raised blood pressure, obesity, raised blood glucose, dyslipidaemia) that increase the risk of developing NCD such as CVD and T2D. Therefore, young people stand to benefit from genotype-based dietary and physical activity advice (NICE, 2007; Stewart-Knox et al., 2013).

In study two provision of personalised advice, with or without genetics did not influence healthy-eating motivation in young adults. Therefore, to effectively implement genotype-based personalised advice to affect behaviour in young adults an understanding of factors that may encourage or prevent engagement is required. Interventions designed to change health-related behaviours are more likely to be successful when theoretical links between the intervention and the behaviour have been considered in the design (Davis et al., 2015; Horne et al., 2017; NICE, 2007; Timlin et al., 2020). One of the most frequently cited behaviour change theories incorporated in health-related interventions is the TPB (Ajzen, 1991; Davis et al., 2015). The TPB states that 'intention' or motivation to perform a behaviour can be predicted from three independent factors; attitude toward the behaviour, subjective norms, and PBC (Ajzen, 1991). 'Attitude toward the behaviour' represents the extent to which an individual has a favourable appraisal of that behaviour, 'subjective norms' is the individual's

perceived social pressure to perform or not perform the behaviour and 'PBC' is an individual's perception of how easy or difficult it is to perform the behaviour. If an individual has a favourable attitude toward the behaviour and a supportive subjective norm then their motivation to perform the behaviour will be high; however, this will only translate into a strong intention to perform the behaviour when PBC is also high (Ajzen, 2020). Each construct of the TPB is influenced by belief composites: behavioural beliefs, normative beliefs, and control beliefs (Ajzen, 1991). 'Attitude toward the behaviour' is affected by 'behavioural beliefs' - the subjective probability that the behaviour will produce a given outcome or experience. 'Subjective norms' are affected by 'normative beliefs' which represents the perceived behavioural expectations of important referent individuals or groups, such as peers or a doctor. 'PBC' is affected by 'control beliefs' - the perceived presence of factors that may facilitate or impede performance of a behaviour (see Figure 1.1, Chapter 1). The 'intention' and 'PBC' have been demonstrated to account for a significant amount of variation in numerous health related behaviours including food choice (Ajzen, 1991; McDermott et al., 2015). Furthermore, background factors such as demographic characteristics, personality traits, and life values can influence intentions to perform a behaviour by affecting TPB constructs (Ajzen, 2020). Investigation of the relationship between background factors and constructs of the TPB may enable explanations of why a background factor influences or fails to influence a behaviour (Ajzen, 2020). There are several background factors that could influence intention to engage with personalised advice in young adults including optimistic bias, HLC, food choice motives, and participant characteristics (Bayer et al., 2021; Poínhos et al., 2014; Rankin et al., 2017; Stewart-Knox et al., 2013, 2021; Vallée Marcotte et al., 2018).

Optimistic bias is the phenomenon by which an individual underestimates their own risk of developing a disease compared to others (Shepherd, 1999). Individuals with high levels of optimistic bias may not believe they need to change their behaviour as they perceive that they are at a lower risk of developing a disease. Optimistic bias is likely to feature highly in young populations that perceive themselves to be healthy (Stewart-Knox et al., 2013). The HLC refers to whether an individual perceives their health to be under their control (internal) or not (external) (Wallston et al., 1976). An internal HLC has been associated with a more positive attitude to genotype-based personalised nutrition (Poínhos et al., 2014). Food choice motives have been shown to relate to intention and motivation towards genotype-based

personalised nutrition. Price and sensory appeal were identified as the most important motives for food choice, and both had a negative association with intention to adopt personalised nutrition (Rankin et al., 2018). Whereas, the motives of health, weight control and mood had a positive association with intention to adopt personalised nutrition (Rankin et al., 2018). Participant characteristics may also influence intention to adopt personalised nutrition in young adults; for example, research suggests that females have a more favourable attitude compared to males (Stewart-Knox et al., 2021). Studies have consistently reported that participants with either a personal or a family history of NCD are more willing to follow genotype-based dietary recommendations (Bayer et al., 2021; Stewart-Knox et al., 2009; Vallée Marcotte et al., 2018). Therefore, perception of being overweight or obese may influence the intention of young adults making them more receptive to genotype-based personalised nutrition.

An understanding of how TPB constructs, belief composites, and background factors relate to intention to engage with personalised nutrition in young adults would inform researchers and health practitioners how best to communicate genotype-based personalised advice to promote healthy lifestyle behaviours in this population. The aim of the present study was to investigate the factors that influence the intention to adopt genotype-based personalised advice for diet and physical activity in young adults. Also, to separately investigate the factors that influence the intention to adopt genotype-based personalised advice for diet and physical activity in young adults that perceive themselves to be a healthy weight and those that perceive themselves to be overweight or obese. The overall aim was broken down into four objectives, described below and presented in Figure 5.1.

Objective 1. Theory of Planned behaviour: Determine the relationship between the constructs of the TPB (attitude, subjective norms, PBC) and intention of young adults to adopt genotype-based personalised advice for diet and physical activity.

Objective 2. Belief composites and TPB constructs: Investigate the association between belief composites (behavioural beliefs, normative beliefs and control beliefs) and direct measures of TPB constructs (attitude, subjective norms and PBC) to understand the most important beliefs in a young adult population.

Objective 3. Characteristics, psychological factors, food choice motives and TPB constructs: Investigate the association between characteristics (gender, education, health perception, physical activity), psychological factors (optimistic bias, internal HLC, external HLC) and food choice motives (health, mood, convenience, sensory appeal, natural content, price, weight control, familiarity, ethical concern) with constructs of the TPB (attitude, subjective norms, PBC).

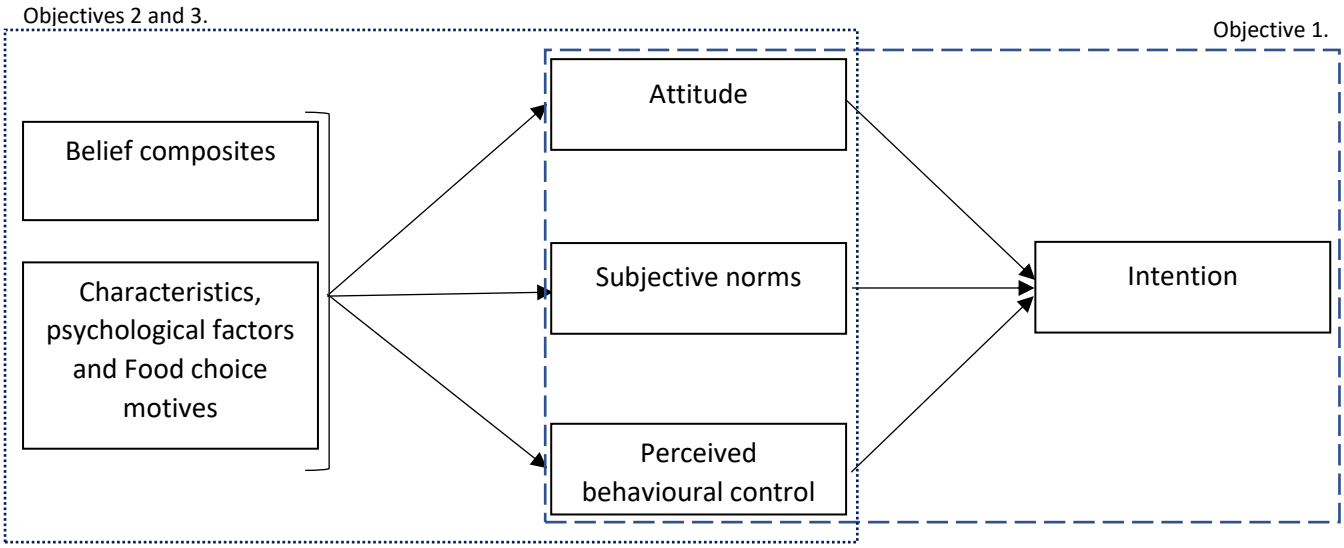

Figure 5.1. Specification of theory of planned behaviour model and study objectives.

5.2. Methods:

5.2.1 Participants:

Three hundred and ninety-six male and female young adults aged 18-25 years, living in the UK, who were not pregnant, lactating, following a restricted diet, or having a diagnosed eating disorder were recruited to take part in the survey. Participants were recruited through advertisements and social media postings. Data was collected between March and November 2022 using Jisc online surveys. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethical Committee (SMEC_2022-23_027). Informed consent was obtained from all participants (Appendix 12). All data were collected and stored according to the Data Protection Act 1998.

5.2.2 Survey development:

A pilot survey was conducted in 35 young adults (18-25 years) (Appendix 13). The pilot survey was carried out to assess the usability of the survey as well as to develop the TPB questionnaire following guidance from Ajzen (2006). Items used to measure the TPB constructs were assessed following the pilot survey for internal consistency and discriminant validity. In order to develop appropriate items to measure belief composites free response questions were used in the pilot study to elicit behavioural outcomes and experiences (perceived advantages, disadvantages and feelings), normative referents (individuals or groups that would approve or disapprove), and control factors (factors that would make it easy or difficult) in relation to the adoption of genotype-based advice to modify dietary or physical activity behaviour. Content analysis of free response questions was used to construct items to be used in the final survey (Ajzen, 2006).

5.2.2.1 Usability of the survey

The majority of participants reported that the survey took them 15-20 minutes to complete (n = 25; 72%); the time reported ranged from 10 – 32 minutes. All participants responded positively to the question to determine if they understood the definition of personalised nutrition; one participant suggested that additional information be provided. Four participants commented on finding the switching of Likert scales from positive to negative for some questions and negative to positive for others confusing. Literature suggests that the use of reverse-scored items in questionnaires is debatable; although it may reduce response set bias, it increases cognitive processing demands and may affect psychometric properties of the question (Tsang et al., 2017). Consequently, reverse-scoring was not used in the final survey.

5.2.2.2 Internal consistency

Internal consistency is a measure of homogeneity or reliability among items used to measure the same construct and was assessed using α (Tavakol & Dennick, 2011). Values for each construct are presented in Table 5.1. An $\alpha > 0.7$ has been suggested to indicate adequate internal consistency (Tavakol & Dennick, 2011). This was met for all constructs except subjective norms. When item 4 was deleted, the α increased but remained below the 0.7 cut-off, $\alpha > 0.6$ has also been described in some literature as acceptable (Taber, 2018). Since

reducing the number of items would reduce the α and the value was close to acceptability, the remaining items to measure subjective norms were retained and internal consistency was reassessed in the final survey with a larger sample size (see section 5.2.3).

Table 5.1. Assessment of internal consistency.

Construct	Cronbach's alpha
Attitudes	0.755
Subjective norms	0.557 (0.567)*
Perceived behavioural control	0.723
Intention	0.735

*Change in Cronbach's alpha following deletion of item 4 for subjective norms.

5.2.2.3. Discriminant validity

Discriminant validity determines whether constructs that are not theoretically related are unrelated to other constructs (Campbell & Fiske, 1959). Discriminant validity was assessed using heterotrait-monotrait ratio of correlations (HTMT) (Henseler et al., 2015). The results of HTMT for each pair of constructs are presented in Table 5.2. The HTMT ratios were all below 0.90 except for attitudes and subjective norms (0.93). Hensler et al. (2015) suggests a HTMT ratio greater than 0.9 signifies a problem with discriminant validity between these constructs. To retain the constructs that suggest a problem with discriminant validity, Henseler et al. (2015) recommend eliminating items that have low correlations with items measuring the same construct. Removal of the fourth item measuring subjective norms increased the monotrait correlation for subjective norms from 0.239 to 0.305. The HTMT ratio for attitudes and subjective norms was subsequently reduced to 0.823 meeting the criteria for discriminant validity. Therefore, item 4 for subjective norms was removed from the final survey.

Table 5.2. Assessment of discriminant validity.

	Attitudes	Subjective norms	Perceived behavioural control
Attitudes			
Subjective norms	0.93 (0.823)*		
Perceived behavioural control	0.85	0.305	
Intention	0.80	0.53	0.71

*Change in HTMT ratio following deletion of item 4 for subjective norms.

5.2.2.4. Constructing items to measure control beliefs

Pilot study items were used to elicit salient outcomes and experiences, normative referents, and control factors related to the adoption of genotype-based advice to modify dietary or physical activity behaviour in a young adult population. A content analysis of participant responses provided a list of modal salient outcomes, referents and control factors. These were used to construct items to assess: i) the strength of behavioural beliefs and evaluation of the outcome experience; ii) normative referents and motivation to comply; and iii) control beliefs and power of control factors (Table 5.3).

Table 5.3. Modal salient beliefs from content analysis and items added to final questionnaire.

Salient belief	Item
Behavioural outcomes and experiences Achieve health and fitness goals Provide motivation Restrictive Effort and time to make changes Prevent disease Concern about risk Cost	**Behavioural belief strength** (likely-unlikely) genotype-based advice to modify dietary or physical activity behaviour will help me to achieve health and fitness goals. genotype-based advice to modify dietary or physical activity behaviour will provide me with motivation to eat healthily and exercise. genotype-based advice to modify dietary or physical activity behaviour will restrict my food choices. genotype-based advice to modify dietary or physical activity behaviour will take effort and time to make changes. genotype-based advice to modify dietary or physical activity behaviour will help me to prevent disease. genotype-based advice to modify dietary or physical activity behaviour will cause me to worry about the risk of developing a disease. genotype-based advice to modify dietary or physical activity behaviour will be expensive. **Outcome evaluation** (good - bad) For me achieving health and fitness goals is For me to prevent the development of disease is For me to be motivated to eat healthily and exercise is For me restriction of my food choices is For me to take effort and time to make changes is For me the expense of genotype-based advice is For me to worry about the risk of developing a disease is
Normative referents Friends Family Influencers Health professionals	**Normative beliefs** (likely-unlikely) My friends would think I should use genotype-based advice to modify dietary or physical activity behaviour. My family would think I should use genotype-based advice to modify dietary or physical activity behaviour. Influencers and people I follow on social media would think I should use genotype-based advice to modify dietary or physical activity behaviour. Health professionals would think I should use genotype-based advice to modify dietary or physical activity behaviour. **Motivation to comply** (agree-disagree) When it comes to matters of health, I want to do what my friends think I should do. When it comes to matters of health, I want to do what my family think I should do. When it comes to matters of health, I want to do what influencers and people I follow on social media think I should do. When it comes to matters of health, I want to do what health professionals think I should do.
Control factors Time Clear guidance Confidence in advice Cost	**Control belief** (rarely - frequently) How often does lack of time prevent you from eating healthily and or exercising? How often does lack of clear guidance prevent you from eating healthily and or exercising? How often does lack of confidence in effectiveness of guidance prevent you from eating healthily and or exercising? How often does lack of money prevent you from eating healthily and or exercising? **Power of control factor** (agree-disagree) Having enough time would enable me to adopt genotype-based advice to modify dietary or physical activity behaviour. Having enough money would enable me to adopt genotype-based advice to modify dietary or physical activity behaviour. Having confidence in the effectiveness of guidance would enable me to adopt genotype-based advice to modify dietary or physical activity behaviour. Having clear guidance would enable me to adopt genotype-based advice to modify dietary or physical activity behaviour.

5.2.3. Final survey:

The final survey was divided into three sections (Appendix 14). The first section 'about you' asked participants about the following characteristics: gender, age, ethnicity, education, perceived health, physical activity behaviour, and their perceived body image. Physical activity was assessed using a single question to determine whether participants were sufficiently active to benefit their health (Milton et al., 2013). To measure perceived body image, participants were asked to indicate their own body figure by choosing a silhouette of the Stunkard Scale (Parzer et al., 2021; Stunkard et al., 1983; Thompson & Altabe, 1991). Males that chose silhouettes 1-4 were classed as normal weight, 5 and 6 overweight and 7-9 obese; females that chose silhouette 1 were classed as underweight, 2-4 normal weight, 5 and 6 overweight, and 7-9 obese (Parzer et al., 2021).

The second section 'your health' asked participants about their HLC, motives for food choice, and optimistic bias. For each scale, internal consistency was checked; α levels for all factors indicated adequate internal consistency (Tavakol & Dennick, 2011). To assess HLC, participants were asked to indicate the extent to which they agree or disagree with six statements. For example: 'I can be as healthy as I want to be.' Response: Completely disagree, Disagree, Neither disagree/nor agree, Agree, Completely agree (Gebhardt, 2001; Poínhos et al., 2014). The internal HLC was calculated from the average score for the first three items (α = 0.77) and external HLC for the second three items (α = 0.70) (Gebhardt, 2001). Motives for food choice were measured using the Food Choice Questionnaire. Participants were asked to respond to the following statement for 36 items. For example: 'It is important to me that the food I eat on a typical day keeps me healthy'. Response: Not at all important, A little important, Moderately Important, Very Important, Extremely important (Steptoe et al. 1995). The 36 items represent nine factors and the mean score from 1-5 was calculated for each factor (health (α = 0.86), mood (α = 0.88), convenience (α = 0.87), sensory appeal (α = 0.82), natural content (α = 0.88), price (α = 0.83), weight control (α = 0.86), familiarity (α = 0.74), ethical concern (α = 0.79). Optimistic bias was estimated by asking participants to respond to the following statement 'How do you think your chances of getting cardiovascular disease in the future compare with those of the average adult of your age and sex? Your chances are: Response: 7-point Likert scale (much lower than average - much higher than average) (Klein,

2020). Participants were also asked with reference to type 2 diabetes and obesity. The mean score of all three items was used to calculate overall optimistic bias (α = 0.86).

The final section of the survey, 'genotype-based personalised advice', asked participants about the disease context of genotype-based personalised advice and how potential outcomes related to genotype-based personalised advice would increase the likelihood of adopting it. These questions were based on a survey from Poínhos et al. (2014). This section also asked questions to determine the constructs of the TPB related to the adoption of genotype-based dietary and physical activity advice. The items to measure the constructs of TPB and how they were constructed from the pilot survey are detailed in the pilot study section; α was reassessed in the final survey and values for each TPB construct are provided (Ajzen, 2006). The direct measures of TPB constructs (attitude (α = 0.88), subjective norms (α = 0.77), PBC (α = 0.81) and intention (α = 0.87) were calculated from the mean score of items for each construct. Belief composites (behavioural, normative, and control beliefs) were calculated as followed: Behavioural beliefs were calculated by multiplying each strength of belief (b) by the respective outcome evaluation (e) and aggregating the products ($\Sigma b_i e_i$). Normative beliefs were calculated by multiplying the strength of each normative belief (n) by the significance of the referent to the participant (s) and aggregating the products ($\Sigma n_i s_i$). Control beliefs were calculated by multiplying the strength of each control belief (c) by the perceived power of the control factor (p) and aggregating the products ($\Sigma c_i p_i$) (Ajzen, 2020).

5.2.4. Statistical Analysis:

A sample size of 384 was calculated based on Krejcie and Morgan's (1970) table of sample size determination. Statistical analysis was carried out using IBM SPSS Statistics 26 for Windows (IBM Corp, New York, USA). Measures of centrality and spread are presented as means ± SD; categorical data are presented as frequencies and percentages. Comparisons were made between participants that perceived themselves to be normal weight with those that perceived themselves to be overweight or obese. Since the aim of the study was to compare participants that perceived themselves to be normal weight with those that considered themselves to be overweight or obese, participants that perceived themselves to be underweight were excluded from analysis (n = 5). Normality of data was assessed using

the Shapiro-Wilk test. Baseline continuous measures were not normally distributed ($p \geq 0.05$) and were compared between groups and between males and females using a Mann-Whitney U test. Categorical variables were compared using a Chi-squared Test or when expected counts were less than five, a Fisher's Exact Test. For *post hoc* analysis a Bonferroni adjustment was made to correct for multiple comparisons. Multiple regression analysis was conducted to identify the relationship between constructs of the TPB and intention to adopt genotype-based personalised nutrition. Analysis was conducted with all participants and separately in those that perceived themselves to be normal weight and those that perceived themselves to be overweight or obese. Linearity was assessed by partial regression plots and a plot of studentised residuals against the predicted values. Independence of residuals was assessed by the Durbin-Watson statistic. Homoscedasticity was assessed by visual inspection of a plot of studentised residuals versus unstandardised predicted values. Multicollinearity was assessed by tolerance values greater than 0.1. Outliers were identified and investigated when studentised deleted residuals were greater than ± 3 standard deviations, leverage values were assessed if greater than 0.2, and values for Cook's distance above 1. The assumption of normality was assessed by a Q-Q Plot. Spearman's rank-order correlation analysis was carried out to determine the relationship between behavioural beliefs, food choice motives, characteristics and psychological factors, and each construct of the TPB. Analysis was conducted with all participants and separately in those that perceived themselves to be normal weight and those that perceived themselves to be overweight or obese. A Bonferroni adjustment was made to correct for multiple comparisons. All tests were two tailed and considered statistically significant when $p < 0.05$.

5.3 Results:

5.3.1 Participant characteristics:

Three hundred and ninety-six participants completed the survey; the mean age of participants was 21 years. The majority were women (61%), were of white ethnicity (68%), were living in England (97%), and listed further education (61%) as the highest level of education that they had completed. The majority of participants considered themselves as healthy (64%) and on average exercised four days a week (Table 5.4). Seventy six percent of participants perceived themselves to be normal weight, with 23% overweight or obese, and one percent underweight. Compared to participants that perceived themselves to be normal weight, participants that perceived themselves to be overweight were more likely to be male (X^2 = 11.7, p = 0.001) and reported to be physically active more frequently (z = -3.417, p = 0.001). There was also a statistically significant difference between proportions for how healthy participants considered themselves (p < 0.001). Compared to participants that perceived themselves to be overweight or obese, a greater proportion of participants that perceived themselves to be normal weight considered themselves to be very healthy compared to healthy, moderately healthy, or unhealthy. Also, a greater proportion considered themselves to be healthy compared to unhealthy (p < 0.05). There was no significant difference between the proportion of participants that perceived themselves to be overweight or obese versus those that perceived themselves to be normal weight based on their age (z = -1.477, p = 0.475), ethnicity (p = 0.063), country of residence (p = 0.179), or highest level of education that they had completed (p = 0.317).

Table 5.4. Characteristics for all participants (n = 396), and for those that perceive themselves to be normal weight (n = 299) and those that perceive themselves to be overweight or obese (n = 92) data presented as n (%) or mean ± sd.

		Normal weight (n = 299)	**Overweight or obese** (n = 92)	**All participants** (n = 396)	***P* value**
Gender	*Men*	103 (34)	50 (54)	153 (39)	***p* = 0.001**
	Women	196 (66)	42 (46)	243 (61)	
Age	(years)	21 ± 2	21 ± 2	21 ± 2	*p* = 0.475
Ethnicity	*Asian or Asian British*	29 (10)	17 (19)	46 (12)	*p* = 0.063
	Black, Black British, Caribbean or African	27 (9)	8 (9)	35 (9)	
	Mixed or multiple ethnic groups	18 (6)	8 (9)	27 (7)	
	White	214 (72)	53 (58)	271 (68)	
	Other ethnic group	11 (4)	6 (7)	17 (4)	
Country of residence	*England*	293 (98)	87 (95)	385 (97)	*p* = 0.179
	Wales	1 (0)	1 (1)	2 (1)	
	Scotland	2 (1)	1 (1)	3 (1)	
	Northern Ireland	3 (1)	3 (3)	6 (2)	
Education	*Secondary School (GCSE or equivalent)*	9 (3)	4 (4)	14 (4)	*p* = 0.317
	Further Education (A Level or equivalent)	187 (63)	53 (58)	243 (61)	
	Bachelor's Degree	86 (29)	26 (28)	112 (28)	
	Master's Degree	16 (5)	7 (8)	24 (6)	
	Prefer not to say	1 (0)	2 (2)	3 (1)	
Health Perception	*Very unhealthy*	3 (1)	2 (2)	5 (1)	***p* < 0.001**
	Unhealthy	5 (2)	9 (10)	14 (4)	
	Moderately unhealthy	48 (16)	27 (29)	77 (19)	
	Healthy	198 (66)	53 (58)	253 (64)	
	Very healthy	45 (15)	1 (1)	47 (12)	
Physical activity	(days/week)	4.2 ± 1.9	3.4 ± 1.9	4.0 ± 2.0	***p* = 0.001**
Perceived body image	*Underweight*	0 (0)	0 (0)	5 (1)	
	Normal weight	299 (100)	0 (0)	299 (76)	
	Overweight	0 (0)	75 (82)	75 (19)	
	Obese	0 (0)	17 (19)	17 (4)	

5.3.2. Psychological factors, motives for food choice, and constructs of the TPB

Compared to participants that perceived themselves to be normal weight, participants that perceived themselves to be overweight or obese had a significantly lower internal HLC, overall optimistic bias, and optimistic bias for developing CVD, and obesity ($p < 0.05$). There were no significant differences between groups for external HLC, food choice motives, or constructs of the TPB ($p \geq 0.05$). Sensory appeal was the highest rated food choice motive, followed by price and health. The lowest rated food choice motive was ethical concern followed by familiarity and weight control in the participants that perceived themselves to be normal weight; in participants that perceived themselves to be overweight or obese, the next lowest rated food choice motive was natural content. Mean scores for all constructs of the TPB were positive (Table 5.5).

Table 5.5. Psychological factors, motives for food choice and constructs of the Theory of Planned Behaviour for all participants, and for those that perceive themselves to be normal weight and those that perceive themselves to be overweight or obese, data presented as mean ± sd.

	Normal weight (n = 299)	**Overweight or obese** (n = 92)	**All participants** (n = 396)
Internal Health locus of control	4.0 ± 0.6	3.8 ± 0.8*	4.0 ± 0.7
External Health locus of control	1.7 ± 0.6	1.8 ± 0.7	1.7 ± 0.6
Optimistic bias	5.2 ± 1.3	4.2 ± 1.3*	5.0 ± 1.4
CVD	5.0 ± 1.3	4.3 ± 1.4*	4.9 ± 1.4
T2D	5.1 ± 1.5	4.2 ± 1.5*	4.9 ± 1.5
Obesity	5.6 ± 1.3	4.2 ± 1.8*	5.3 ±1.6
Food choice motives			
Health	3.5 ± 0.7	3.4 ± 0.8	3.5 ± 0.7
Mood	3.3 ± 0.9	3.4 ± 0.8	3.3 ± 0.9
Convenience	3.2 ±0.8	3.2 ± 1.0	3.1 ± 0.9
Sensory appeal	3.7 ± 0.8	3.6 ± 0.9	3.7 ± 0.8
Natural content	3.1 ± 1.0	2.9 ± 1.1	3.0 ± 1.0
Price	3.5 ± 0.8	3.6 ± 0.8	3.6 ± 0.9
Weight control	2.8 ± 1.0	3.0 ± 1.1	2.8 ± 1.1
Familiarity	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.9
Ethical concern	2.2 ± 0.9	2.1 ± 0.9	2.1 ± 0.9
TPB constructs			
Attitude	5.0 ±1.1	4.9 ± 1.2	5.0 ± 1.1
Subjective Norms	4.8 ± 1.1	4.6 ± 1.3	4.7 ± 1.2
Perceived Behavioural Control	4.8 ± 1.1	4.7 ± 1.0	4.8 ± 1.1
Intention	4.5 ± 1.3	4.5 ± 1.2	4.5 ± 1.3

*significantly different to participants that perceive themselves to have a normal body weight
$p < 0.05$. CVD: cardiovascular disease, T2D: type 2 diabetes; TPB: theory of planned behaviour.

Compared to male participants, female participants had a significantly lower internal HLC, overall optimistic bias, and optimistic bias for developing CVD, and obesity ($p < 0.05$). There were no significant differences between males and females for external HLC, food choice motives, or constructs of the TPB ($p \geq 0.05$). Data are presents in Table 5.6.

Table 5.6. Psychological factors, motives for food choice and constructs of the Theory of Planned Behaviour for all participants, and for male and female participants, data presented as mean ± sd.

	Female (n = 238)	**Male** (n = 153)	**All participants** (n = 396)
Internal Health locus of control	3.9 ± 0.7	4.1 ± 0.7*	4.0 ± 0.7
External Health locus of control	1.7 ± 0.6	1.7 ± 0.7	1.7 ± 0.6
Optimistic bias	4.8 ± 1.3	5.2 ± 1.4*	5.0 ± 1.4
CVD	4.7 ± 1.3	5.1 ± 1.4*	4.9 ± 1.4
T2D	4.7 ± 1.5	5.1 ± 1.6	4.9 ± 1.5
Obesity	5.1 ± 1.5	5.5 ± 1.7*	5.3 ±1.6
Food choice motives			
Health	3.5 ± 0.7	3.5 ± 0.7	3.5 ± 0.7
Mood	3.4 ± 0.8	3.2 ± 0.9	3.3 ± 0.9
Convenience	3.2 ± 0.9	3.2 ± 0.9	3.1 ± 0.9
Sensory appeal	3.8 ± 0.8	3.6 ± 0.8	3.7 ± 0.8
Natural content	3.1 ± 1.0	2.9 ± 1.0	3.0 ± 1.0
Price	3.6 ± 0.9	3.5 ± 0.8	3.6 ± 0.9
Weight control	2.9 ± 1.0	2.8 ± 1.1	2.8 ± 1.1
Familiarity	2.6 ± 0.9	2.5 ± 0.9	2.5 ± 0.9
Ethical concern	2.2 ± 0.9	2.0 ± 0.9	2.1 ± 0.9
TPB constructs			
Attitude	5.1 ± 1.1	4.9 ± 1.1	5.0 ± 1.1
Subjective Norms	4.8 ± 1.2	4.6 ± 1.1	4.7 ± 1.2
Perceived Behavioural Control	4.8 ± 1.1	4.8 ± 1.1	4.8 ± 1.1
Intention	4.6 ± 1.3	4.4 ± 1.2	4.5 ± 1.3

*significantly different to female participants $p < 0.05$. CVD: cardiovascular disease, T2D: type 2 diabetes; TPB: theory of planned behaviour.

5.3.3 Objective 1: Theory of Planned behaviour

Relationship between attitude, subjective norm and PBC with intention to adopt genotype-based personalised nutrition.

Multiple regression models significantly predicted intention to adopt genotype-based personalised nutrition for all participants (F (3, 387) = 155.074, $p < 0.001$, adj. $R^2 = 0.54$), those that perceived themselves to be normal weight (F (3, 295) = 138.122, $p < 0.001$, adj. $R^2 = 0.58$), and those that perceived themselves to be overweight or obese (F (3, 88) = 21.246, $p < 0.001$,

adj. R^2 = 0.40). The contributions of attitude, subjective norm and PBC are presented in Table 5.7 and summarised in figure 5.2.

Table 5.7 Multiple regression results for intention to adopt genotype-based personalised nutrition from TPB constructs for all participants, participants that perceived themselves normal weight, and participants that perceived themselves overweight or obese.

Intention	***B***	**95% CI for *B***		**SE *B***	***β***	***R^2***	**Δ *R^2***
All						.546	.542*
Constant	-.025	-.448	.398	.215			
PBC	.447*	.339	.555	.055	.390*		
SN	.250*	.152	.347	.050	.234*		
Attitude	.243*	.135	.352	.055	.223*		
NW						.584	.580*
Constant	-.189	-.655	.278	.237			
PBC	.463*	.339	.588	.063	.407*		
SN	.254*	.134	.374	.061	.227*		
Attitude	.250*	.125	.374	.063	.224*		
OW						.420	.400*
Constant	.514	-.508	1.537	.514			
PBC	.384**	.148	.620	.119	.323**		
SN	.240**	.061	.419	.090	.258**		
Attitude	.225	-.002	.452	.114	.219		

Model: Stepwise method; B: unstandardized regression coefficient; CI: confidence interval; SE B: standard error of the coefficient; β: standardised coefficient; R^2: coefficient of determination; Δ R^2: adjusted R^2; SN: subjective norms; PBC: perceived behavioural control, All: all participants (n = 391); NW: participants that perceive themselves to be normal weight (n = 299); OW: participants that perceive themselves to be overweight or obese (n = 92). * $p < 0.001$.

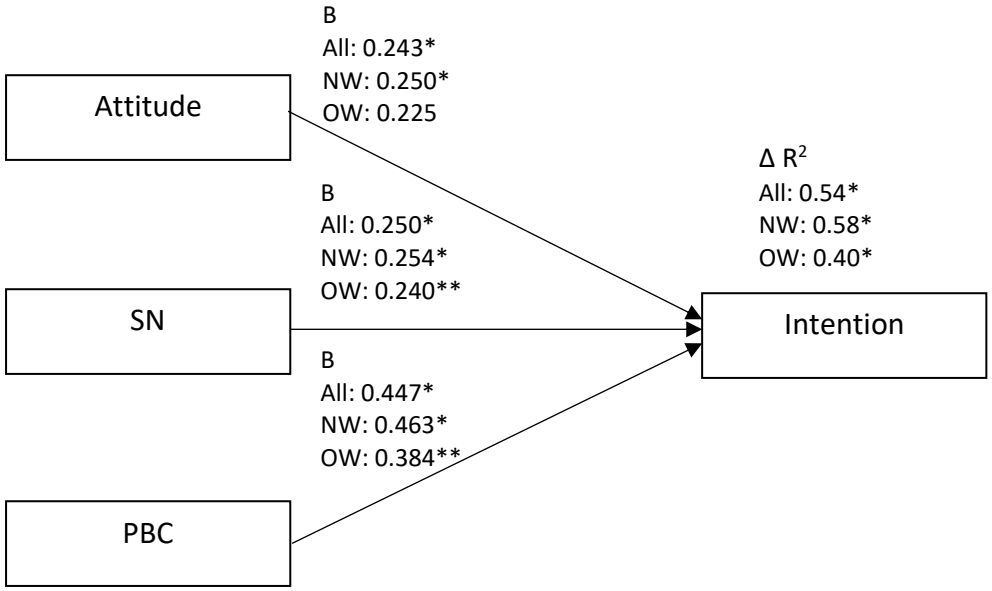

Figure 5.2 Summary of unstandardized regression coefficients and adjusted R^2 of constructs of TPB, for all participants, participants that perceive themselves to be normal weight and participants that perceive themselves to be overweight or obese.

B: unstandardized regression coefficient; Δ R^2: adjusted R^2; SN: subjective norms; PBC: perceived behavioural control; All: all participants (n = 391); NW: participants that perceive themselves to be normal weight (n = 299); OW: participants that perceive themselves to be overweight or obese (n = 92). * $p < 0.001$; ** $p < 0.05$.

5.3.4 Objective 2. Belief composites and TPB constructs

Relationship between behavioural beliefs and attitude to adopt genotype-based personalised nutrition.

A Spearman's rank-order correlation was run to assess the relationship between behavioural beliefs and attitude to adopt genotype-based personalised nutrition. Analysis in all participants and in participants that perceived themselves to be normal weight revealed a statistically significant, positive correlation between behavioural beliefs of 'achieving health and fitness goals', 'motivation to eat healthily and exercise', 'restricting food choices', 'taking time and effort to make changes', 'prevent disease', and 'expense' with attitude towards genotype-based personalised advice ($p < 0.05$). For participants that perceived themselves to be overweight or obese statistically significant, positive correlations were observed for behavioural beliefs of 'achieving health and fitness goals', 'motivation to eat healthily and exercise', 'taking time and effort to make changes', and 'prevent disease' with attitude towards genotype-based personalised advice ($p < 0.05$). Correlation coefficients and

significance values for each behavioural belief and attitude towards genotype-based personalised advice are presented in Table 5.8.

Table 5.8 Spearman's correlation analysis for attitude towards genotype-based personalised nutrition from behavioural beliefs for all participants, participants that perceived themselves normal weight, and participants that perceived themselves overweight or obese.

	All	**NW**	**OW**
	r_s	**r_s**	**r_s**
Health and fitness	.643*	.648*	.627*
Motivation	.663*	.667*	.641*
Restrict food	.140*	.201*	-.061
Time and effort	.470*	.503*	.355*
Prevent disease	.587*	.590*	.579*
Worry	.042	.099	-.143
Expensive	.279*	.318*	.157

r_s: Spearman's correlation coefficient; All: all participants (n = 391); NW: participants that perceive themselves to be normal weight (n = 299); OW: participants that perceive themselves to be overweight or obese (n = 92). *$p < 0.05$.

Relationship between normative beliefs and subjective norms

Normative beliefs for family and health professionals were significantly, positively associated with subjective norms in analysis for all groups ($p < 0.05$). Correlation coefficients for each normative belief and subjective norms are presented in Table 5.9.

Table 5.9 Spearman's correlation analysis for subjective norms and normative beliefs for all participants, participants that perceived themselves normal weight, and participants that perceived themselves overweight or obese.

	All	**NW**	**OW**
	r_s	**r_s**	**r_s**
Friends	.087	.089	.113
Family	.209*	.202*	.261*
Influencers	.022	.041	-.003
Health professionals	.451*	.435*	.489*

r_s: Spearman's correlation; All: all participants (n = 391); NW: participants that perceive themselves to be normal weight (n = 299); OW: participants that perceive themselves to be overweight or obese (n = 92). *$p < 0.05$.

Relationship between control beliefs and perceived behavioural control

Control beliefs for 'lack of time' and 'lack of money' were significantly, positively associated with PBC in analysis for all groups ($p < 0.05$). Control beliefs of' clear guidance' and 'confidence in effectiveness of guidance' were significantly positively correlated with PBC in analysis of all participants and those that perceived themselves to be normal weight ($p < 0.05$). Correlation coefficients and significance values for each control belief and PBC are presented in Table 5.10.

Table 5.10 Spearman's correlation analysis for perceived behavioural control and control beliefs for all participants, participants that perceived themselves normal weight, and participants that perceived themselves overweight or obese.

	All	**NW**	**OW**
	r_s	**r_s**	**r_s**
Time	.220*	.223*	.226*
Clear guidance	.233*	.268*	.146
Confidence	.170*	.204*	.081
Money	.233*	.243*	.212*

r_s: Spearman's correlation; All: all participants (n = 391); NW: participants that perceive themselves to be normal weight (n = 299); OW: participants that perceive themselves to be overweight or obese (n = 92). *$p < 0.05$.

5.3.5 Objective 3: Characteristics, psychological factors, food choice motives and TPB constructs

Attitude towards adopting genotype-based personalised nutrition.

A Spearman's rank-order correlation was run to assess the relationship between participant characteristics, psychological factors and food choice motives with attitude towards adopting genotype-based personalised nutrition. Analysis in all groups revealed a significant positive correlation between the food choice motive of 'health' and a significant negative relationship between external HLC with attitude towards genotype-based advice. ($p < 0.05$). All other correlations did not reach statistical significance ($p \geq 0.05$). Correlation coefficients and significance values for participant characteristics, psychological factors and food choice motives with attitude towards genotype-based personalised advice are presented in Table 5.11.

Table 5.11 Spearman's correlation analysis for attitude towards genotype-based personalised nutrition with participant characteristics, psychological factors and food choice motives for all participants, participants that perceived themselves normal weight, and participants that perceived themselves overweight or obese.

	All	**NW**	**OW**
	r_s	**r_s**	**r_s**
Education	.066	.111	-.071
Health perception	.069	.058	.072
Physical activity	.084	.088	.054
IHLC	.119	.080	.233
EHLC	-.374*	-.376*	-.342*
Optimistic bias	.078	.064	.120
Food choice motives:			
Health	.237*	.211*	.322*
Mood	.121	.124	.123
Convenience	-.036	-.021	-.067
Sensory Appeal	.099	.111	.082
Natural content	.122	.144	.046
Price	.100	.092	.162
Weight control	.036	-.021	.236
Familiarity	-.133	-.119	-.167
Ethical concern	.049	.074	-.038

r_s: Spearman's correlation All: all participants (n = 391); NW: participants that perceive themselves to be normal weight (n = 299); OW: participants that perceive themselves to be overweight or obese (n = 92). *$p < 0.05$.

Subjective norms

A Spearman's rank-order correlation was run to assess the relationship between participant characteristics, psychological factors and food choice motives with subjective norms. Analysis in all participants and participants that perceived themselves to be normal weight revealed a significant negative relationship between external HLC with subjective norms ($p < 0.05$). All other correlations did not reach statistical significance ($p \geq 0.05$). Correlation coefficients for participant characteristics, psychological factors and food choice motives with subjective norms are found in Table 5.12.

Table 5.12 Spearman's correlation analysis for subjective norms with participant characteristics, psychological factors and food choice motives for all participants, participants that perceived themselves normal weight, and participants that perceived themselves overweight or obese.

	All	**NW**	**OW**
	r_s	**r_s**	**r_s**
Education	-.024	.061	.105
Health perception	.081	-.012	.100
Physical activity	-.011	.031	-.151
IHLC	.036	.019	.061
EHLC	-.203*	-.277*	.046
Optimistic bias	.048	-.010	.134
Food choice motives:			
Health	.130	.112	.177
Mood	.121	.092	.222
Convenience	.020	.021	.024
Sensory Appeal	.108	.110	.098
Natural content	.098	.066	.168
Price	.039	.019	.129
Weight control	.009	-.061	.228
Familiarity	-.047	-.062	-.009
Ethical concern	.071	.032	.208

r_s: Spearman's correlation All: all participants (n = 391); NW: participants that perceive themselves to be normal weight (n = 299); OW: participants that perceive themselves to be overweight or obese (n = 92). *$p < 0.05$.

Perceived behavioural control.

A Spearman's rank-order correlation was run to assess the relationship between participant characteristics, psychological factors and food choice motives with PBC. Analysis in all participants and participants that perceived themselves to be normal weight revealed a significant positive correlation between the food choice motives of health and natural content and a significant negative relationship between external HLC with PBC ($p < 0.05$). All other correlations did not reach statistical significance ($p \geq 0.05$). Correlation coefficients for participant characteristics, psychological factors and food choice motives with PBC are presented in Table 5.13.

Table 5.13 Spearman's correlation analysis for perceived behavioural control with participant characteristics, psychological factors and food choice motives for all participants, participants that perceived themselves normal weight, and participants that perceived themselves overweight or obese.

	All	**NW**	**OW**
	r_s	**r_s**	**r_s**
Education	.081	.105	.009
Health perception	.139	.100	.193
Physical activity	.138	.160	-.001
IHLC	.141	.115	.187
EHLC	-.318*	-.352*	-.172
Optimistic bias	.039	.074	-.181
Food choice motives:			
Health	.246*	.238*	.250
Mood	.083	.109	.008
Convenience	-.064	-.050	-.123
Sensory Appeal	.044	.070	-.030
Natural content	.178*	.192*	.102
Price	.117	.091	.225
Weight control	.034	.013	.127
Familiarity	-.069	-.074	-.056
Ethical concern	.089	.109	.029

r_s: Spearman's correlation All: all participants (n = 391); NW: participants that perceive themselves to be normal weight (n = 299); OW: participants that perceive themselves to be overweight or obese (n = 92). *$p < 0.05$.

5.3.7 Disease context of genotype-based advice

The majority of participants (51%) neither disagreed/ nor agreed with the statement that they would only want genotype-based personalised advice about predisposition of curable diseases. However, participants (45%) agreed with the statement that they would only want genotype-based personalised advice about a disease if it is preventable. The majority of participants agreed that they would like genotype-based personalised advice about their risk of developing CVD (66%), T2D (64%) and obesity (55%) (Table 5.14). Chi-squared analysis revealed there was no significant difference in proportions of responses for the items between participants that perceived themselves to be normal weight and those that perceived themselves to be overweight or obese ($p \geq 0.05$, data not presented).

Table 5.14. Participant responses to questions regarding the disease context of genotype-based personalised nutrition and physical activity advice, n (%).

Item	Disagree	Neither disagree/nor agree	Agree
I only want genotype-based personalised advice about predisposition of curable diseases.	77 (20)	199 (51)	115 (29)
I only want genotype-based personalised advice about a disease if I can prevent this disease.	84 (22)	132 (34)	175 (45)
Concerning genetic advice, I want genotype-based personalised advice about my risk of developing cardiovascular disease.	25 (6)	108 (28)	258 (66)
Concerning genetic advice, I want genotype-based personalised advice about my risk of developing type II diabetes.	23 (6)	118 (30)	250 (64)
Concerning genetic advice, I want genotype-based personalised advice about my risk of developing obesity.	45 (12)	131 (34)	215 (55)

5.3.8 Outcomes that would increase likelihood of adopting personalised nutrition

With the exception of losing weight (34%) and gaining weight (23%), the majority of participants reported that potential outcomes would strongly or extremely increase their likelihood of adopting genotype-based personalised nutrition or physical activity advice. The most positive response was for preventing a future illness (74%), followed by improving health, improving quality of life, and preventing the expression of hereditary illness (all 69%).

The proportion of responses for the losing weight outcome differed significantly between participants that perceived themselves to be overweight or obese (53% strongly or extremely) and those who perceived themselves to be normal weight (28%) (x^2 = 43.16, p < 0.001). Proportions were also significantly different for the gaining weight outcome between those who perceived themselves to be overweight or obese (27%) and those who perceived themselves to be normal weight (22%) (x^2 = 10.29, p = 0.036). There were no significant differences in proportions of responses between groups for all other outcomes (Table 5.15).

Table 5.15. Participant responses to which potential outcomes would increase their likelihood of adopting genotype-based personalised nutrition or physical activity advice n (%).

	Not at all	Slightly	Moderately	Strongly	Extremely
Knowing what foods are best for me					
All	16 (4)	59 (15)	107 (27)	152 (39)	57 (15)
NW	15 (5)	41 (14)	87 (29)	113 (38)	43 (14)
OW or OB	1 (1)	18 (20)	20 (22)	39 (42)	14 (15)
Losing weight**					
All	71 (18)	89 (23)	98 (25)	81 (21)	52 (13)
NW	66 (22)	69 (23)	81 (27)	60 (20)	23 (8)
OW or OB	5 (5)	20 (22)	17 (18)	21 (23)	29 (32)
Gaining weight*					
All	127 (32)	74 (19)	101 (26)	61 (16)	28 (7)
NW	92 (31)	56 (19)	87 (29)	47 (16)	17 (6)
OW or OB	35 (38)	18 (20)	14 (15)	14 (15)	11 (12)
Fitness					
All	18 (5)	46 (12)	101 (26)	145 (37)	81 (21)
NW	15 (5)	34 (11)	76 (25)	114 (38)	60 (20)
OW or OB	3 (3)	12 (13)	25 (27)	31 (34)	21 (23)
Improving my family's health					
All	11 (3)	37 (9)	98 (25)	136 (35)	109 (28)
NW	10 (3)	24 (8)	70 (23)	107 (36)	88 (29)
OW or OB	1 (1)	13 (14)	28 (30)	29 (32)	21 (23)
Improving my health					
All	6 (2)	32 (8)	83 (21)	153 (39)	117 (30)
NW	4 (1)	28 (9)	60 (20)	116 (39)	91 (30)
OW or OB	2 (2)	4 (4)	23 (25)	37 (40)	26 (28)
Improving my quality of life					
All	6 (2)	30 (8)	82 (21)	146 (37)	127 (32)
NW	6 (2)	23 (8)	62 (21)	113 (38)	95 (32)
OW or OB	0 (0)	7 (20)	8 (22)	7 (20)	8 (22)
Improving my sports performance					
All	32 (6)	51 (13)	80 (20)	105 (27)	123 (31)
NW	25 (8)	36 (12)	64 (21)	79 (26)	95 (32)
OW or OB	7 (8)	15 (16)	16 (17)	26 (28)	28 (30)
Preventing a future illness					
All	7 (2)	31 (8)	65 (17)	132 (34)	156 (40)
NW	7 (2)	22 (7)	45 (15)	105 (35)	120 (40)
OW or OB	0 (0)	9 (10)	20 (22)	27 (29)	36 (39)
Preventing the expression of a hereditary illness					
All	13 (3)	30 (8)	76 (19)	107 (27)	165 (42)
NW	8 (3)	25 (8)	59 (20)	80 (27)	127 (42)
OW or OB	5 (5)	5 (5)	17 (18)	27 (29)	38 (41)

***** statistically significant difference in proportions between participants that perceive themselves to be overweight or obese compared to those that perceive themselves to be normal weight (*$p < 0.001$; **$p < 0.05$). NW: normal weight; OW: overweight; OB: obese.

5.4 Discussion

The aim of the present study was to investigate the factors that influence the intention to adopt genotype-based personalised advice on diet and physical activity in young adults that perceive themselves to be a healthy weight versus those that perceive themselves to be overweight or obese.

5.4.1 Theory of planned behaviour

The primary objective of this research was to use the TPB as a model to understand the intentions of young adults for the use of genotype-based personalised advice for dietary or physical activity behaviour. On average, young adults have a positive intention to adopt genotype-based advice for dietary and physical activity behaviour, driven by a favourable attitude, a positive perception of social pressure, and perceived ability to perform the behaviour. These findings were consistent in participants that perceived themselves to be normal weight and overweight or obese. The constructs of TPB were able to explain a significant amount of variance in participants intention to adopt genotype-based advice in all participants (54%) and, when analysed separately, based on participants perception of their body image (normal weight (58%); overweight or obese (40%)). To understand what factors influence the proximal constructs (attitude towards the behaviour, subjective norms and PBC) of intention to adopt genotype-based personalised advice, the relationship between belief composites (objective 2), characteristics, psychological factors, and food choice motives (objective 3) were determined for each construct and are discussed below. Findings are put into context of two previous reports from the Food4Me study. The Food4Me study was a multi-centred European study investigating the effect of varying levels of personalised nutrition advice on eating patterns and health outcomes, compared to general dietary advice (Celis-Morales, Livingstone, et al., 2015). These reports investigated the effect of psychological factors (Poínhos et al., 2014) and food choice motives (Rankin et al., 2018) on attitudes and intention to adopt personalised nutrition in adults (18-65 years) from nine European countries. Those studies did not investigate the effect of factors on subjective norms or PBC; in these aspects the present study is novel. Therefore, the findings from these two constructs will be discussed within the context of wider literature.

5.4.2 Attitude towards the behaviour

A positive mean attitude score suggests participants had a favourable appraisal of adopting genotype-based dietary and physical activity advice (Ajzen, 1991). Attitude added significantly to the prediction of intention in the model including all participants, and the one including participants that perceived themselves to be normal weight, but not in the model for participants that perceived themselves to be overweight or obese. These findings suggest that a favourable appraisal towards the behaviour may be less important in determining the intention to adopt genotype-based advice in participants that perceive themselves to be overweight or obese.

Behavioural outcomes and experiences related to the adoption of genotype-based advice to modify dietary or physical activity behaviour of young adults were investigated to determine which behavioural beliefs were important in forming the attitude of young adults towards genotype-based advice (Ajzen, 2020). Apart from 'causing worry about the risk of developing a disease' all salient behavioural beliefs that had been elicited from the pilot study were significantly and positively associated with attitude towards the adoption of genotype-based advice when analysis was carried out in all participants. A similar pattern was observed when analysis was carried out in participants that perceived themselves to be normal weight. However, in participants that perceived themselves to be overweight or obese only the behavioural beliefs of 'achieve health and fitness goals', 'motivation to eat healthily and exercise', 'take time and effort to make changes' and 'prevent disease' were significant. In all three analyses the strongest correlation with attitude towards adoption of genotype-based advice was observed with 'motivation to eat healthily and exercise' followed by 'achieve health and fitness goals' and 'prevent disease'. The relative importance of different behavioural beliefs is important to understand when implementing an intervention in young adults. Consequently, when delivering genotype-based advice to a young adult population a focus on how such advice can improve health and fitness outcomes and prevent disease may increase uptake.

The relationship between psychological factors, characteristics, and food choice motives with attitude towards genotype-based advice was also investigated. External HLC had a significant negative association with attitude in all groups. This suggests that participants that perceive their health not to be under their control had a less favourable attitude towards genotype-

based personalised diet and physical activity advice (Wallston et al., 1976). However, the low mean external HLC score suggested that the majority of participants perceived health to be under their control and external HLC scores did not differ significantly between participants based on their body weight perception. In contrast to the present findings, previous research has suggested that internal HLC had greater capacity to explain variance in diet-related behaviour than external HLC (Cohen & Azaiza, 2007). A study into psychological factors that predict intention to adopt personalised nutrition reported that higher internal HLC was positively related to attitude (Poínhos et al., 2014). Internal HLC was positively associated with attitude in the present study (r = 0.12) but did not reach significance; furthermore, the negative relationship between external HLC and attitude was stronger and significant (r = -0.34). Poínhos et al. (2014) also reported a stronger association between external compared to internal HLC and attitude (although in their study external HLC items were reversed scored and labelled 'health commitment'). Therefore, when investigating personalised nutrition, it appears that external rather than internal HLC has a stronger relationship with attitude. In the present study, internal HLC was significantly lower in women compared to men, and in participants that perceived themselves to be overweight or obese compared to those that perceived themselves to be normal weight. The findings suggest that challenging participants perception that their health is not under their control could improve their attitude towards personalised advice for diet and physical activity and that this may be particularly important when advice is targeted towards women or those that perceive themselves to be overweight or obese.

The food choice motive 'health' had a significant positive relationship with attitude in all models. None of the other food choice motives were significantly associated with attitude towards genotype-based advice. The relationship between 'health' and attitude towards genotype-based advice was strongest in the participants that perceived themselves to be overweight or obese. Previous research has highlighted a positive association with the food choice motive of 'health' and attitude towards both healthy eating in young adults (Sun, 2008) and attitude towards personalised nutrition in European adults (Rankin et al., 2018). Furthermore, a study comparing food choice motives of participants that had or had not been previously genotyped, reported a significantly higher 'health' food choice motive in those that had been genotyped (Kapellou et al., 2022). In this study 'health' was the third highest rated

food choice motive after 'sensory appeal' and 'price'. 'Sensory appeal' and 'price' are commonly reported in the literature as the highest rated motives for food choice (Markovina et al., 2015; Steptoe et al., 1995; Sun, 2008). Consequently, for health motives to be considered in food choice, the food should be deemed to have sensory appeal and good value. In their analysis, in addition to a positive association between the food choice motive of 'health' and attitude towards personalised nutrition, Rankin et al. (2018) reported significant positive associations between food choice motives of 'mood', 'weight control', and 'ethical concern' with attitude towards personalised nutrition. In addition to significant negative associations between 'price' and 'familiarity' with attitude towards personalised nutrition. Although the food choice motive of 'weight control' was not significantly associated with attitude towards genotype-based personalised advice in the present study. Significantly more participants who perceived themselves to be overweight or obese (55%) stated that weight loss as a potential outcome of genotype-based personalised advice would increase their likelihood of adoption, compared to 28% of those who perceived themselves to be normal weight. Previous research has identified the potential for weight loss as a perceived benefit of personalised nutrition (Rankin et al., 2017) as well as being a significant predictor of attitude, intention (Rankin et al., 2018) and acceptance of personalised nutrition advice (Bouwman et al., 2022). Differences in findings between the present study and those of Rankin et al. (2018) and Poínhos et al. (2014) may reflect the different populations of the two studies; the Food4Me study included adults aged 18-65 years from nine European countries, whereas the present study included young adults living in the UK. Food motives have been reported to differ with age (Konttinen et al., 2021), and consequently different motives may have influenced attitude in our young adult population.

5.4.3 Subjective norms

Subjective norms, the individual's perceived social pressure to perform or not perform the behaviour (Ajzen, 1991), was a significant predictor of intention in all three models. 'Normative beliefs' represents the perceived behavioural expectations of important referent individuals or groups. In all analysis 'health professionals' were significantly positively associated with subjective norms; 'family' was also a significantly positively associated with subjective norms in all groups. Consequently, communication of information to young adults about the benefits of personalised dietary and physical activity advice may be most effective

when delivered by a health professional with support and understanding of family members. This is in agreement with previous research that has reported face-to-face delivery by a health care professional as the preferred method of delivery of personalised nutrition advice (Bayer et al., 2021; Fallaize et al., 2015).

External HLC was negatively associated with subjective norms in models for all participants and those that perceived themselves to be normal weight. This finding suggests that participants that perceived that their health was outside of their own control were less influenced by perceived social pressure to engage with genotype-based personalised dietary or physical activity advice. Since this was observed in the group that perceived themselves to be normal weight it may suggest that these individuals are less influenced by social pressure and may be at greater risk of developing diet and physical activity behaviours that may result in them becoming overweight later in life. None of the other characteristics, psychological factors or food choice motives were significantly associated with subjective norms.

5.4.4 Perceived behavioural control

PBC added significantly to the prediction of intention to adopt genotype-based advice for dietary and physical activity behaviour and had the highest *B*-coefficient in all three regression models. These findings suggest that those participants that perceived the adoption of genotype-based dietary or physical activity advice to be easy were more likely to intend to adopt it (Ajzen, 1991); moreover, of the TPB constructs that influence intention to adopt genotype-based personalised advice, PBC was the most important. All salient control beliefs elicited from the pilot study were significantly positively associated with PBC when analysis was conducted in all participants and in participants that perceived themselves to be normal weight. In participants that perceived themselves to be overweight or obese only control beliefs 'time' and 'money' were significantly associated with PBC. These findings suggest that having enough time and money are important factors for all young adults to enable them to adopt genotype-based advice. However, clarity and effectiveness of guidance were also deemed to be important in young adults that perceive themselves to be normal weight. Previous research has reported perceived benefits of personalised advice to have the strongest relationship with attitude, intention (Berezowska et al., 2015; Poínhos et al., 2014; Reinders et al., 2020), and acceptance (Bouwman et al., 2022) of personalised nutrition. Confidence in the effectiveness of guidance may represent a proportion of what participants

would perceive as benefits of personalised advice. Conversely, perceived risk (which was not measured in the present study) has been reported to have a negative, although less influential, relationship with attitude and intention (Berezowska et al., 2015; Poínhos et al., 2014).

As seen with the other TPB constructs, external HLC was a significant negative predictor of PBC in analysis of all participants and in those that perceived themselves to be normal weight. This relationship between participants perceived control over their own health (HLC) and perceived control over performing the behaviour (related to genotype-based advice for diet and physical activity) is intuitive. Participants that perceived greater control over their own health perceived themselves to have greater control over the health-related behaviour. This consistent finding between external HLC and each construct of the TPB once again highlights the importance of communicating to this population how lifestyle behaviour can be equally as important as genetics in determining risk of disease (Khera et al., 2016) and, in terms of increasing PBC, explaining how they can achieve or maintain healthy behaviours.

The food motive of 'health' influenced participants perception of their ability to adopt genotype-based personalised advice to modify their dietary or physical activity behaviour in a similar manner to attitude and subjective norms. Participants that rated 'health' as an important motive had a more positive perception of their ability to adopt genotype-based advice. Despite a similar correlation coefficient this relationship was not significant in participants that perceived themselves to be overweight or obese. The lack of significance may be due to the smaller sample of participants that perceived themselves to be overweight or obese (n = 92) compared to normal weight (n = 299). 'Natural content' also had a significant positive relationship with PBC for all participants and those that perceived themselves to be normal weight. The food choice motive of 'natural content' reflects participants concern of the use of additives and natural ingredients, previous research has shown food choice motives of 'health' and 'natural content' to be highly correlated (r = 0.59-0.63) (Steptoe et al., 1995). 'Natural content' was not identified as a significant factor in the study by Rankin et al. (2018) and this may be because they only looked at the relationship between food choice motives and attitude and intention to adopt personalised nutrition. The findings of the present study suggest that although there are some consistent patterns between food choice motives and TPB constructs, there are also some differences both between constructs and between

participants based on their perception of their body weight. For example, having and increased external HLC significantly reduced attitude in all groups; however, a negative relationship between external HLC with subjective norms and PBC was only apparent in analysis of all participants and those that perceived themselves to be overweight or obese. An understanding of which factors influence which constructs of the TPB helps to understand the context of how advice should be communicated to young adults; whether it should be phrased to address their appraisal of genotype-based advice (attitude) or their ability to carry out necessary changes in their behaviour (PBC).

5.4.5 Recommendations

Based on the findings of the present study, there are some recommendations for the delivery of genotype-based personalised advice to motivate healthy dietary and physical activity behaviour in young adults that appear to be generically applicable to this population. Firstly, in order to appreciate the need to meet dietary and physical activity advice, young adults need to accept the strong effect that these lifestyle behaviours can have on their subsequent health and, importantly, that this is under their control. This should be clearly communicated, and the advice provided should be delivered in the context of improving health and preventing disease. The sensory appeal and cost of food should be considered in the delivery of dietary recommendations and communication of advice should preferably be delivered via a health professional. Of the TPB constructs, PBC has the greatest influence over intention in young adults; therefore, advice should be clear on how to meet dietary and physical activity advice; for example, if a reduction in sodium intake is recommended, advice should explain which foods are high in salt and provide alternative food choices to enable the advice to be met. The findings also suggest that in order to motivate behaviour change, advice should be tailored based on young adults individual characteristics. In young adults that perceive themselves to be overweight or obese, advice for weight control may increase their intention to adopt advice. Young adults that believe they are already engaged in healthy lifestyle behaviours or perceive themselves to be normal weight are less likely to perceive a need to adopt genotype-based advice (Shepherd, 1999). Optimistic bias has been suggested as a potential barrier to adoption of personalised nutrition, particularly in younger populations (Stewart-Knox et al., 2013). Although optimistic bias was not significantly associated with the proximal constructs of TPB, it was significantly higher in men as well as participants that

perceived themselves to be normal weight. Women have been reported to be more conscious of health and demonstrate greater engagement with preventative behaviours (Hiller et al., 2017). In a large study of young adults living in 23 different countries, men reported lower adherence to and belief in healthy eating recommendations compared to women (Wardle et al., 2004). Advice provided to this group should highlight how genes can interact with lifestyle behaviours to affect disease risk, in order to challenge their optimistic bias. Furthermore, previous research has suggested that men are less likely than women to be willing to have a genetic test (Stewart-Knox et al., 2009, 2021) and, for many aspects of genotype-based personalised nutrition, advice provided may be more effective if it is personalised by sex (Corella et al., 2018). For example, a meta-analysis of 114 studies was carried out to determine sex-specific effects of genetic variants on BMI and waist-to-hip ratio adjusted for BMI by the GIANT consortium (Winkler et al., 2015). Although no sex-dependent effects were identified for BMI, 44 loci were identified with sex-specific effects for waist-to-hip ratio adjusted for BMI, 28 of which had larger effects in women than in men, five in men than in women, and 11 had opposite effects between men and women. Our findings support those of previous research that have suggested that additional tailoring of personalised advice based on individual characteristics such as sex and unhealthy eating motivations may enhance the effectiveness of personalised nutrition interventions (Hiller et al., 2017; Livingstone et al., 2020).

5.4.6 Strengths and limitations

Strengths of the present study include a specific focus on a young adult population who stand to benefit the most from genotype-based personalised advice. The majority of previous studies in this area were conducted before the COVID-19 pandemic, a necessity of which was increased self-testing and delivery of health services online which may have changed acceptability of such services; therefore, an update of previous findings is required (Stewart-Knox et al., 2021). The use of the TPB provided a framework to understand the factors that influence the intention to adopt genotype-based personalised advice. The relationship between background factors and subjective norms and PBC in addition to attitude was included and was novel to this research area. However, the study was not without limitations; the nature of the cross-sectional survey meant that the behaviour component of TPB was unable to be measured; therefore, it is not possible to determine if intention to adopt

genotype-based dietary and physical activity advice would translate to actual adoption of advice. Additional background factors that may have influenced TPB constructs, and intention were not included, the most important of which was a measure of risk and benefit. This has previously been well researched in this area and findings are relatively consistent that benefits have a greater influence than risks on intention to adopt genotype based advice (Berezowska et al., 2015, 2017; Bouwman et al., 2022; Poínhos et al., 2014; Reinders et al., 2020; Stewart-Knox et al., 2013). Since the risk/benefit relationship with adoption of personal nutrition is relatively well understood it was not included for further investigation in the present study; however, it may account for a proportion of the unexplained variance in the models. Finally, although the target population for the present study was all young adults living in the UK, the sampling frame utilised may have resulted in over representation of well-educated young adults with an interest in nutrition. Therefore, caution should be taken when generalising findings to the wider young adult population, since background factors and their influence on intention to adopt genotype-based advice may differ from the present sample.

5.4.7 Conclusions

In conclusion, the current study provides support for the use of the TPB in understanding the intention of young adults to adopt genotype-based advice for dietary and physical activity behaviour. Background factors including belief composites, HLC, sex, and food choice motives of 'health', and 'natural content' interact with TPB constructs. In addition to perceived body weight, these background factors should be utilised to inform the delivery of advice in behaviour change interventions that seek to use genotype-based personalised advice in young adult populations. Finally, the recommendations for the use of genotype-based dietary and physical activity advice in young adults, based on the findings of the present study, need to be evaluated within an intervention study.

Chapter 6: General discussion

In this chapter I discuss the findings from the four research studies together. It is divided into four sections. The first section defines how the aims of the programme of research were achieved. The second section discusses the findings from the four research studies together to answer the overall research question and contribute to knowledge regarding the effects of genotype-based advice on changes in dietary and physical activity behaviour. In the third section, limitations, implications, and directions for future research are discussed. The final section presents the conclusions.

6.1 Aims achieved

The four research studies addressed the following aims:

6.1.1 Determine the effect of personalised nutrition advice on dietary intake in participants informed of a high-risk genotype compared to those informed of non-risk genotype.

The first study answered the question of how personalised advice affects dietary behaviour in individuals informed of a high-risk compared to a non-risk genotype. Genotype-based personalised nutrition advice led to favourable dietary changes in participants who were not meeting dietary recommendations, in participants informed of a risk or non-risk genotype. However, only those informed of a risk *APOE* genotype met saturated fat recommendations following personalised nutrition advice.

6.1.2 Determine the efficacy of genotype-based personalised dietary and physical activity advice on healthy-eating motivation in young adults.

The second intervention study answered the question of whether genotype-based personalised advice could affect healthy-eating motivation in young adults. Genotype-based personalised advice for the prevention of obesity did not affect healthy-eating motivation in young adults. This finding was consistent in students informed of meeting and those informed of not meeting recommendations for healthy body fat percentage and BMI.

6.1.3 Evaluate the efficacy of genotype-based dietary or physical activity advice on behaviour change to reduce the risk of CVD, T2D or obesity in the general population and individuals that are at-risk of CVD or T2D.

The systematic review and meta-analysis achieved the third aim of evaluating the efficacy of genotype-based advice on behaviour change. The meta-analysis suggested that the use of genotype-based advice to promote dietary or physical activity behaviour is no more effective than general advice or advice based on lifestyle or phenotypic measures. This finding was consistent in studies that had recruited participants from the general population as well as studies that had recruited participants from populations at-risk of CVD or T2D.

6.1.4 Investigate the factors that influence the intention to adopt genotype-based personalised advice for diet and physical activity in young adults that perceive themselves to be a healthy weight versus those that perceive themselves to be overweight or obese.

The survey achieved the fourth aim to investigate factors that influence the intention of young adults to use genotype-based personalised advice. The research provides support for the use of the TPB in understanding the intention of young adults to adopt genotype-based advice for dietary and physical activity behaviour. Background factors including belief composites, HLC, sex, and food choice motives of 'health', and 'natural content' interact with TPB constructs.

6.2 Overall findings and contribution to knowledge

6.2.1 Genotype-based personalised advice for behaviour change

6.2.1.1 Addressing the overall aim

The overall aim for this programme of work was to determine the efficacy of genotype-based personalised advice to motivate and promote dietary and physical activity behaviour change, in the context of reducing the risk of obesity, T2D, and CVD. The first three studies of this programme of research investigated the effect of genotype-based advice on dietary intake (Study 1), healthy-eating motivation (Study 2) and dietary and physical activity behaviour (Study 3). Using a pre-test post-test design, Study 1 found a significant change in dietary behaviour following genotype-based personalised advice (King et al., 2022). This agrees with previous research that had demonstrated that genotype-based personalisation of dietary advice leads to greater changes in dietary behaviour compared to general dietary advice (Nielsen & El-Sohemy, 2014). Personalisation of advice can be provided on three different

levels. Level 1 incorporates advice based on reported dietary intake; level 2 provides advice in response to phenotypic or clinical measures; and level 3 personalises advice based on genotype. Each subsequent level builds on the previous one, so level 3 or genotype-based advice is personalised based on reported dietary intake, phenotypic or clinical measures, plus genotype (Grimaldi et al., 2017; Stewart-Knox et al., 2013). Previous research has suggested that any level of personalisation can increase dietary behaviour change compared to generic advice or no advice (Jinnette et al., 2020; Li et al., 2016). Therefore, the second study investigated change in healthy-eating motivation in a group receiving genotype based personalised advice, a group receiving non-genotype-based personalised advice, and a group that received no advice. There was no effect of advice on healthy-eating motivation in any of the groups. The contradictory findings from the first two studies add to the mixed findings that have been reported by other researchers investigating the effect of genotype-based personalised advice on dietary and physical activity behaviour (Arkadianos et al., 2007; Chao et al., 2008; Frankwich et al., 2015; Grant et al., 2013; Hietaranta-Luoma et al., 2014; Nielsen & El-Sohemy, 2014). Consequently, for the third study a systematic review and meta-analysis of studies that had used genotype-based personalised advice to change dietary or physical activity behaviour was conducted. Included studies compared behaviour change in the genotype-based personalised advice group to a comparator group that had received non-genotype-based personalised advice, generic advice or no advice. The meta-analysis revealed that there was no significant difference in dietary or physical activity behaviour change following genotype-based personalised advice compared to non-genotype-based personalised advice, generic advice, or no advice (King et al., 2023).

In terms of contribution to knowledge, the findings of the meta-analysis supersede those of earlier meta-analysis by Marteau et al. (2010) and Hollands et al. (2016). Marteau et al. (2010) had analysed early studies and suggested a significantly greater change in dietary behaviour in response to genetic advice. When the meta-analysis was updated following the completion of additional studies in 2016 by Hollands and colleagues, a significant effect on dietary intake was no longer reported. Both previous meta-analyses found no significant effect of genetic advice on physical activity behaviour. The findings of Study 3 confirm that there is no significant effect of genotype-based advice on dietary or physical activity behaviour that is aimed to reduce the risk of obesity, T2D or CVD. Although this appears to contradict the

significant change in behaviour observed in Study 1, this may be explained by the fact that in the meta-analysis (Study 3), genotype-based advice was compared to non-genotype-based personalised advice, generic advice, or no advice. Where studies had multiple arms, the comparator group selected was the one which most clearly isolated the effect of genotype-based advice from other levels of personalisation. Therefore, where available, genotype-based advice was compared to non-genotype-based personalised advice. Previous systematic reviews have suggested that any level of personalisation of advice can increase dietary behaviour change (Horne, Gilliland, O'Connor, et al., 2020; Jinnette et al., 2020; Li et al., 2016). In Study 3, the only study that reported a significant change in dietary behaviour following genotype-based advice had a comparator group that received general healthy eating advice, although the control group were informed of their current intake (Nielsen & El-Sohemy, 2014). Two studies reported a significant improvement in dietary behaviour following genotype-based advice but only in comparison to the control group that received general advice (Celis-Morales et al., 2017; Fallaize et al., 2016), a further two studies reported a significant improvement in dietary behaviour from baseline in both the genotype-based advice group and the comparator group (Leskinen et al., 2021; Roke et al., 2017). This is in line with our findings from Study 1, where genotype-based advice resulted in a significant improvement in folate and saturated fat intake in participants informed that they were not meeting the recommendation. Together these findings suggest that any level of personalisation can be used to promote dietary behaviour change; the inclusion of genetics in addition to dietary, biochemical and phenotypic measures does not appear to motivate greater behaviour change than other levels of personalisation.

6.2.1.2 Risk v non-risk genotype

An important consideration of personalisation of advice based on genotype is the response of those informed of a risk-associated genotype and those informed of a non-risk-associated genotype. It is possible that if the direction of behaviour change in the risk informed group is opposite to that of the non-risk informed group, this may mask the effect of genotype-based advice on behaviour. Hollands et al. (2016) suggest three potential responses to disclosure of a risk-associated genotype; firstly, that knowledge of a risk-associated genotype will motivate a greater change in the associated lifestyle behaviour as a consequence of greater personal salience of the advice; secondly, that knowledge of an increased risk of disease due to

genotype will demotivate behaviour change as a consequence of genetic fatalism. Genetic fatalism may occur due to the incorrect perception that risk of disease as a consequence of genetics cannot be addressed with lifestyle behaviours (Ehrlinger et al., 2017; Marteau & Weinman, 2006); and thirdly, that knowledge of a risk-associated genotype will make only a small and inconsistent change in the associated lifestyle behaviour. Previous research from vignette studies has investigated the predicted response of participants who had been provided with hypothetical scenarios related to their genetic risk of obesity. Participants informed of an obesity risk-associated genotype reported greater motivation to make healthy changes to lifestyle behaviours in comparison to when informed of an average risk (Ahn & Lebowitz, 2018; Frosch et al., 2005; Meisel et al., 2012; Sanderson et al., 2010). This effect was observed in a student population (Frosch et al., 2005; Meisel et al., 2012), the general population (Ahn & Lebowitz, 2018; Sanderson et al., 2010), and in participants with weight concerns (Meisel et al., 2012). The results of Study 1 suggested that those informed of a risk-associated *APOE* genotype made appropriate changes to their saturated fat intake to subsequently meet recommendations (King et al., 2022). However, in our meta-analysis when we compared change in dietary behaviour in participants informed of a risk-associated genotype to those informed of a non-risk-associated genotype there was no significant difference observed (King et al., 2023).

One of the proposed mechanisms for using genotype-based advice to motivate behaviour change is to make recommendations more personally salient to an individual and to challenge their optimistic bias. Optimistic bias is where an individual has a reduced perception of their own risk of developing a disease (Shepherd, 1999). However, an additional concern of genotype-based advice is that those informed of a non-risk genotype may have an increased perception of optimistic bias, compared to others (Hunter et al., 2008). Findings from vignette studies had suggested that this may result in a so called 'genetic invincibility effect', whereby the importance of a healthy diet and exercise were significantly reduced, and as such, participants reported an increased likelihood to select unhealthy food (Ahn & Lebowitz, 2018). In Study 1, participants that were informed of a non-risk-associated genotype and that they were not meeting recommendations reported favourable dietary changes following advice (King et al., 2022). As mentioned above, in our meta-analysis, when change in dietary behaviour was compared between risk and non-risk informed participants there was no

significant difference (King et al., 2023). This is in line with previous research that has reported favourable changes in participants informed of a non-risk genotype (Fallaize et al., 2016; Nielsen & El-Sohemy, 2014). Therefore, we can conclude that genotype-based advice does not appear to increase optimistic bias in those informed of a non-risk genotype. Furthermore, in response to the three possible outcomes suggested by Hollands et al. (2016), based on our findings it appears that genotype-based advice makes a small and inconsistent change in lifestyle behaviour. However, there are a number of factors that may explain the inconsistent findings.

6.2.1.3 Variability in studies investigating genotype-based advice

Studies that have investigated the effect of genotype-based personalised advice on behaviour change are heterogenous. The genes selected, dietary outcomes assessed, and the disease context in which advice is delivered have varied between and within studies. In our first study we investigated the effect of *APOE* genotype on saturated fat intake and *MTHFR* genotype on folate intake in the context of CVD. In participants not meeting recommendations for saturated fat or folate a favourable change in dietary behaviour was reported following advice, irrespective of genotype. However, we found that risk informed participants that were not meeting saturated fat recommendations changed their dietary intake to meet recommendations following advice, non-risk informed participants also reduced their intake of saturated fat, although reported intake remained above recommendations. *APOE* and *MTHFR* were two of five genes for which advice was given in the Food4Me study; also, advice for both were delivered in the context of CVD (Celis-Morales, Livingstone, et al., 2015). In accordance with our findings, in participants advised to reduce their saturated fat intake, a significant reduction was reported in participants informed of *APOE* risk and non-risk genotype (Fallaize et al., 2016). However, contrary to our findings, in participants advised to increase their intake of folate, no significant change in folate intake was reported for risk or non-risk informed participants (O'Donovan et al., 2016). In an earlier study by Chao et al. (2008), the effect of disclosure of *APOE* genotype on health behaviour change was also investigated, but this time in the context of AD. They found that participants that were informed of a risk-associated genotype were more likely to report an AD related health behaviour change than those informed of a non-risk genotype. The disease context in which advice was delivered based on *APOE* genotype may explain why Chao et al. (2008) reported a

significant effect of genotype-based advice, whereas Fallaize et al. (2016) reported no significant difference between risk and non-risk informed groups. A recent survey carried out in Australian adults reported that 29% of participants were most fearful of developing AD, second to fear of developing cancer (34%), only 7% of participants reported to be most fearful of developing CVD (Watson et al., 2023), similar findings were reported in an earlier UK survey (Cancer Research UK, 2011). Since the aim of genotype-based personalised advice is to encourage behaviour change by increasing the personal salience of advice to an individual, this may be more effective when the disease context of the advice promotes fear arousal. Fear arousal is likely to be higher for most individuals when advice is delivered in the context of risk of cancer or AD compared to CVD (Cancer Research UK, 2011; Watson et al., 2023; Wilson, 2007). This suggests that the disease context in which genotype-based advice is delivered may influence the response observed.

The heterogeneity of findings in studies investigating the effect of genotype-based advice on behaviour may also be explained due to variation in the outcome measured to determine if dietary or physical activity behaviour has changed. In Study 1 dietary behaviour change was measured for saturated fat and folate intake using a 24-hour recall. In Study 2, planned measurement of dietary or physical activity behaviour was not completed due to implications of the COVID-19 pandemic and therefore healthy-eating motivation was measured as an antecedent to actual healthy-eating behaviour. In Study 3, included studies measured a wide range of dietary behaviour outcomes ranging from a specific nutrient component such as omega-3 polyunsaturated fat (Roke et al., 2017) to a more global measure of overall diet such as the HEI (Celis-Morales et al., 2017). As a consequence of this variation between measurement of outcomes, in addition to interventions delivered, certainty of evidence was downgraded by one level for both the dietary behaviour outcome and the physical activity outcome. Therefore, a GRADE assessment of overall quality of evidence for the dietary behaviour outcome was judged to be ‘low’, which means the true effect may be markedly different to the estimated effect. For physical activity behaviour, the GRADE assessment of quality of evidence was ‘moderate’, which means the true effect is probably close to the estimated effect (King et al., 2023; Schünemann et al., 2013). Although, in some studies physical activity behaviour was measured objectively using accelerometers, all measures of dietary behaviour were reported subjectively by the participants. Previous research has used

objective clinical measures to determine the effect of genotype-based advice on weight loss. For example, an often cited study by Arkadianos et al. (2007) compared weight loss maintenance in a group of participants that received a diet tailored by genetics to a group that were provided with non-genotype-based dietary advice. Weight loss maintenance was significantly greater in the group that had received genotype-based advice; however, it is not possible to determine whether this was due to the advice being more effective for weight loss because it was tailored to their genotype or whether genotype-based advice had increased their motivation and adherence to the diet. Consequently, to determine the effect of genotype-based advice on actual behaviour change requires a measure of that behaviour and currently, for dietary behaviour, this will need to be reported by the participants. Therefore, unless new technologies are developed to capture diet more objectively, dietary behaviour research cannot escape the widely acknowledged limitations of measuring diet (Goldberg et al., 1991; Laville et al., 2017; Mirmiran et al., 2021) and should be clearly acknowledged when judging the evidence and the potential impact this may have on the strength of conclusions that can be drawn.

Finally, the heterogeneity in study findings that have investigated the effect of genotype-based advice on behaviour change may be due to differences between the interventions which genotype-based advice have been incorporated within. The interventions utilised across research studies have varied widely. Study 1 and Study 2 delivered advice remotely via written advice within an email. A number of studies included in our meta-analysis also delivered advice remotely (Celis-Morales et al., 2017; Godino et al., 2016; Hietaranta-Luoma et al., 2014; Nielsen & El-Sohemy, 2014; Roke et al., 2017; Silarova et al., 2019), whilst others delivered advice in person (Horne, Gilliland, O'Connor, et al., 2020; Kullo et al., 2016; Voils et al., 2015). In-person delivery of genetic information has been shown to result in greater understanding and more accurate interpretation of results (Haga, Barry, et al., 2014). Consequently, the mode of delivery of genotype-based advice may influence participants understanding and therefore their response to the advice. Intervention studies that aim to change behaviour, have been demonstrated to be more effective when behaviour change theory has been incorporated in the design. This will be discussed in the next section.

6.2.2 Incorporation of behaviour change theory

Previous systematic reviews have highlighted a lack of consideration of behaviour change theory in the design and delivery of intervention studies investigating the effect of genotype-based advice on health behaviour change (French et al., 2017; Horne et al., 2018; Jinnette et al., 2020). In both intervention studies conducted in this programme of research BCT were incorporated into the delivery of the intervention. Michie et al. (2013) developed a taxonomy of BCT to improve the reporting, implementation, and evaluation of behaviour change interventions. The same four BCT were utilised in the delivery of genotype-based advice in both of our intervention studies. Firstly, '*providing information on consequences of behaviour to the individual*': participants were informed of their genotype and how their dietary or physical activity behaviour could interact with their genotype to affect their risk of CVD (Study 1) or obesity (Study 2). '*Goal setting*': participants were informed of their current intake of saturated fat and folate (Study 1) or BMI and body fat percentage (Study 2), of current recommendations and whether they were meeting the recommendation. Participants were then given advice to enable them to meet recommendations to facilitate behaviour change '*providing instruction on how to perform the behaviour*'. Finally, '*fear arousal*' is a BCT where the intervention presents fear-inducing information aimed at motivating change (Wilson, 2007). It has been suggested that making an individual fearful of a health risk that they are personally susceptible to may be more effective in inducing behaviour change (Wilson, 2007). In the first study, for *MTHFR,* those with a risk-associated genotype were informed "You have a genetic variation in the *MTHFR* gene that is associated with a higher cardiovascular disease risk; consequently, it is beneficial for you to keep a healthy intake of folate." In the second study, participants that received genotype-based advice were informed "obesity is a risk factor for numerous chronic diseases including diabetes, cardiovascular disease and cancer. The risk of individuals to develop obesity is highly variable. Some of this variation may be explained by the interaction between an individual's DNA variation (genotype) and their diet and physical activity. You can reduce your risk of becoming obese by adhering to the diet and physical activity advice below". Five of the studies included in our meta-analysis reported the inclusion of behaviour change theory in the delivery of their intervention (Celis-Morales et al., 2017; Hietaranta-Luoma et al., 2014; Horne, Gilliland, O'Connor, et al., 2020; Kullo et al., 2016; Silarova et al., 2019). Although the remaining six studies did not explicitly state that behaviour change concepts had been

incorporated, it is likely that they were to some extent; for that reason, sub-group analysis was not carried out to compare studies that did or did not state behaviour change concepts were incorporated. The variability of interventions delivered between the different studies included in our meta-analysis has already been discussed as a limitation; if interventions delivered are not consistently of a high quality design it is not possible to determine if a lack of an effect of genotype-based advice on behaviour change is due to the genotype-based advice or the manner in which it was delivered (King et al., 2023). In 2017 Horne et al. set out a call to action for the incorporation of the TPB into personalised healthcare behaviour change research. This would ensure that studies investigating the effect of genotype-based advice to change lifestyle behaviours would be fit for purpose (Horne et al., 2017).

The TPB has been described in detail in Section 1.5.7 and presented in Figure 1.1. Briefly, the TPB aims to explain and predict behaviour. The immediate antecedent of behaviour is intention; the stronger the intention to perform the behaviour of interest, the more likely it will be performed (Ajzen, 2020). Intention to perform the behaviour is determined by three proximal constructs. Attitude towards the behaviour (perception of the behaviour as enjoyable or unenjoyable, healthy or unhealthy), subjective norms (perceived social pressure to perform or not perform the behaviour), and PBC (perception of how easy or difficult it is to perform the behaviour). Each of the proximal constructs of intention are formed from the respective belief composites; attitude is formed from behavioural beliefs, subjective norms from normative beliefs, and PBC from control beliefs (Ajzen, 2020). In our intervention studies the BCTs utilised in the delivery of genotype-based advice were incorporated to influence the proximal constructs of intention. The BCTs of 'fear arousal' and 'consequences to them as an individual' should create a more positive attitude towards the behaviour by affecting participants behavioural beliefs. 'Goal setting' and 'how to perform the behaviour' should strengthen participants PBC by influencing their control beliefs. Finally, the provision of advice from a registered nutritionist and University lecturer should have a positive effect on participants subjective norms by influencing their normative beliefs. In Study 1 the BCTs used appeared to influence participants intention and subsequently dietary behaviour changed to reflect advice. Participants not meeting recommended intakes for folate and/or saturated fat subsequently increased their folate intake or decreased their intake of saturated fat. Therefore, we would hypothesise that this was a consequence of BCTs employed influencing

the proximal constructs of intention for these participants. Conversely, in Study 2 intention or motivation to eat a healthy diet was not significantly affected following an intervention including the same BCTs. Therefore, in Study 2 the same BCTs were not able to influence the proximal constructs to an extent to affect intention to eat a healthy diet. The different populations in which Study 1 (healthy adults) and Study 2 (young adults starting university) were conducted may provide an explanation for these discordant findings.

Young adults are an important population to target for the prevention of NCDs in later life. As discussed above, our research (Study 1 and 3) and that of others suggests that any level of personalised advice can motivate behaviour change (Horne, Gilliland, O'Connor, et al., 2020; Jinnette et al., 2020; Li et al., 2016), although this was not observed in a young adults starting university (Study 2). Since personalised advice based on genotype can be delivered earlier in the lifespan before unhealthy lifestyle behaviours have developed, young adults stand to benefit the most from genotype-based advice. Although research suggests young adults are willing to use genotype-based advice (Bayer et al., 2021), they have also been identified as a population with high levels of optimistic bias (Stewart-Knox et al., 2013) and as a consequence are less motivated to change their behaviour. A greater understanding of what factors effect young adults intention to adopt genotype-based advice would enable researchers and health care practitioners to deliver genotype-based advice to a young adult population more affectively.

Therefore, in the final study conducted in this programme of research we investigated factors that explained the intention of young adults to adopt genotype-based personalised advice. Following the guidance from Ajzen (2006, 2020), we developed a TPB questionnaire to measure each of the TPB constructs and belief composites. The belief composites provide a means to understand the behavioural beliefs, normative beliefs, and control beliefs that influence attitude, subjective norms, and PBC and, as a consequence, intention to adopt genotype-based personalised advice. Analysis of the results revealed that the attitude, subjective norms, and PBC were able to explain the intention to adopt genotype-based personalised nutrition advice in young adults. Therefore, we were able to use the TPB as a framework to understand which proximal constructs (attitude, subjective norms and PBC) and background factors influenced the intention to adopt genotype-based advice. The influence of background factors will be discussed in the following section.

6.2.3 Influence of background factors

Background factors, such as participant characteristics, psychological factors, and food choice motives, may explain some of the heterogeneity observed in participant response to genotype-based personalised advice. An understanding of which factors influence the proximal constructs of intention to adopt genotype-based personalised advice enables those researchers and health professionals, that are providing genotype-based personalised health care advice, to tailor interventions to suit the populations or individual targeted (Poínhos et al., 2014; Rankin et al., 2018). Overall, the young adults that participated in Study 4 reported a positive attitude, perception of social pressure, perceived ability to adopt, and ultimately, intention towards adoption of genotype-based advice. Subsequent analysis identified which background factors were associated with each of the TPB constructs in this young adult population.

Differences in the importance of background factors were identified between constructs and between groups of the population based on their sex and perception of their BMI. In our study we found that internal HLC and optimistic bias were higher in male compared to female participants and in participants that perceived themselves to be normal weight compared to those that perceived themselves to be overweight or obese. Higher levels of optimistic bias in young adults have been suggested to be a barrier towards the adoption of genotype-based advice (Stewart-Knox et al., 2013). These findings suggest that young men who perceive themselves to be normal-weight may be less likely to have a positive attitude towards genotype-based personalised advice. Previous research has suggested that women are more health-conscious than men, and show greater engagement and belief in recommendations for disease prevention behaviours (Hiller et al., 2017; Wardle et al., 2004). Men have also been reported to be less willing to undergo genetic testing than women (Stewart-Knox et al., 2009, 2021). Corella et al. (2018) suggested that due to potential sex-gene or sex-phenotype associations genotype-based personalised recommendations should also be personalised based on sex/gender. Our research corroborates this recommendation, genotype-based advice aimed to motivate behaviour change in young men should be tailored to encourage a more positive attitude towards adoption of advice; this can be achieved by further emphasis of the relationship between current lifestyle behaviours and subsequent health and fitness benefits. In our analysis of normative beliefs 'health professionals' were identified to have the

strongest association with participant subjective norms. Previous research has also suggested that the preferred method of delivery of genotype-based advice is face-to-face via a health professional (Bayer et al., 2021; Fallaize et al., 2015). Therefore, face-to-face delivery of advice by a health professional may increase perceived social pressure to adopt the advice and could explain the lack of an effect of genotype-based advice delivered to young adults on healthy-eating motivation in Study 2.

The influence of background factors on TPB constructs also varied between young adults that perceived themselves to be normal weight and those that perceived themselves to be overweight or obese. The behavioural beliefs that form participants attitude towards adoption of genotype-based personalised advice were influenced by perception of BMI. In all groups a 'motivation to eat healthily and exercise', 'achieve health and fitness goals', 'prevent disease', and 'take time and effort to make changes' was positively associated with attitude. Additionally, in participants that perceived themselves to be normal weight the need to 'restrict food choices', and 'expense' were positively associated with attitude towards genotype-based personalised advice. Although the behavioural beliefs with the strongest association with attitude towards genotype-based advice were common between groups these findings suggest that the factors that motivate participants to adopt genotype-based personalised advice are different depending upon how participants perceive their body weight. Indeed, significantly more participants that perceived themselves to be overweight or obese reported weight loss as a potential outcome of genotype-based advices would increase their likelihood of adoption compared to participants that perceived themselves to be normal weight. This is in line with previous research, although not specifically in an overweight population that reported weight loss as a perceived benefit of (Rankin et al., 2017), and positive predictor of attitude and intention to adopt genotype-based advice (Rankin et al., 2018). These findings suggest that highlighting the use of genotype-based advice to control weight would be an attractive intervention for young adults that perceive themselves as overweight or obese.

Optimistic bias was above average overall; this was expected in a young adult population (Stewart-Knox et al., 2013). Optimistic bias was not a significant predictor of any of the proximal constructs of intention to adopt genotype-based personalised nutrition. However, it was significantly lower in young adults that perceive themselves to be overweight or obese

compared to those that perceive themselves to be normal weight. Young adults that perceived themselves to be overweight or obese estimated their chances of developing CVD, T2D and obesity in the future, compared with those of the average adult of the same age and sex, as 'average'. In contrast, young adults that perceived themselves to be normal weight estimated their chances as 'slightly lower than average'. Optimistic bias has been suggested as a barrier to the adoption of genotype-based personalised advice (Stewart-Knox et al., 2013). Since the risk of NCDs such as obesity increases with age (Moody, 2020), preventing the development of unhealthy lifestyle behaviours is an important preventative strategy in young adults. Therefore, genotype-based personalised advice can be used as a tool to challenge optimistic bias in young adults who perceive themselves to be normal weight and consequently at a lower risk of developing CVD, T2D and obesity.

Participants' perception of their own health, the importance of health, and the control that they perceive they have of their health were also identified as important factors in young adults' intention to adopt genotype-based advice. The HLC refers to whether an individual perceives their health to be under their control (internal) or not (external) (Wallston et al., 1976). Overall, participants in Study 4 had a high internal HLC and low external HLC. However, internal HLC was significantly lower in women compared to men, and in participants that perceived themselves to be overweight or obese compared to those that perceived themselves to be normal weight. Furthermore, external HLC was negatively associated with all three constructs (attitude, subjective norm and PBC). Our findings confirm those of Poínhos et al. (2014) who reported external HLC to be a significant negative predictor of attitude towards genotype-based personalised nutrition in a large study of European adults. Internal HLC was a significant positive predictor of attitude in the study by Poínhos et al. (2014), whereas in our study internal HLC was not significantly associated with TPB constructs. An external HLC is associated with the perception that your health is not under your control (Wallston et al., 1976). Therefore, an individual with a higher external HLC may be more likely to have a fatalistic response to disclosure of a risk-associated genotype and therefore less likely to adopt genotype-based advice. Although, discussed above in section 6.2.1, findings from our intervention studies (Study 1 and 2) and our meta-analysis (Study 3) do not suggest that genotype-based advice results in a fatalistic response, this conclusion is based on the mean response of participants; there may be a minority of individuals that do have a high

external HLC and as a consequence a fatalistic response to advice. Therefore, it is very important to ensure that delivery of advice to participants makes clear the potential for lifestyle behaviours to modify the association between their genotype and the subsequent risk of disease (Khera et al., 2016).

The food choice motive of 'health' was identified as having a significant positive association with attitude towards genotype-based advice in all groups, and with PBC in all participants and participants that perceived themselves to be normal weight. The positive relationship between the food choice motive of 'health' and attitude towards genotype-based personalised advice was also reported by Rankin et al. (2018). Additionally, Sun et al. (2008) reported a positive association between 'health' as a food choice motive and attitude towards healthy eating in young adults and Kapellou et al. (2022) reported that the food choice motive of 'health' was higher in participants that had been previously genotyped compared to those that had not. Overall, the food choice motive 'health' was ranked third in our young adult population after 'sensory appeal' and 'price', which is a common pattern (Markovina et al., 2015; Steptoe et al., 1995; Sun, 2008). As such, in order for 'health' to be considered when making food choice decisions it is important that the taste and cost of food recommendations be considered in the advice.

In summary, studies by Poínhos et al., (2014) and Rankin et al. (2018) had previously suggested the importance of psychological factors and food choice motives on attitude towards and intention to adopt genotype-based personalised nutrition. Our findings contribute to the research area by adding to those of Poínhos et al., (2014) and Rankin et al. (2018) by also investigating the association of background factors on subjective norms and PBC. The association of background factors varied depending on which proximal construct of intention was analysed and on the characteristics of participants, including sex and perceived BMI. The strengths, limitations, and implications of these findings and those of our first three studies will be discussed in the following section, as well as directions for future research.

6.3 Strengths, limitations, implications and directions for future research

6.3.1 Strengths and limitations

The strengths and limitations of each study have been discussed within chapters two - five; therefore, in this section, the overarching strengths and limitations for this program of

research will be discussed. Firstly, a predominant strength is the incorporation of behaviour change theory within each of the included studies. There are numerous behaviour change models that could have been utilised; however, NICE guidelines do not recommend use of a particular behaviour change model (NICE, 2007). For this research the TPB was chosen as a model of behaviour change since it has been used widely in health-related behaviour change research (Ajzen, 1991; Davis et al., 2015), including a number of studies investigating genotype-based advice (Horne, Gilliland, O'Connor, et al., 2020; Poínhos et al., 2014; Rankin et al., 2018). Furthermore, Horne et al. (2017) have proposed how the TPB model may be extended to include personalisation. A further strength of the programme of research is the focus on specific populations. In studies 2 and 4 we investigated genotype-based advice for behaviour change in a young adult population. As previously mentioned, for prevention of NCDs such as obesity, T2D, and CVD, genotype-based personalised advice may be most useful in a young adult population. Moreover, in study three we compared the effect of genotype-based advice in healthy adult populations and those that were at risk of cardiometabolic disease.

The main limitation of our research and indeed much nutrition-related research is the measurement of dietary behaviour. Reported dietary intake is subject to consistent systematic error as a consequence of misreporting (Goldberg et al., 1991). In the best scenario, the effect of measurement error is a reduction in precision; the worst scenario is spurious results or failure to identify a true effect (Keogh et al., 2016). Estimations of error can be made by analysing an appropriate biomarker such as doubly labelled water or urinary sodium excretion. However, these methods are expensive, in the case of doubly labelled water, or burdensome for the participant, in the case of urinary sodium (Keogh et al., 2016). In an attempt to control for underreporting in Study 1, saturated fat intake was analysed as a percentage of TEI and folate as µg per 10 MJ, rather than using absolute values. Furthermore, in our meta-analysis using the GRADE assessment, the dietary behaviour outcome was downgraded by two levels to 'low', which means the true effect may be markedly different to the estimated effect (King et al., 2023). With this in mind, the limitations of using reported dietary intake as an outcome should be considered when making conclusions regarding the effect of genotype-based advice on dietary behaviour. Another major limitation from this programme of research is due to the variability in the interventions, disease context, and

study populations used to determine the efficacy of genotype-based personalised advice. These limitations have been discussed at length above (section 6.2.1). However, due to this variability the extent to which the research can be combined to determine the true effect of genotype-based personalised advice on dietary and physical activity behaviour is limited.

Finally, although sample size calculations were met for each of the experimental studies (Study, 1, 2, and 4), analysis between sub-groups may not have been adequately powered. Furthermore, participant drop-out in Study 1 meant that the number of participants completing the study was below the sample size calculation. Reduced statistical power may have increased the chance of a type II error (Andrade, 2020). Furthermore, both intervention studies (Study 1 and 2) were of relatively short duration. In Study 1 dietary behaviour change was measured 10 days after advice was received and in Study 2 seven days after advice was received. Consequently, these findings can only determine the initiation of behaviour change. Importantly to enable the health benefits of changes in dietary and physical activity behaviours to be realised behaviour changes need to be maintained. Therefore, a limitation of study designs utilised in Study 1 and 2 is that they are not able to determine if any changes in behaviour were maintained.

6.3.2 Implications

In this section the implications of our findings for the use of genotype-based personalised advice to motivate behaviour change will be discussed. The main findings of this programme of research suggest that provision of genotype-based dietary or physical activity advice does not consistently result in favourable changes in dietary or physical activity behaviour. However, our findings also suggest that there is considerable variation between studies investigating the effect of genotype-based advice and have suggested that this may explain some of the inconsistent findings observed. Our findings also suggest that the way in which genotype-based advice is delivered should be tailored to the characteristics of the target population. We found the TPB to be an appropriate framework on which to investigate the intention of a young adult population to adopt genotype-based advice.

To tackle the increasing prevalence of NCDs, including CVD, T2D, and obesity, dietary and physical activity behaviours need to change (Ezzati et al., 2003). General public health recommendations are not affective in changing dietary or physical activity behaviour (Health Survey for England, 2017; Roberts et al., 2018). Personalisation of advice may motivate behaviour change to a greater extent than general recommendations; however, personalisation based on genotype has not been demonstrated to be more effective than other levels of personalisation. Compared to other levels of personalisation, genotype-based advice can be delivered earlier in the lifespan, as a tool within behaviour change interventions, to demonstrate the personal salience of advice to young adults and to challenge optimistic bias. However, based on our findings from Study 2 healthy-eating motivation was not affected by genotype-based personalised advice in young adults. Therefore, we would recommend that researchers and health care practitioners, looking to change behaviours using genotype-based advice, tailor the way in which they frame advice to have the greatest impact. As we and other researchers have suggested, background factors such as individual characteristics, psychological characteristics, and food choice motives should be considered. Based on our findings in a young adult population we would recommend tailoring the framing of advice based on sex or whether a young adult perceives themselves to be normal weight or overweight. For example, a young adult that perceived themselves to overweight may be more likely to respond favourably if genotype-based advice is framed in the context of weight-loss. Future studies of genotype-based advice for changing behaviour should incorporate behaviour change theory explicitly in their design and consider participant characteristics in the delivery of advice.

Importantly, our findings also confirm those of other researchers that suggest genotype-based advice does not result in unfavourable changes in behaviour (Fallaize et al., 2016; Nielsen & El-Sohemy, 2014). Therefore, even if personalisation of advice based on genotype does not motivate greater changes in behaviour than other levels of personalisation, since genotype-based advice can be more effective due to gene-diet interactions, the consequence of this advice may result in more advantageous changes in disease related markers such as BMI or blood cholesterol levels compared to other levels of personalisation (Grimaldi et al., 2017).

Further research has been suggested following each of the studies within the study chapter. In this section the findings of all studies will be considered together to determine recommendations for further research. As mentioned, one of the most important contributions to the research area from this programme of research is how background characteristics of young adults can influence their intention to adopt genotype-based personalised diet and physical activity advice. The findings from this research should be used to inform the design and delivery of a genotype-based diet and physical activity intervention in a young adult population. The delivery of advice should incorporate factors identified in Study 4 that are important in a young adult population, such as: challenging optimistic bias, consideration of food choice motives, delivery of advice by a health professional and incorporation of procedural advice. Advice should also be stratified and tailored to reflect characteristics of young adults such as sex and perception of body weight. In order to determine whether genotype-based personalised advice that is also personalised by participants characteristics is more effective than other levels of personalised advice an RCT with three arms would be required (control, non-genotype-based personalised advice, stratified genotype-based personalised advice). To evaluate the effectiveness of the advice to change behaviour and target different constructs of the TPB, measures of both behaviour and TPB constructs should be compared between and within arms, before and after delivery of the intervention. If this proves successful, the intention to adopt genotype-based advice should be investigated in other population groups in order to tailor and stratify advice delivered in subsequent interventions appropriately. Further, as more studies are published using genotype-based advice to motivate behaviour change, it would be useful to conduct separate meta-analyses of research studies that focus on a specific disease context, within specific populations and genes utilised.

6.4 Conclusions

The findings from this programme of research add to those of previous researchers that suggest genotype-based advice does not motivate or promote greater behaviour change to reduce the risk of obesity, T2D and CVD, compared to non-genotype-based advice or general advice. A systematic review of the literature identified that behaviour change theory has not consistently been adequately considered in the design and implementation of interventions

that have incorporated genotype-based advice. For prevention of NCDs in later life young adults were identified as a population that stand to benefit from the potential use of genotype-based advice to motivate behaviour change as a component of a behaviour change intervention. Using the TPB as a framework, an investigation of factors that influence the intention to adopt genotype-based advice in young adults has provided recommendations for how genotype-based advice delivered to a young adult population could be tailored. These recommendations should be used by health care practitioners and researchers that intend to use genotype-based advice in a young adult population. Finally, the effectiveness of the recommendations to motivate and change behaviour following genotype-based advice should be investigated in an intervention study in a young adults.

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Appendix

Appendix 1: Ethical approval

St Mary's University Twickenham London

12 June 2018 SMEC_2017-18_130

Alexandra King (SHAS): Changes to 'The effect of ApoE genotype, MTHFR genotype and dietary intake on intermediate cardiovascular disease risk factors. Does personalised nutrition advice based on ApoE and MTHFR genotype affect dietary behaviour?'

Dear Ammi

University Ethics Sub-Committee

I can confirm that the changes to your previously approved ethics application (to incorporate data collection by MSc students and extension of data collection period) is approved.

Yours sincerely

Prof Conor Gissane
Chair, Ethics Sub-Committee

Cc Dr Yiannis Mavrommatis

St Mary's University Twickenham London

16 August 2019 SMEC_2018-19_052

Alexandra King (SHAS): 'A longitudinal study to determine the effect of gene-based personalised diet and physical activity advice on adiposity indices in university students'

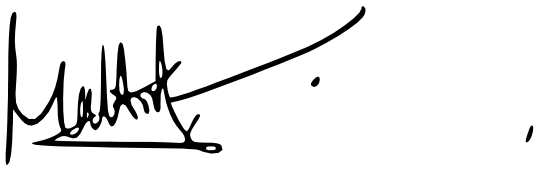
Dear Ammi

University Ethics Sub-Committee

Thank you for re-submitting your ethics application for consideration.

I can confirm that all required amendments have been made and that you therefore have ethical approval to undertake your research.

Yours sincerely



Matthew James
Acting Chair, Ethics Sub-Committee

Cc Yiannis Mavrommatis, Leta Pilic

St Mary's University Twickenham London

Faculty of Sport, Health & Applied Science

4/3/22

Dear Ammi King,

Re. Investigation of factors that influence young adults' intention to adopt gene-based personalised advice for diet and physical activity.

Thank you for submitting your ethics application for consideration.

I can confirm that your application has been considered by the SHAS Ethics Committee and that ethical approval is granted. Please find attached your signed approval form.

Yours sincerely,

John Pattison

Faculty of SAHPS Ethics Committee

Appendix 2: Information sheet Study 1

Section A: The Research Project

Project Title: The effect of ApoE genotype, MTHFR genotype and dietary intake on intermediate cardiovascular disease risk factors. Does personalised nutrition advice based on ApoE and MTHFR genotype affect dietary behaviour?

Cardiovascular disease (CVD) is a preventable cause of premature death and risk factors associated with CVD can be modified by diet. However, the response of individuals to dietary modification is highly variable. Some of this variation may be explained by the interaction between an individual's genotype and their diet. Therefore, the 'one size fits all' approach to public health nutrition cannot address individual dietary requirement. The proposed study will aim to determine the effect of genotype (Apo E and MTHFR) and diet (fat and folate) combined or in isolation on intermediate CVD risk factors. Also to determine if personalised nutrition advice based on genotype affects dietary change.

You are invited to take part in a study at St Mary's University to investigate the relationship between diet and genetics on cardiovascular disease risk. The study will be organised by Alexandra King as part of her PhD under the supervision of Dr Yiannis Mavrommatis. The results of the study will be analysed and presented as part of a PhD and may also be published in a peer reviewed academic journal or presented at an academic conference. The research is funded by St Mary's University. For further information please contact Alexandra King (alexandra.king@stmarys.ac.uk)

Section B: Your Participation in the Research Project

You have been invited to take part in the study because you are 18 years of age or older without a current diagnosis of coronary heart disease (including angina or heart attack) or stroke/transient ischaemic attack.

You can refuse to take part or withdraw from the project at any time, by informing Alexandra King or returning the withdraw slip at the bottom of your consent form.

If you agree to take part in the study you will take part in two data collection periods. At the initial data collection session you will be required to provide a saliva sample which will be used to determine your genotype for two genes associated with cardiovascular disease risk (MTHFR and ApoE). In addition you will need to provide a capillary blood sample (finger prick) to determine levels of lipids in your blood. This in addition to your height, weight and a number of additional questions will be used to determine your risk of cardiovascular disease in the next 10 years. It is estimated that along with providing informed consent and answering any questions you may have that this data collection session will take approximately 30 minutes The second data collection session will occur after you have received personalised nutrition advice based on your genotype and reported dietary intake and will require you to repeat the dietary recall, this will take approximately 20 minutes. You will receive personalised feedback on your diet and genotype approximately one month after the first data collection session. The second data collection

session will occur one-three weeks after you have received personalised nutrition advice. Consequently, you will be involved in the study for a period of approximately two months.

Some studies have reported negative effects such as demotivation for behaviour change and increased anxiety following the provision of genotype information. If you decide to take part in this study you will have your genotype and recommendations for dietary change clearly explained in addition to how this may affect your risk of cardiovascular disease. Any information you provide as part of this study will be anonymised. Samples provided for this research will be kept until the end of the study. Data will be presented collectively rather than for individual participants and will be managed in line with The Data Protection Act 1998. On completion of the study you will gain knowledge about your cardiovascular disease risk and will receive personalised dietary advice based on your current diet and genotype.

YOU WILL BE GIVEN A COPY OF THIS FORM TO KEEP TOGETHER WITH A COPY OF YOUR CONSENT FORM

Appendix 3: Consent form Study 1

St Mary's University Twickenham London

Name of Participant: _____

Title of the project: The effect of ApoE genotype, MTHFR genotype and dietary intake on intermediate cardiovascular disease risk factors. Does personalised nutrition advice based on ApoE and MTHFR genotype affect dietary behaviour?

Main investigator and contact details: Alexandra King alexandra.king@stmarys.ac.uk

Members of the research team: Yiannis Mavrommatis yiannis.mavrommatis@stmarys.ac.uk

1. I agree to take part in the above research. I have read the Participant Information Sheet which is attached to this form. I understand what my role will be in this research, and all my questions have been answered to my satisfaction.
2. I understand that I am free to withdraw from the research at any time, for any reason and without prejudice.
3. I have been informed that the confidentiality of the information I provide will be safeguarded.
4. I am free to ask any questions at any time before and during the study.
5. I have been provided with a copy of this form and the Participant Information Sheet.

Data Protection: I agree to the University processing personal data which I have supplied. I agree to the processing of such data for any purposes connected with the Research Project as outlined to me.

Name of participant (print)……..

Signed…….. Date…….....

If you wish to withdraw from the research, please complete the form below and return to the main investigator named above.

Title of Project: The effect of ApoE genotype, MTHFR genotype and dietary intake on intermediate cardiovascular disease risk factors. Does personalised nutrition advice based on ApoE and MTHFR genotype affect dietary behaviour?

I WISH TO WITHDRAW FROM THIS STUDY

Name: _____

Signed: _____ Date: _____

Appendix 4: 24-hour recall Study 1

24-hour dietary recall

Page 1: 24-hour dietary recall

1. Please enter the unique identification number provided in this email (e.g. 101). *Required*

2. Please enter your date of birth *Required*

Dates need to be in the format 'DD/MM/YYYY', for example 27/03/1980.

Thank you for choosing to take part in this study!

We would like you to tell us everything you had to eat and drink yesterday. **Please include all meals, snacks and drinks (including alcohol).**

This survey has 5 sections (A - Quick list, B - Forgotten foods list, C - Occasion , D - Details about food and drink, and E - Final step). **Please read and answer all of them.**

This survey will take approximately 20 minutes to complete.

A - Quick list

3. Please list all the foods you have eaten in the past 24-hours (from midnight to midnight). Please also include all beverages, including water and alcohol. **We will ask you to return to this question and add additional information throughout the survey.** *Required*

B - Forgotten foods list

Please choose (tick) **all** foods from the list below that you have consumed in the same 24-hour period but you may have forgotten to list in the question 2. **Also, go back to question 2 and add them to your food list, together with any other food or drink you have just remembered but have not included in question 2.**

4. Non-alcoholic beverages

- [ ] Tea
- [ ] Coffee
- [ ] Hot chocolate
- [ ] Diet fizzy drink
- [ ] Fizzy drink
- [ ] Pure fruit juice (e.g. 100% orange or apple)
- [ ] Fruit squash or cordial
- [ ] Milk (e.g. with tea or coffee)

5. Alcoholic beverages

- [ ] Wine
- [ ] Beer

- [ ] Cider
- [ ] Liqueur (e.g. port, sherry, vermouth) Spirit
- [ ] (e.g. gin, brandy, whiskey, vodka)

6. Sweets and snacks

- [ ] Biscuits/cookies
- [ ] Cake
- [ ] Pastry
- [ ] Pie
- [ ] Milk pudding
- [ ] Ice cream
- [ ] Chocolate (single or squares)
- [ ] Chocolate bar
- [ ] Sweets
- [ ] Toffees
- [ ] Crisps or other packet snacks
- [ ] Peanuts or other nuts Crackers
- [ ] Sugar (e.g. with tea or coffee)

7. Fruit

- [ ] Apple
- [ ] Pear
- [ ] Orange
- [ ] Satsuma
- [ ] Mandarin

- [ ] Grapes
- [ ] Tinned fruit
- [ ] Dried fruit

8. Vegetables

- [ ] Carrots
- [ ] Peas
- [ ] Beans
- [ ] Green salad or lettuce Cucumber
- [ ] Celery
- [ ] Tomatoes
- [ ] Sweetcorn
- [ ] Avocado

9. Cheese and dairy

- [ ] Sour cream
- [ ] Double cream
- [ ] Yoghurt
- [ ] Dairy dessert
- [ ] Cheese (e.g. Cheddar, Brie, Edam) Cottage
- [ ] cheese or low fat soft cheese

10. Breads and rolls

- [ ] Breads and rolls (white, wholemeal, brown)
- [ ] Wraps
- [ ] Scones
- [ ] Crumpets

11. Condiments

- [ ] Ketchup
- [ ] Mayonnaise
- [ ] Coleslaw

C - Occasion

Now tell us the occasion at which you ate each food from the section A (e.g. breakfast at home, dinner at the restaurant, watching TV). Think about the activities you had throughout the day and list all the food you may have forgotten in the section A. Think about the activities such as watching TV, working on the computer, going to a cinema, restaurant or a bar. Also, try to remember the food you would not typically have or you had in between meals. **Return to question 2 and add it to the food list.**

D - Details about food and drink

Describe the food you have listed and chosen in the section A and B in as much detail as possible. It is important that you tell us the brand (if known) and any brand variation (e.g. reduced salt, sugar etc.), how was the food prepared (e.g. fried, roasted, boiled), was the food raw or canned. Also tell us how much you ate. Use exact quantities if known or household measures such as teaspoon, tablespoon, mug, cup, bowl (small, medium, large), plate (small, medium, large). **Return to question 2 and add it to the food list.**

If you need help with the portion sizes, scroll down to the end of the questionnaire where you will be able to find some photographs. If you do not need help, continue filling in the survey.

E - Final step

This is the final step. Look over all the food you have listed and described so far and add any food or drink that you may have forgotten, including the occasion and details of the food and drink. **Return to question 2 and add it to the food list.**

Thank you for participating!

Appendix 5: Study 1: Personalised advice email

Dear

Thank you for taking part in our research study.

Please read below for information about your DNA, current diet and personalised dietary advice based on your genotype that may reduce your risk of cardiovascular disease.

Cardiovascular disease is a preventable cause of premature death and risk factors associated with cardiovascular disease can be modified by diet. However, the response of individuals to dietary modification is highly variable. Some of this variation may be explained by the interaction between an individual's DNA variation (genotype) and their diet. Therefore, the 'one size fits all' approach to public health nutrition cannot address individual dietary requirement.

The information below provides an overview of your genotype for two genes associated with cardiovascular disease risk (ApoE and MTHFR), your current dietary intake of nutrients that are associated with these genes (saturated fat and folate) and personalised dietary advice based on your genotype. More detailed information on each factor can be found in the report.

Overview: *(insert values and delete as appropriate)*

Genotype	**Diet**	**Advice based on genotype**
ApoE: E2/E3 **Risk** **Non-risk** *(see page 2)*	**Saturated Fat intake:** **13%** percentage of total energy intake **Not meeting recommendation** **Meeting recommendation** *(see page 2)*	**Risk**: it is beneficial for you to keep a normal level of blood cholesterol and a healthy intake of saturated fat *(see page 3-5)* **Non-risk**: follow healthy eating guidelines as recommended in the Eatwell Guide *(see page 8)*
MTHFR: CC **Risk** **Non-risk** *(see page 6)*	**Folate intake:** …..µg **Not meeting recommendation** **Meeting recommendation** *(see page 6)*	**Risk**: it is beneficial for you to keep a healthy intake of folate *(see page 7)* **Non-risk**: follow healthy eating guidelines as recommended in the Eatwell Guide *(see page 8)*

ApoE Personalised Feedback:

Genotype: E3/E3

……. Percent of the population have this genotype

Risk

"You have a genetic variation in the ApoE gene that is associated with a substantially higher cardiovascular disease risk; consequently, it is beneficial for you to keep a normal level of blood cholesterol and a healthy intake of saturated fat."

Non-risk

"You do not have a genetic variation in the ApoE gene that is associated with a higher cardiovascular disease risk; you should follow healthy eating guidelines as recommended in the Eatwell Guide."

Dietary intake of saturated fat:

Your reported intake of saturated fat was …….g which is …… percent of your total energy intake.

Your current intake is **above** / **meets** recommendations.

UK health guidelines recommend that:

The recommended intake for saturated fat is no more than 11% of total energy intake. This is approximately 20 g of saturated fat for an average woman with an energy intake of 2000 kcal per day and approximately 30 g saturated fat for an average man with an energy intake of 2500 kcal.

Practical tips to help you eat less saturated fat

Eating lots of saturated fat can raise your cholesterol and increase your risk of heart disease.

Saturated fat is found in:

- butter, ghee, suet, lard, coconut oil and palm oil
- cakes
- biscuits
- fatty cuts of meat
- sausages
- bacon
- cured meats like salami, chorizo and pancetta
- cheese
- pastries, like pies, quiches, sausage rolls and croissants
- cream, crème fraîche and sour cream
- ice cream
- coconut milk and cream
- milk shakes
- chocolate and chocolate spreads

These tips can help you cut the total amount of fat in your diet:

- Compare food labels when shopping so you can pick foods lower in fat – use the Be Food Smart app.
- Choose lower fat or reduced fat dairy products.
- Grill, bake, poach or steam food rather than frying or roasting.
- Measure oil with a teaspoon to control the amount you use, or use an oil spray.
- Trim visible fat and take the skin off meat and poultry before cooking.
- Choose leaner cuts of meat that are lower in fat, like turkey breast and reduced fat mince.
- Make your meat stews and curries go further by adding veg and beans.
- Try reduced fat spreads, such as those based on olive or sunflower oils.
- How to cut down on saturated fat
- Practical tips to help you specifically cut down on saturated fat:
- At the shops
- Nutrition labels on the front and back of packaging can help you cut down on saturated fat. Look out for "saturates" or "sat fat" on the label.

High: More than 5g saturates per 100g. May be colour-coded red.

Medium: Between 1.5g and 5g saturates per 100g. May be colour-coded amber.

Low: 1.5g saturates or less per 100g. May be colour-coded green.

This is an example of a label that shows an item is high in saturated fat because the saturates section is colour-coded **red**.

Aim to choose products with **green** or **amber** for saturated fat. There can be a big difference in saturated fat content between similar products.

Pick the one lower in saturated fat. Serving sizes can vary, so make sure you're comparing like for like. The easiest way to do this is by looking at the nutritional content per 100g.

At home:

Spaghetti Bolognese: use a lower fat mince, as it's lower in saturated fat. If you aren't using lower fat mince, brown the mince first, then drain off the fat before adding other ingredients. Alternatively, mix meat mince with a meat-free mince alternative.

Pizza: choose a lower fat topping, such as vegetables, chicken, tuna and other seafood instead of extra cheese or cured meats like pepperoni, salami and bacon.

Fish pie: use reduced fat spread and 1% fat milk to reduce the fat in the mash and sauce. Try this healthy fish pie recipe.

Chilli: use lower fat mince or mix in a meat-free mince alternative. Or, make a vegetarian chilli using mixed beans, some lentils and vegetables – try this healthy chilli con carne recipe. Beans and lentils can count towards your 5 A Day, too.

Chips: choose thick, straight-cut chips instead of french fries or crinkle-cut to reduce the surface area exposed to fat. If you're making your own, cook them in the oven with a little sunflower oil and the skins on, rather than deep frying.

Potatoes: make your roast potatoes healthier by cutting them into larger pieces than usual and using just a little sunflower or olive oil.

Mashed potato: use reduced fat spread instead of butter, and 1% fat milk or skimmed milk instead of whole or semi-skimmed milk.

Chicken: go for leaner cuts, such as chicken breast. Before you eat it, take the skin off to reduce the saturated fat content. Try this healthy lemon chicken recipe.

Bacon: choose back bacon instead of streaky bacon, which contains more fat. Grill instead of frying.

Eggs: prepare eggs without oil or butter. Poach, boil or dry fry your eggs.

Pasta: try a tomato-based sauce on your pasta. It's lower in saturated fat than a creamy or cheesy sauce.

Milk: use 1% fat milk on your cereal and in hot drinks. It has about half the saturated fat of semi-skimmed.

Cheese: when using cheese to flavour a dish or sauce, try a strong-tasting cheese, such as reduced fat mature cheddar, as you'll need less. Make cheese go further by grating instead of slicing it.

Yoghurt: choose a lower fat and lower sugar yoghurt. There can be a big difference between different products.

Eating out

Coffee: swap large whole milk coffee for regular "skinny" ones. Avoid adding cream on top.

Curry: go for dry or tomato-based dishes, such as tandoori or madras, instead of creamy curries like korma, pasanda or masala. Choose plain rice and chapatti instead of pilau rice and naan.

Kebabs: go for a shish kebab with pitta bread and salad rather than a doner kebab.

Chinese: choose a lower fat dish, such as steamed fish, chicken chop suey or Szechuan prawns.

Thai: try a stir-fried or steamed dish containing chicken, fish or vegetables. Watch out for curries that contain coconut milk, which is high in saturated fat. If you choose one of these, try not to eat all the sauce.

Snack time: swap foods high in sugar, salt and fat, such as chocolate, doughnuts and pastries, for:

- some fruit
- wholegrain toast
- low-fat and lower sugar yoghurt
- a small handful of unsalted nuts
- a currant bun
- a slice of fruit loaf
- a slice of malt loaf

MTHFR Personalised feedback:

Genotype: CC

……. Percent of the population have this genotype

Risk

"You have a genetic variation in the MTHFR gene that is associated with a higher cardiovascular disease risk; consequently it is beneficial for you to keep a healthy intake of folate."

Non-risk

"You do not have a genetic variation in the MTHFR gene that is associated with a higher cardiovascular disease risk, you should follow healthy eating guidelines as recommended in the Eatwell Guide."

Dietary intake of folate:

Your reported intake of folate was …….µg.

Your current intake is **above** / **meets** recommendations.

UK health guidelines recommend that:

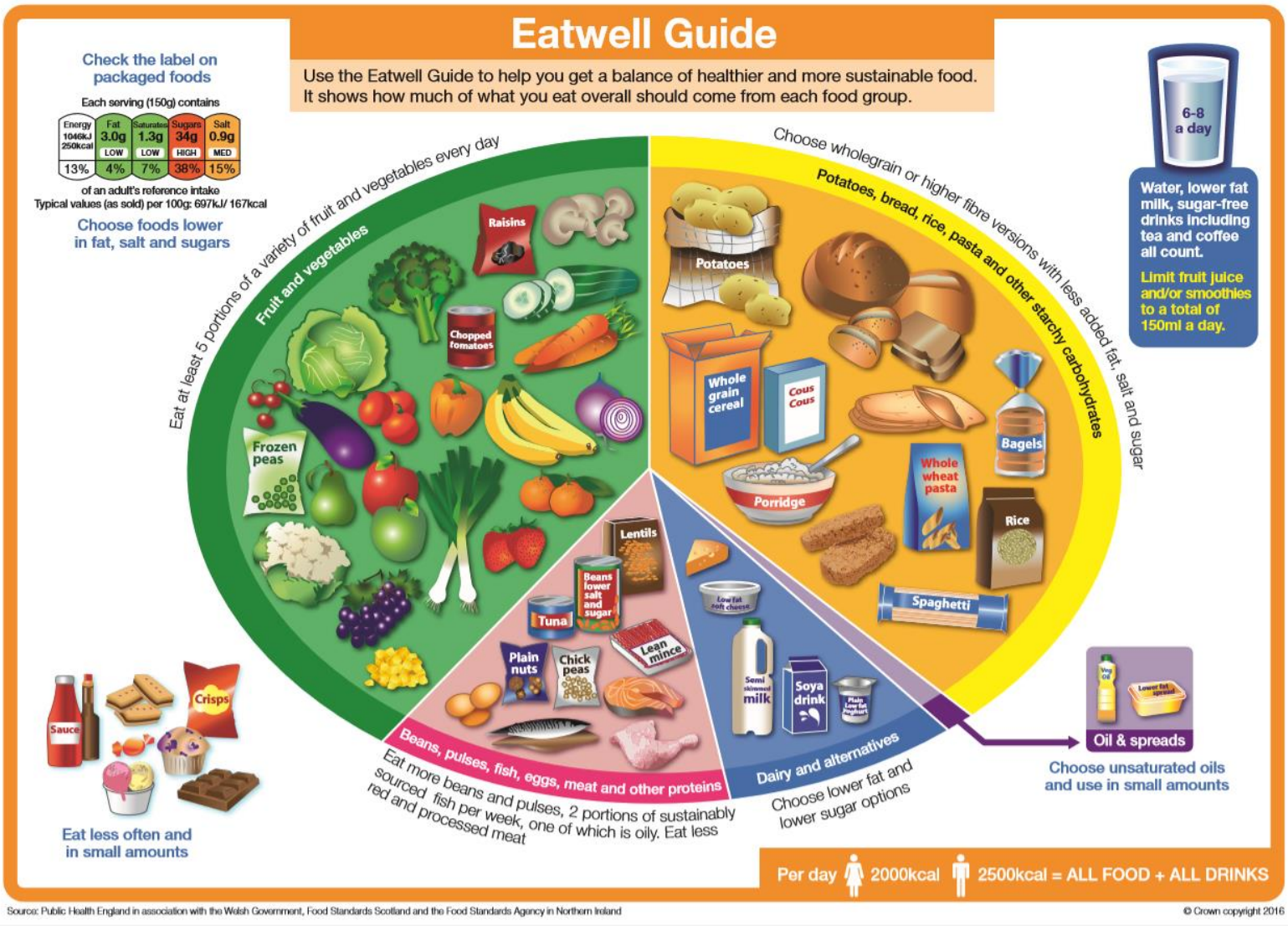
Folate intake should be greater than 200 µg per day. Unless you are pregnant or lactating, in which case your requirements are higher.

Practical tips to help you eat more folate

Folate is found in green leafy vegetables; good sources of folate include:

- broccoli
- Brussels sprouts
- asparagus
- peas
- chickpeas
- brown rice

Eatwell Guide



Appendix 6: Information sheet – Study 2

Section A: The Research Project

Project Title: A longitudinal study to determine the effect of gene-based personalised diet and physical activity advice on adiposity indices in university students.

The prevalence of obesity continues to rise and is associated with an increased risk of chronic disease. The transition to higher education and subsequent years at university is a period of risk for weight gain. Weight loss is difficult to maintain therefore prevention rather than treatment of obesity is a more favourable approach. A gene-based personalised approach to dietary recommendations may motivate individuals to make positive changes in their dietary behaviour. The proposed study aims to determine the effect of genetics based personalised dietary and physical activity advice on obesity indices.

You are invited to take part in a study at St Mary's University to investigate the effect of genetics based personalised dietary and physical activity advice on obesity indices. The study will be organised by Alexandra King as part of her PhD under the supervision of Dr Yiannis Mavrommatis and Dr Leta Pilic. The results of the study will be analysed and presented as part of a PhD and may also be published in a peer reviewed academic journal or presented at an academic conference. The research is funded by St Mary's University.

For further information please contact Alexandra King (alexandra.king@stmarys.ac.uk)

Supervisors contact details: Yiannis Mavrommatis (yiannis.mavrommatis@stmarys.ac.uk)
Leta Pilic (leta.pilic@stmarys.ac.uk)

Section B: Your Participation in the Research Project

You have been invited to take part in the study because you are a level 4 undergraduate student (18 -25 years of age) without a current diagnosis of chronic disease and are not pregnant, lactating, have a history of disordered eating or following a restricted diet.

Although we are introducing the study in parallel to your university induction you are under no obligation to take part even if your friends choose to do so. If you agree to take part in the study, you still have the option to withdraw from the project at any time by informing Alexandra King.

If you agree to take part in the study you will take part in a data collection period each September for the next three years, final data collection will take place in September 2022. At the initial data collection session you will be required to provide a saliva sample which will be used to determine your genotype for a genes associated with obesity risk (*FTO*). In addition, we will measure your

height, weight, body mass index (BMI), waist circumference (WC), body fat percentage (BF%), healthy eating motivation, dietary intake and physical activity. We will also ask you for your ethnicity and socio-economic status because they can help to explain someone's risk of obesity. Socio-economic status will be determined by asking you to provide the first half of your postcode. Neither of these data will be used in a way that could identify you. We will also ask if you smoke and who you live with. Following this you will be randomised to one of four different groups (1. Control: no advice, 2. Non genetic personalised advice: dietary and physical activity advice based on reported intake and physical activity, 3. Genotype- based personalised advice (high risk): dietary and physical activity advice based on genotype, reported intake and physical activity and 4. Genotype- based personalised advice (low risk): dietary and physical activity advice based on genotype, reported intake and physical activity). Following allocation to groups if you are in group 2, 3 or 4 you will receive dietary and physical advice via email and all participants will complete the healthy eating motivation questionnaire for a second time. In April/May 2020 follow up variables (smoking status, weight, BMI, WC, BF%, healthy eating motivation, dietary intake and physical activity) will be measured again. These follow up variables will be measured every September and April/May until September 2022. If you are in the control group you will be able to find out information about your dietary intake, physical activity and genotype on completion of the study. If you are in the non-genetic personalised advice group you will be able to find out your genotype on completion of the study.

Some studies have reported negative effects such as demotivation for behaviour change and increased anxiety following the provision of genotype information. If you decide to take part in this study you may have your genotype and recommendations for dietary change clearly explained in addition to how this may affect your risk of obesity. Any information you provide as part of this study will be anonymised. Samples provided for this research will be kept until the end of the study. Data will be presented collectively rather than for individual participants and will be managed in line with The Data Protection Act 2018. On completion of the study you will gain knowledge about your obesity risk and will receive personalised dietary and physical activity advice based on your current diet and genotype.

YOU WILL BE GIVEN A COPY OF THIS FORM TO KEEP TOGETHER WITH A COPY OF YOUR CONSENT FORM

Appendix 7: Epic Physical Activity Questionnaire (EPAQ2)

ID Number

PHYSICAL ACTIVITY QUESTIONNAIRE

This questionnaire is designed to find out about your physical activity in your everyday life.

Please try to answer every question, except when there is a specific request to skip a section.

THE QUESTIONNAIRE IS DIVIDED INTO 3 SECTIONS

- **Section A** asks about your physical activity patterns in and around the house.
- **Section B** is about travel to work and your activity at work.

  It may be skipped by people who have not worked at any stage during the last 12 months.

- **Section C** asks about recreations that you may have engaged in during the last 12 months.

What is your date of birth?

What is today's date?

day / month / year

Your sex *(Please tick (✓) appropriate box)*? Male ☐ Female ☐

Section A HOME ACTIVITIES

GETTING UP AND GOING TO BED

*Please put a time in **each** box*

	Average over the past year	
	At what time do you normally get up?	At what time do you normally go to bed?
On a weekday		
On a weekend day		

GETTING ABOUT — Apart from going to work

Which form of transport do you use **most often** apart from your journey to and from work?

Please tick (✓) one box ***ONLY*** *per line*

Distance of journeys	**Usual mode of transport**			
	Car	Walk	Public transport	Cycle
less than one mile				
1–5 mile(s)				
More than 5 miles				

TV OR VIDEO VIEWING

*Please put a tick (✓) on **every** line*

Hours of TV or Video watched per day	Average over the last 12 months					
	None	less than 1 hour a day	1 to 2 hours a day	2 to 3 hours a day	3 to 4 hours a day	More than 4 hours a day
On a weekday before 6 pm						
On a weekday after 6 pm						
On a weekend day before 6 pm						
On a weekend day after 6 pm						

STAIR CLIMBING AT HOME

*Please put a tick (✓) on **every** line*

Number of times you climbed up a flight of stairs (approx 10 steps) each day at home	Average over the last 12 months					
	None	1 to 5 times a day	6 to 10 times a day	11 to 15 times a day	16 to 20 times a day	More than 20 times a day
On a weekday						
On a weekend day						

ACTIVITIES IN AND AROUND THE HOME

*Please put a tick (✓) on **every** line*

Approximate number of hours each week	Average over the last 12 months						
	None	Less than 1 hour a week	1 to 3 hours a week	3 to 6 hours a week	6 to 10 hours a week	10 to 15 hours a week	More than 15 hours a week
Preparing food, cooking and washing up							
Shopping for food and groceries							
Shopping and browsing in shops for other items (e.g. clothes,toys)							
Cleaning the house							
Doing the laundry and ironing							
Caring for pre-school children or babies at home (not as paid employment)							
Caring for handicapped, elderly or disabled people at home (not as paid employment)							

Section B ACTIVITY AT WORK

Please answer this section **only** if you have been in paid employment at any time during the last 12 months or you have done regular, organised voluntary work.

If not please go to page 9

TYPES OF WORK DURING THE LAST TWELVE MONTHS

- We would like to know what full or part-time jobs you have done in the last 12 months.
- You may have held a single job or have held two jobs at once.
- If you have changed jobs with the same employer, you should enter it as a change of job **only** if it entailed a substantial change in physical effort.

EXAMPLE

Someone who worked full-time for 6 months, then retired, rested for 3 months and then started a voluntary job for 6 hours a week, would complete the questions as follows.

	Job 1	Job 2
Name of occupation	*nurse*	*shop work*
How many hours **per week** did you usually work?	*38*	*6*
For how many months in the last 12 months did you do this work?	*6*	*3*

ACTIVITY LEVELS AT YOUR WORK

Now we would like you to take the total number of hours you worked per week in each job and divide them up according to your activity level.

Please complete EACH line

	Job 1			Job 2		
	No	Yes	Hours per week	No	Yes	Hours per week
Sitting — light work e.g. desk work, or driving a car or truck		✓	6	✓		
Sitting — moderate work e.g. working heavy levers or riding a mower or forklift truck	✓				✓	2
Standing — light work e.g. lab technician work or working at a shop counter		✓	30		✓	4
Standing — light/moderate work e.g. light welding or stocking shelves		✓	2	✓		

The number of hours in each activity should add up to the number of hours that you worked in each job e.g. 6+30+2=38 (nurse)

What jobs have you held in the last 12 months, and how many months in the year did you do them?

Please complete EACH line

	Job 1	**Job 2**
Name of occupation		
How many hours **per week** did you usually work?		
For how many months in the last 12 months did you do this work?		

ACTIVITY LEVELS AT YOUR WORK

Now we would like you to take the total number of hours you worked per week in each job and divide them up according to your activity level.

Please complete EACH line

	Job 1			Job 2		
	No	Yes	Hours per week	No	Yes	Hours per week
Sitting — light work e.g. desk work, or driving a car or truck						
Sitting — moderate work e.g. working heavy levers or riding a mower or forklift truck						
Standing — light work e.g. lab technician work or working at a shop counter						
Standing — light/moderate work e.g. light welding or stocking shelves						
Standing — moderate work e.g. fast rate assembly line work or lifting up to 50 lbs every 5 minutes for a few seconds at a time						
Standing — moderate/heavy work e.g. masonry/painting or lifting more than 50 lbs every 5 minutes for a few seconds at a time						
Walking at work — carrying nothing heavier than a briefcase e.g. moving about a shop						
Walking — carrying something heavy						
Moving, pushing heavy objects objects weighing over 75lbs						

STAIR OR STEP CLIMBING AT WORK

Please put a tick (✓) on EACH line where appropriate

Number of times you climbed up a flight of stairs (10 steps) at work	AVERAGE OVER THE LAST 12 MONTHS					
	None	1 to 5 times a day	6 to 10 times a day	11 to 15 times a day	16 to 20 times a day	More than 20 times a day
Job 1						
Job 2						

Please put a tick (✓) on EACH line where appropriate

Number of times you climbed up a ladder at work	AVERAGE OVER THE LAST 12 MONTHS					
	None	1 to 5 times a day	6 to 10 times a day	11 to 15 times a day	16 to 20 times a day	More than 20 times a day
Job 1						
Job 2						

KNEELING AND SQUATTING AT WORK IN JOB 1

In an average working day in Job 1 did you

kneel for more than one hour in total? No ☐ Yes ☐ Don't know ☐

squat for more than one hour in total? No ☐ Yes ☐ Don't know ☐

get up from kneeling or squatting more than 30 times? No ☐ Yes ☐ Don't know ☐

KNEELING AND SQUATTING AT WORK IN JOB 2

In an average working day in Job 2 did you

kneel for more than one hour in total? No ☐ Yes ☐ Don't know ☐

squat for more than one hour in total? No ☐ Yes ☐ Don't know ☐

get up from kneeling or squatting more than 30 times? No ☐ Yes ☐ Don't know ☐

TRAVEL TO AND FROM WORK

JOB 1

Please complete EVERY line

Roughly how many miles was it from home to Job 1?	
How many times a week did you travel from home to Job 1?	

Please tick (✓) one box ONLY per line

How did you normally travel to Job 1?	Always	Usually	Occasionally	Never or rarely
By car				
By works or public transport				
By bicycle				
Walking				

JOB 2 *(if appropriate)*

Please complete EVERY line

Roughly how many miles was it from home to Job 2?	
How many times a week did you travel from home to Job 2?	

Please tick (✓) one box ONLY per line

How did you normally travel to Job 2?	Always	Usually	Occasionally	Never or rarely
By car				
By works or public transport				
By bicycle				
Walking				

Section C RECREATION

The following questions ask about how you spent your leisure time.

Please indicate how often you did each activity on average over the last 12 months.

For activities that are seasonal, e.g. cricket or mowing the lawn, please put the average frequency during the season when you did the activity.

Please indicate the average length of time that you spent doing the activity on each occasion.

EXAMPLE

If you had mowed the lawn every fortnight in the grass cutting season and took 1 hour and 10 minutes on each occasion.

If you went walking for pleasure for 40 minutes once a week.

You would complete the table below as follows:

Please give an answer for the AVERAGE TIME you spent on each activity and the NUMBER OF TIMES you did that activity in the past year.

	Number of times you did the activity in the last 12 months								Average time per episode	
	None	Less than once a month	Once a month	2 to 3 times a month	Once a week	2 to 3 times a week	4 to 5 times a week	Every day	Hours	Mins
Mowing the lawn				✓					*1*	*10*
Walking for pleasure					✓					*40*

Now please complete the table on pages 10 and 11

Please give an answer for the NUMBER OF TIMES you did the following activities in the last 12 months and the AVERAGE TIME you spent on each activity.

Please complete EACH line

	Number of times you did the activity in the last 12 months								Average time per episode	
	None	Less than once a month	Once a month	2 to 3 times a month	Once a week	2 to 3 times a week	4 to 5 times a week	6 times a week or more	Hours	Mins
Swimming — competitive										
Swimming — leisurely										
Backpacking or mountain climbing										
Walking for pleasure — you should not include walking as a means of transportation as this was included in Sections A & B										
Racing or rough terrain cycling										
Cycling for pleasure — you should not include cycling as a means of transportation										
Mowing the lawn — during the grass cutting season										
Watering the lawn or garden in the summer										
Digging, shovelling or chopping wood										
Weeding or pruning										
DIY e.g. carpentry, home or car maintenance										
High impact aerobics or step aerobics										
Other types of aerobics										
Exercises with weights										
Conditioning exercises e.g. using an exercise bike or rowing machine										

Please complete EACH line

	Number of times you did the activity in the last 12 months								Average time per episode	
	None	Less than once a month	Once a month	2 to 3 times a month	Once a week	2 to 3 times a week	4 to 5 times a week	6 times a week or more	Hours	Mins
Floor exercises e.g. stretching, bending, keep fit or yoga										
Dancing e.g. ballroom or disco										
Competitive running										
Jogging										
Bowling — indoor, lawn or 10 pin										
Tennis or badminton										
Squash										
Table tennis										
Golf										
Football, rugby or hockey (during the season)										
Cricket (during the season)										
Rowing										
Netball, volleyball or basketball										
Fishing										
Horse-riding										
Snooker, billiards or darts										
Musical instrument playing or singing										
Ice-skating										
Sailing, wind-surfing or boating										
Martial arts, boxing or wrestling										

Appendix 8: Healthy Eating Motivation Score

Healthy Eating Motivation Questionnaire

Page 1: Personal information

• Please enter the unique participant number you were assigned in the email: *Required*

• Please enter your date of birth: *Required*

Dates need to be in the format 'DD/MM/YYYY', for example 27/03/1980.

(dd/mm/yyyy)

3. What is your sex? *Required*

Page 2: Healthy Eating Motivation Questionnaire

4. Please respond to the following statements, where a score of 1 means you strongly disagree and a score of 7 means you strongly agree: *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 8 answer(s).

	1	2	3	4	5	6	7
It is important that the food I eat contains vitamins and minerals	☐	☐	☐	☐	☐	☐	☐
It is important that the food I eat keeps me healthy	☐	☐	☐	☐	☐	☐	☐
It is important that the food I eat is nutritious	☐	☐	☐	☐	☐	☐	☐
It is important that the food I eat is good for my appearance (skin/teeth/hair/nails etc.)	☐	☐	☐	☐	☐	☐	☐
I always follow a healthy and balanced diet	☐	☐	☐	☐	☐	☐	☐
I eat what I like and I do not worry about healthiness of food	☐	☐	☐	☐	☐	☐	☐
The healthiness of food has little impact on my food choices	☐	☐	☐	☐	☐	☐	☐
It is important that the food I eat helps me control my weight	☐	☐	☐	☐	☐	☐	☐

Page 3: Final page

You have finished!

Thank you for your time

Appendix 9: Personalised advice email: Study 2

Hello (Name)

You may remember back in September when you joined St Mary's that you agreed to take part in our research study looking at *'genetic risk of obesity and weight gain in university students'*.

In one week's time I will ask you to complete an online questionnaire to assess your healthy eating motivation, this will take less than two minutes to complete. I will then arrange a time at the end of the semester to measure your BMI, body fat percentage and WC for a second time.

Thank you once again for your time.

This email is divided into two parts:

> **Part A: Your results:** this section contains information about your results (your DNA, body mass index (BMI), body fat percentage and current physical activity)
>
> **Part B: Your advice:** this section provides information about what you can do to reduce your risk of weight gain. You have been provided with personalised dietary and physical activity advice based on your genotype to reduce your risk of obesity

Why all of this matters: Obesity is a risk factor for numerous chronic diseases including diabetes, cardiovascular disease and cancer. The risk of individuals to develop obesity is highly variable. Some of this variation may be explained by the interaction between an individual's DNA variation (genotype) and their diet and physical activity. You can reduce your risk of becoming obese by adhering to the diet and physical activity advice below.

Part A: Your results: The information below provides an overview of your genotype for the *FTO* gene (which is associated with obesity risk), your current BMI, body fat percentage and physical activity level.

Your results:

Your DNA (FTO Genotype)	**Your genotype:** **AT = Risk** **Approximately 47 percent of participants in this study have this genotype** **Risk advice:** "You have a genetic variation in the *FTO* gene that is associated with a higher risk of obesity; consequently, it is important for you to meet recommendations for physical activity and dietary intake of energy, saturated fat and sugar." • Research suggests that individuals with your genotype are more likely to become obese. • Obesity is linked to numerous chronic diseases such as cardiovascular disease, diabetes and cancer. • Individuals with your genotype that are more physically active are less likely to become obese. • Individuals with your genotype that eat less saturated fat are less likely to become obese.
Your BMI	**Recommendation:** It's recommended that your body mass index (BMI) should be between 18.5-25 kg/m^2. **Your BMI:** Your BMI was **24.3 kg/m^2**. You are currently **meeting the recommendation.**
Your body fat percentage	**Recommendation:** It's recommended that your body fat percentage should be below **31%**. **Your body fat percentage:** Your body fat percentage was **35.7**. You are currently **not meeting the recommendation.**
Your physical activity	**Recommendation:** It's recommended that you spend at least 75 minutes doing vigorous physical activity **or** 150 minutes doing moderate intensity physical activity **Your physical activity:** Based on your physical activity questionnaire you are currently **meeting the recommendation**. A dose-response relationship exists between physical activity and health benefits. Meeting the recommendation provides substantial benefit, and amounts of activity above this range have even more benefit.

Part B: Your advice: this section provides information about what you can do to reduce your risk of weight gain. You have been provided with personalised dietary and physical activity advice based on your genotype to reduce your risk of obesity

Risk advice: “You have a genetic variation in the *FTO* gene that is associated with a higher risk of obesity; consequently, it is important for you to meet recommendations for physical activity and dietary intake of energy, saturated fat and sugar.”

- Research suggests that individuals with your genotype are more likely to become obese.
- Obesity is linked to numerous chronic diseases such as cardiovascular disease, diabetes and cancer.
- Individuals with your genotype that are more physically active are less likely to become obese.
- Individuals with your genotype that eat less saturated fat are less likely to become obese.

These practical tips cover the basics of physical activity and healthy eating to help you make healthier choices.

- The key to a healthy diet is to eat the right amount of calories for how active you are so you balance the energy you consume with the energy you use.
- If you eat or drink more than your body needs, you'll put on weight because the energy you do not use is stored as fat. If you eat and drink too little, you'll lose weight.
- You should also eat a wide range of foods to make sure you're getting a balanced diet and your body is receiving all the nutrients it needs.
- Most adults in the UK are eating more calories than they need and should eat fewer calories.

1. Physical Activity Advice:

Get active and be a healthy weight

As well as eating healthily, regular exercise may help reduce your risk of getting serious health conditions. It's also important for your overall health and wellbeing.

- Being overweight or obese can lead to health conditions, such as type 2 diabetes, certain cancers, heart disease and stroke. Being underweight could also affect your health.
- Most adults need to lose weight by eating fewer calories.
- If you're trying to lose weight, aim to eat less and be more active. Eating a healthy, balanced diet can help you maintain a healthy weight.
- Start the NHS weight loss plan, a 12-week weight loss guide that combines advice on healthier eating and physical activity.
- If you're worried about your weight, ask your GP or a dietitian for advice.

Physical activity recommendations:

2. Dietary Advice:

Base your meals on higher fibre starchy carbohydrates

- Starchy carbohydrates should make up just over a third of the food you eat. They include potatoes, bread, rice, pasta and cereals.
- Choose higher fibre or wholegrain varieties, such as wholewheat pasta, brown rice or potatoes with their skins on.
- They contain more fibre than white or refined starchy carbohydrates and can help you feel full for longer.
- Try to include at least 1 starchy food with each main meal. Some people think starchy foods are fattening, but gram for gram the carbohydrate they contain provides fewer than half the calories of fat.
- Keep an eye on the fats you add when you're cooking or serving these types of foods because that's what increases the calorie content – for example, oil on chips, butter on bread and creamy sauces on pasta.

Eat lots of fruit and veg

- It's recommended that you eat at least 5 portions of a variety of fruit and veg every day. They can be fresh, frozen, canned, dried or juiced.
- Getting your 5 A Day is easier than it sounds. Why not chop a banana over your breakfast cereal, or swap your usual mid-morning snack for a piece of fresh fruit?
- A portion of fresh, canned or frozen fruit and vegetables is 80g. A portion of dried fruit (which should be kept to mealtimes) is 30g.
- 150ml glass of fruit juice, vegetable juice or smoothie also counts as 1 portion, but limit the amount you have to no more than 1 glass a day as these drinks are sugary and can damage your teeth.

Eat more fish, including a portion of oily fish

- Fish is a good source of protein and contains many vitamins and minerals.
- Aim to eat at least 2 portions of fish a week, including at least 1 portion of oily fish.
- Oily fish are high in omega-3 fats, which may help prevent heart disease.
- You can choose from fresh, frozen and canned, but remember that canned and smoked fish can be high in salt.

<u>Oily fish include:</u>

- salmon
- trout
- herring
- sardines
- pilchards
- mackerel

<u>Non-oily fish include:</u>

- haddock
- plaice
- coley
- cod
- tuna
- skate
- hake

Cut down on saturated fat and sugar: Saturated fat

- You need some fat in your diet, but it's important to pay attention to the amount and type of fat you're eating.
- There are 2 main types of fat: saturated and unsaturated. Too much saturated fat can increase the amount of cholesterol in the blood, which increases your risk of developing heart disease.
- On average, men should have no more than 30g of saturated fat a day. On average, women should have no more than 20g of saturated fat a day.
- Try to cut down on your saturated fat intake and choose foods that contain unsaturated fats instead, such as vegetable oils and spreads, oily fish and avocados.
- For a healthier choice, use a small amount of vegetable or olive oil, or reduced-fat spread instead of butter, lard or ghee.
- When you're having meat, choose lean cuts and cut off any visible fat.
- All types of fat are high in energy, so they should only be eaten in small amounts.

<u>Saturated fat is found in many foods, such as:</u>

- fatty cuts of meat
- sausages
- butter
- hard cheese
- cream
- cakes
- biscuits
- lard
- pies

Sugar

- Regularly consuming foods and drinks high in sugar increases your risk of obesity and tooth decay.
- Sugary foods and drinks are often high in energy (measured in kilojoules or calories), and if consumed too often can contribute to weight gain. They can also cause tooth decay, especially if eaten between meals.
- Free sugars are any sugars added to foods or drinks, or found naturally in honey, syrups and unsweetened fruit juices and smoothies.
- This is the type of sugar you should be cutting down on, rather than the sugar found in fruit and milk.
- Many packaged foods and drinks contain surprisingly high amounts of free sugars.
- Food labels can help. Use them to check how much sugar foods contain.
- More than 22.5g of total sugars per 100g means the food is high in sugar, while 5g of total sugars or less per 100g means the food is low in sugar.

<u>Free sugars are found in many foods, such as:</u>

- sugary fizzy drinks
- sugary breakfast cereals
- cakes
- biscuits
- pastries and puddings
- sweets and chocolate
- alcoholic drinks

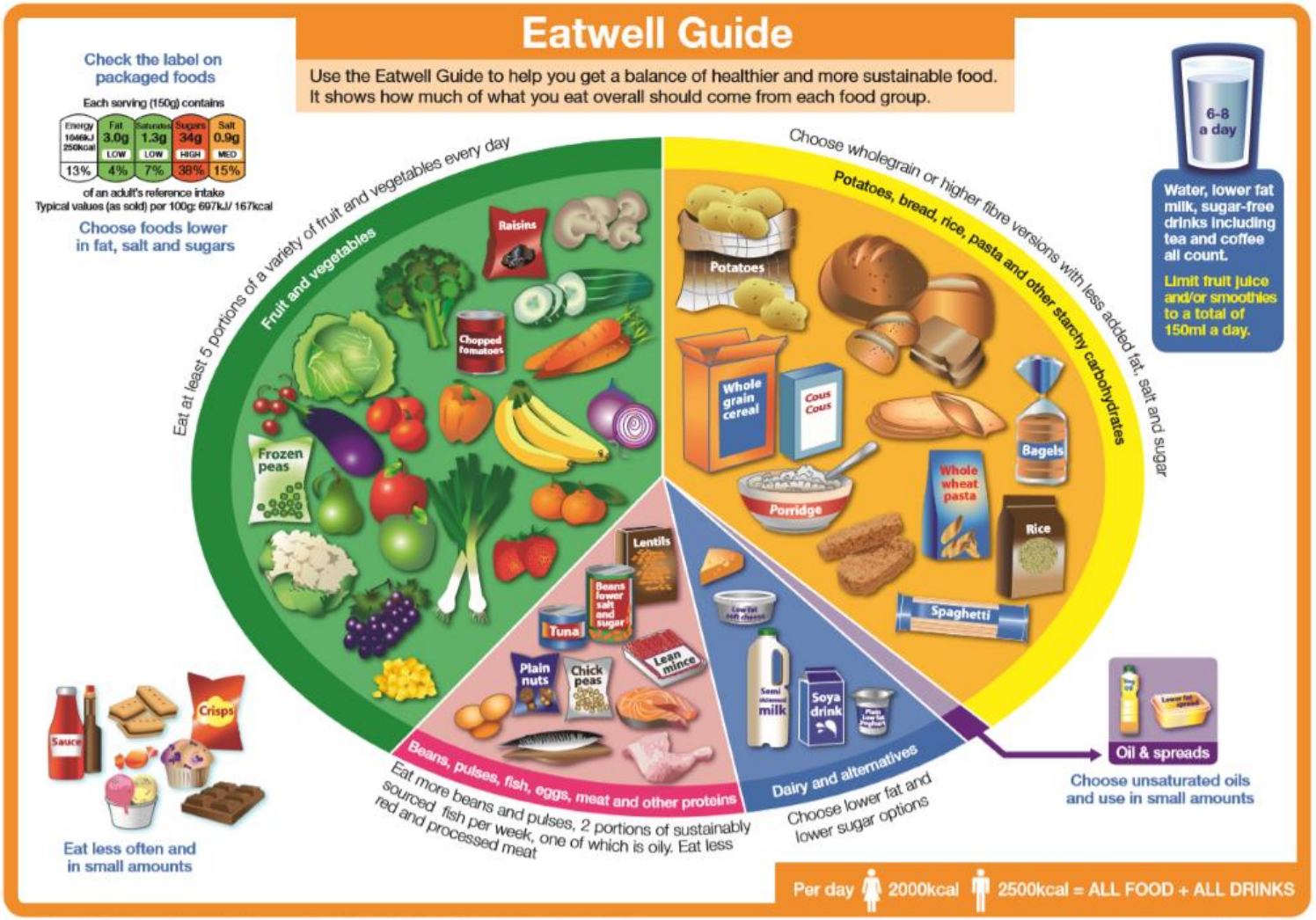
Do not get thirsty

- You need to drink plenty of fluids to stop you getting dehydrated. The government recommends drinking 6 to 8 glasses every day. This is in addition to the fluid you get from the food you eat.
- All non-alcoholic drinks count, but water, lower fat milk and lower sugar drinks, including tea and coffee, are healthier choices.
- Try to avoid sugary soft and fizzy drinks, as they're high in calories. They're also bad for your teeth.
- Even unsweetened fruit juice and smoothies are high in free sugar.
- Your combined total of drinks from fruit juice, vegetable juice and smoothies should not be more than 150ml a day, which is a small glass.
- Remember to drink more fluids during hot weather or while exercising.

Do not skip breakfast

- Some people skip breakfast because they think it'll help them lose weight.
- But a healthy breakfast high in fibre and low in fat, sugar and salt can form part of a balanced diet, and can help you get the nutrients you need for good health.
- A wholegrain lower sugar cereal with semi-skimmed milk and fruit sliced over the top is a tasty and healthier breakfast.

Dietary intake recommendations:



Appendix 10: PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplemental information
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9-10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 11

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 11-12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 11-12
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 10, 12
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 16-17
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 9-10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 12
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 12 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 13
Study characteristics	17	Cite each included study and present its characteristics.	Page 13-14 Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 14 -15 Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 3-6 Tables 3-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Tables 3-4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 16-18 Figures 3-6 Tables 3-4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 16-17
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 14-15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 15-16 Tables 3-4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 18, 20-

Section and Topic	Item #	Checklist item	Location where item is reported
			21
	23b	Discuss any limitations of the evidence included in the review.	Page 19-20
	23c	Discuss any limitations of the review processes used.	Page 25-26
	23d	Discuss implications of the results for practice, policy, and future research.	Page 21-26
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	page 27
Competing interests	26	Declare any competing interests of review authors.	Page 27
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Appendix 11: Search strategies

Figure S2. Full search strategies for all databases

Searches	Search terms	PubMed
1	exp genetic services/	56700
2	exp Genetic predisposition to disease/	140019
3	(gene* AND (test* OR assess* OR risk* OR susceptib* OR predispos* OR disease*)): ab,ti	2190331
4	'dna-based test' OR (personalised AND medicine) OR (personalised AND nutrition) OR (nutritional AND genomic*) OR nutrigenetic* OR nutrigenomic*:ab,ti	21115
5	'direct-to-consumer genetic testing'	753
6	('personal genome' AND test*): ab,ti	167
7	Or/1-6	2267847
8	Exp risk reduction behavior/	13087
9	Exp health behavior/	324277
10	Exp patient compliance/	77595
11	(adher* OR motivation OR interest OR facilitate OR 'health decision' OR 'risk reduction behavior'):ab,ti	931602
12	Or/8-11	1214648
13	Exp obesity/	217043
14	('body weight' OR 'body mass index' OR bmi OR overweight):ab,ti	476716
15	weight AND (gain OR loss OR change):,ab,ti	230056
16	Or/13-15	725066
17	Exp Diabetes mellitus, type 2/	135792
18	('type 2 diabetes' OR 'type two diabetes' OR 'type 2 diabetes mellitus' OR 'type two diabetes mellitus' OR T2D OR niddm) ab,ti	138897
19	Or/17-18	188155
20	Exp cardiovascular diseases	2413283
21	(cvd OR 'heart disease' OR 'coronary artery disease' OR hypercholesterol* OR hyperlipid* OR lipoprotein OR atherosclerosis) ab,ti	507552
22	Or/20-21	2617638
23	22 or 19 or 16	3322903
24	23 and 12 and 7	18575

25	randomized controlled trial.pt.	518659
26	controlled clinical trial.pt.	607740
27	randomized OR randomised (ti.ab)	645742
28	placebo.ab.	218693
29	randomly.ab.	345876
30	trial.ab.	623252
31	groups.ab.	2147829
32	Intervention ti.ab	617,121
33	Or/25-32	3554676
34	exp animals/ not humans.sh.	4758958
35	33 not 34	3084947
36	24 and 35	5999

Searches	**Search terms**	**PsycInfo**
1	genetic services.ab,id,ti.	187
2	"Genetic prediction*".ab,id,ti.	26
3	(gene* AND (test* OR assess* OR risk* OR susceptib* OR predispos* OR disease*)).ab,id,ti	378354
4	'dna-based test' OR (personalised AND medicine) OR (personalised AND nutrition) OR (personalized AND medicine) OR (personalized AND nutrition) OR (nutritional AND genomic*) OR nutrigenetic* OR nutrigenomic*ab,id,ti	1372
5	‘direct-to-consumer genetic testing’	1437
6	('personal genome' and test*).ab,id,ti.	7
7	1 or 2 or 3 or 4 or 5 or 6	379528
8	Risk Taking/	12747
9	health behavior.ab,hw,id,ti.	31593
10	exp Compliance/	19967
11	(adher* OR motivation OR interest OR facilitate OR 'health decision' OR 'risk reduction behavior').ab,id,ti	343765
12	8 or 9 or 10 or 11	391550

13	exp obesity/	24957
14	('body weight' OR 'body mass index' OR bmi OR overweight):ab,id,ti	49793
15	weight and (gain or loss or change)).ab,id,ti	28596
16	13 OR 14 OR 15	74997
17	exp Type 2 Diabetes/	4666
18	('type 2 diabetes' OR 'type two diabetes' OR 'type 2 diabetes mellitus' OR 'type two diabetes mellitus' OR T2D OR niddm). ab,id,ti	7345
19	17 OR 18	8547
20	exp Cardiovascular Disorders/	62985
21	(cvd or 'heart disease' or 'coronary artery disease' or hypercholesterol* or hyperlipid* or lipoprotein or atherosclerosis).ab,id,ti.	20074
22	20 OR 21	72059
23	16 or 19 or 22	147857
24	7 AND 12 AND 23	2206
25	“random*".ab,hw,id,ti.	206563
26	"trial*".ab,hw,id,ti.	187931
27	placebo*.ab,hw,id,ti.	41102
28	((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ab,hw,id,ti	29702
29	(cross over or crossover or factorial* or latin square).ab,hw,id,ti	31250
30	(assign* or allocat* or volunteer*) .ab,hw,id,ti	168492
31	Treatment Effectiveness Evaluation/	25051
32	Mental Health Program Evaluation/	2148
33	exp Experimental Design/	58464
34	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	527461
35	(animal not (human and animal)).po.	364303
36	34 NOT 35	493002
37	36 AND 24	502

Searches	Search terms	Embase
1	exp genetic service/	115527
2	exp genetic susceptibility/	106565
3	(gene* adj (test* or assess* or risk* or susceptib* or predispos* or disease*)).ab,ti.	144357
4	DNA based test.ab,ti.	106
5	(personalised adj medicine).ab,ti.	1875
6	(personalized adj nutrition).ab,ti.	14917
7	(personalised adj nutrition).ab,ti.	175
8	(personalized adj medicine).ab,ti.	431
9	(nutritional adj genomic*).ab,ti.	187
10	nutrigenetic*.ab,ti.	468
11	nutrigenomic*.ab,ti.	1107
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	18685
13	'direct-to-consumer genetic testing'.af	391
14	(personal genome adj test*).ab,ti.	40
15	1 or 2 or 3 or 12 or 13 or 14	327197
16	exp behavior change/	37520
17	exp health behavior/	421966
18	exp patient compliance/	161929
19	(adher* OR motivation OR interest OR facilitate OR 'health decision' OR 'risk reduction behavior').ab,ti.	1226214
20	16 or 17 or 18 or 19	176529
21	exp obesity/	532321
22	('body weight' OR 'body mass index' OR bmi OR overweight).ab,ti.	746711
23	weight adj (gain OR loss OR change).ab,ti.	227417
24	21 or 22 or 23	116643
25	Exp non insulin dependent diabetes mellitus	263094
26	('type 2 diabetes' OR 'type two diabetes' OR 'type 2 diabetes mellitus' OR 'type two diabetes mellitus' OR T2D OR niddm).ab,ti.	207434

27	25 or 26	303262
28	exp cardiovascular disease	4143683
29	(cvd OR 'heart disease' OR 'coronary artery disease' OR hypercholesterol* OR hyperlipid* OR lipoprotein OR atherosclerosis).ab,ti.	684746
30	28 or 29	4301919
31	24 or 27 or 30	5238739
32	15 and 20 and 31	4142
33	exp randomized controlled trial	633610
34	exp controlled clinical trial	821482
35	randomized OR randomised.ab,ti.	930001
36	Placebo.ab	307206
37	Randomly.ab	46043
38	Trial.ab	772465
39	Groups.ab	2964590
40	intervention.ab,ti.	921773
41	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	4926428
42	(animal NOT human).sh	1091754
43	41 NOT 42	4796531
44	32 and 43	965

Searches	**Search terms**	**CENTRAL**
1	(genetic next service*):kw in Clinical Trials	8
2	"genetic predisposition":kw in Clinical Trials	1068
3	((gene or genes or genetic* or genotype*) NEAR/3 (test* or assess* or risk* or susceptib* or predispos* or disease* or screen*)):ti,ab in Clinical Trials	4208
4	('dna-based test' OR (personalised AND medicine) OR (personalised AND nutrition) OR (personalized AND medicine) OR (personalized AND nutrition) (nutritional AND genomic*) OR (nutrigenetic* OR nutrigenomic*)):ti,ab in Clinical Trials	121
5	‘direct-to-consumer genetic testing’	14

6	(‘personal genome’ AND test*):ti,ab in Clinical Trials	20
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	5014
8	“behavior change” kw in Clinical Trials	2018
9	("health behavior" or "health behaviour"):kw in Clinical Trials	3506
10	"patient compliance":kw in Clinical Trials	14911
11	(adher* OR motivation OR interest OR facilitate OR 'health decision' OR 'risk reduction behavior'):ti,ab in Clinical Trials	60336
12	Or/8-11	74642
13	“obesity”:kw in Clinical Trials	19883
14	('body weight' OR 'body mass index' OR bmi OR overweight):ti,ab in Clinical Trials	61532
15	weight AND (gain OR loss OR change):ti,ab in Clinical Trials	33476
16	Or/13-15	81691
17	"Diabetes mellitus, type 2":kw in Clinical Trials	14634
18	('type 2 diabetes' OR 'type two diabetes' OR 'type 2 diabetes mellitus' OR 'type two diabetes mellitus' OR T2D OR niddm):ti,ab in Clinical Trials	30683
19	Or/17-18	33484
20	“cardiovascular diseases”:kw in Clinical Trials	6312
21	(cvd OR 'heart disease' OR 'coronary artery disease' OR hypercholesterol* OR hyperlipid* OR lipoprotein OR atherosclerosis):ti,ab in Clinical Trials	48689
22	Or/20-21	52132
23	22 or 19 or 16	143719
24	23 and 12 and 7	175

Appendix 12: Information sheet: Study 4

Appendix A: Participant Information

Section A: The Research Project

Project Title: Investigation of factors that influence young adults intention to adopt gene-based personalised advice for diet and physical activity.

On the one hand, the nutrients we consume can affect the way our genes are expressed; on the other, our genes are able to influence how our bodies respond to these nutrients. Personalised nutrition is looking at the complex interaction between nutrients and genes to create tailored diets which complement a person's unique genetic profile. Not only will personalised nutrition optimise the health of the individual, but it may also work on a larger scale to help prevent society-wide diseases such as obesity, Type 2 diabetes, cardiovascular disease, cancer, and malnutrition.

Gene-based personalised advice is healthy eating and physical activity advice that is tailored to suit an individual based on their own personal health status, lifestyle and genetics. There are a number of benefits to personalised advice based on genetics compared to general health advice. The advice provided is more precise and effective for you as an individual, risk of diet and physical activity related diseases can be communicated at a younger age to encourage behaviour change and prevent subsequent health problems.

The aim of this survey is to understand factors that influence intention to adopt gene-based personalised nutrition in a young population. This may enable a greater understanding of how gene-based advice can be utilised as a preventative public health tool in young adults.

You are invited to take part in an online survey to investigate the factors that influence the attitude and intention of young adults to utilise gene-based personalised advice for diet and physical activity. The survey is organised by Alexandra King as part of her PhD under the supervision of Dr Yiannis Mavrommatis and Dr Leta Pilic. The results of the study will be analysed and presented as part of a PhD and may also be published in a peer reviewed academic journal or presented at an academic conference. The research is funded by St Mary's University.

For further information please contact Alexandra King (alexandra.king@stmarys.ac.uk).

Supervisors contact details: Yiannis Mavrommatis (yiannis.mavrommatis@stmarys.ac.uk)

Leta Pilic (leta.pilic@stmarys.ac.uk)

Section B: Your Participation in the Research Project

You have been invited to take part in the study because you are a young adult (18 -25 years of age), are not pregnant, lactating, following a restricted diet or have a diagnosed eating disorder. You are under no obligation to take part in the survey.

The survey will take approximately 20 minutes to complete, you will be asked questions about your attitude and intention to adopt gene-based advice for your diet and physical activity. To understand factors that influence your attitude and intention you will also be asked questions about your perception of your health, food choice, body weight, physical activity and characteristics. You will not be asked to provide your name or date of birth so your survey response will be anonymous. This means once you have completed the survey your response will not be identifiable or able to be withdrawn. If you would like a copy of this information or the findings of the survey, please email Alexandra King (alexandra.king@stmarys.ac.uk).

If you would like to be entered into a draw to win a £50 voucher of your choice, please provide your email address at the end of the survey.

Appendix 13: Pilot survey

St Mary's University Twickenham London

Pilot Survey

Page 1: Page 1

Hello,

Thank you for your interest in taking part in our survey, before you agree to take part please read the information provided on the next page and then check the consent form.

If you would like to be entered into a draw to win a £50 voucher of your choice please provide your email address at the end of the survey.

Thank you for your time.

Page 2: Information about the survey

Section A: The Research Project

Project Title: Investigation of factors that influence young adults intention to adopt gene-based personalised advice for diet and physical activity.

On the one hand, the nutrients we consume can affect the way our genes are expressed; on the other, our genes are able to influence how our bodies respond to these nutrients. Personalised nutrition is looking at the complex interaction between nutrients and genes to create tailored diets which complement a person's unique genetic profile. Not only will personalised nutrition optimise the health of the individual, but it may also work on a larger scale to help prevent society-wide diseases such as obesity, Type 2 diabetes, cardiovascular disease, cancer, and malnutrition.

Gene-based personalised advice is healthy eating and physical activity advice that is tailored to suit an individual based on their own personal health status, lifestyle and genetics. There are a number of benefits to personalised advice based on genetics compared to general health advice. The advice provided may be more precise and effective for you as an individual, risk of diet and physical activity related diseases may be communicated at a younger age to encourage behaviour change and prevent subsequent health problems.

The aim of this survey is to understand factors that influence intention to adopt gene-based personalised nutrition in a young population. This may enable a greater understanding of how gene-based advice can be utilised as a preventative public health tool in young adults.

You are invited to take part in an online survey to investigate the factors that influence the attitude and intention of young adults to utilise gene-based personalised advice for diet and physical activity. The survey is organised by Alexandra King as part of her PhD under the supervision of Dr Yiannis Mavrommatis and Dr Leta Pilic. The results of the study will be analysed and presented as part of a PhD and may also be published in a peer reviewed academic journal or presented at an academic conference. The research is funded by St Mary's University.

For further information please contact Alexandra King (alexandra.king@stmarys.ac.uk).

Supervisors contact details: Yiannis Mavrommatis (yiannis.mavrommatis@stmarys.ac.uk)

Leta Pilic (leta.pilic@stmarys.ac.uk)

Section B: Your Participation in the Research Project

You have been invited to take part in the study because you are a young adult (18 -25 years of age), are not pregnant, lactating, following a restricted diet or have a diagnosed eating disorder. You are under no obligation to take part in the survey.

The survey will take approximately 20 minutes to complete, you will be asked questions about your attitude and intention to adopt gene-based advice for your diet and physical activity. To understand factors that influence your attitude and intention you will also be asked questions about your perception of your health, food choice, body weight, physical activity and characteristics. You will not be asked to provide your name or date of birth so your survey response will be anonymous. This means once you have completed the survey your response will not be identifiable or able to be withdrawn. If you would like a copy of this information or the findings of the survey, please email Alexandra King (alexandra.king@stmarys.ac.uk).

Page 3: Consent

Project Title: Investigation of factors that influence young adults intention to adopt gene-based personalised advice for diet and physical activity.

Main investigator and contact details: Alexandra King alexandra.king@stmarys.ac.uk

Members of the research team:

Yiannis Mavrommatis yiannis.mavrommatis@stmarys.ac.uk

Leta Pilic leta.pilic@stmarys.ac.uk

- I agree to take part in the above research. I have read the Participant Information section. I understand what my role will be in this research, and all my questions have been answered to my satisfaction.
- I understand that I am free to withdraw from the research at any time before completion of the survey, for any reason and without prejudice. After which I understand my response will not be able to be identified and therefore withdrawn.
- I have been informed that the confidentiality of the information I provide will be safeguarded.
- I am free to ask any questions at any time by emailing the main investigator.
- I am 18 -25 years of age, not pregnant, lactating, following a restricted diet or have a diagnosed eating disorder

Data Protection: I agree to the University processing personal data which I have supplied. I agree to the processing of such data for any purposes connected with the Research Project as outlined to me.

1. Please read the statement below and check if you agree: *Required*

I agree with all statements above and provide my informed consent to take part in the study.

Page 4: Introduction

Hello,

Thank you for agreeing to take part in the development of our survey. We greatly appreciate your willingness to participate in a preliminary assessment of this survey. After you have finished filling out the questionnaire, we will ask you to provide feedback on your understanding of the individual items in the survey. We would like to thank you in advance for this assistance.

The survey will ask a series of questions about your attitude towards and intention to adopt gene-based personalised diet and physical activity advice.

Before you start we would like to provide a definition of gene-based personalised diet and physical activity advice:

“healthy eating and physical activity advice that is tailored to suit an individual based on their own personal health status, lifestyle and genetics’’

As described in the information section: There are a number of benefits to personalised advice based on genetics compared to general health advice. The advice provided may be more precise and effective for you as an individual, risk of diet and physical activity related diseases may be communicated at a younger age to encourage behaviour change and prevent subsequent health problems.

In this survey we are interested in your opinions, there are no right or wrong answers. All answers are anonymous.

There is no option to save the survey so please make sure you complete all questions in one go, it should take about 20 minutes to complete.

Thanks again!

Page 5: Section 1: About You

5. What gender do you identify as? *Required*

- [ ] Male
- [ ] Female
- [ ] Other
- [ ] Prefer not to say

3. Please state your age in years *Required*

4. Please specify your ethnicity *Required*

- ( ) Asian or Asian British
- ( ) Black, Black British, Caribbean or African
- ( ) Mixed or multiple ethnic groups
- ( ) White
- ( ) Other ethnic group

5. Where is your home located? *Required*

- ( ) England
- ( ) Wales
- ( ) Scotland
- ( ) Northern Ireland

6. What is the highest degree or level of education you have completed? *Required*

- ( ) Secondary School (GCSE or equivalent)
- ( ) Further Education (A Level or equivalent)
- ( ) Bachelor's Degree
- ( ) Master's Degree
- ( ) Ph.D. or higher
- ( ) Prefer not to say

7. How healthy do you consider yourself? *Required*

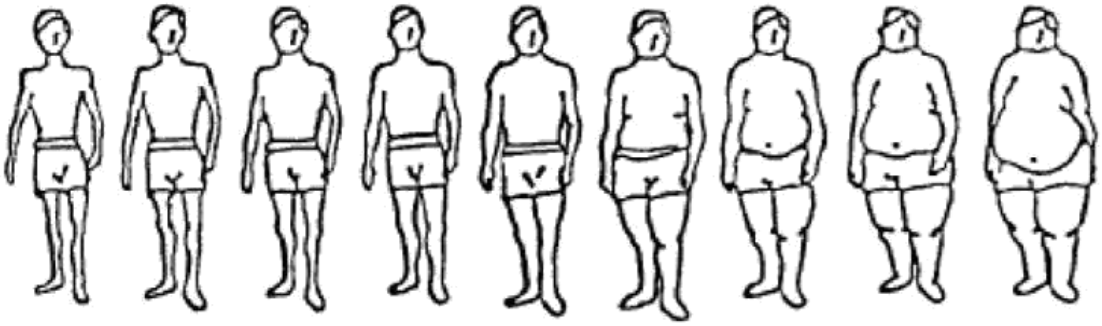
- Very unhealthy
- Unhealthy
- Moderately unhealthy
- Healthy
- Very Healthy

8. 'In the past week, on how many days have you done a total of 30 min or more of physical activity, which was enough to raise your breathing rate? This may include sport, exercise, and brisk walking or cycling for recreation or to get to and from places, but should not include housework or physical activity that may be part of your job.' *Required*

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7

9.

MALE Body Types



01 ☐ 02 ☐ 03 ☐ 04 ☐ 05 ☐ 06 ☐ 07 ☐ 08 ☐ 09 ☐

FEMALE Body Types

10 ☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18 ☐

Please select the figure that you believe most closely resembles your body image: *Required*

○ 1	2	○	3 ○
○ 4	5	○	6 ○
○ 7	8	○	9 ○
○ 10	11	○	12 ○
○ 13	14	○	15 ○
○ 16	17	○	18 ○

Page 6: Section 2: Your health

10. Please indicate the extent to which you agree or disagree with the following statements: *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 6 answer(s).

	Completely disagree	Disagree	Neither disagree/nor agree	Agree	Completely agree
I can be as healthy as I want to be	☐	☐	☐	☐	☐
I am in control of my health	☐	☐	☐	☐	☐
I can pretty much stay healthy by taking care of myself	☐	☐	☐	☐	☐
Efforts to improve your health are a waste of time	☐	☐	☐	☐	☐
I am bored by all the attention that is paid to health and disease prevention	☐	☐	☐	☐	☐
What's the use of concerning yourself about your health you'll only worry yourself to death	☐	☐	☐	☐	☐

11. Please give your position on the following statements. It is important to me that the food I eat on a typical day: *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 36 answer(s).

	Not at all important	A little important	Moderately Important	Very Important	Extremely important
Contains a lot of vitamins and minerals	☐	☐	☐	☐	☐
Keeps me healthy	☐	☐	☐	☐	☐
Is nutritious	☐	☐	☐	☐	☐
Is high in protein	☐	☐	☐	☐	☐
Is good for my skin/teeth/hair/nails etc.	☐	☐	☐	☐	☐
Is high in fibre and roughage	☐	☐	☐	☐	☐
Helps me cope with stress	☐	☐	☐	☐	☐
Helps me to cope with life	☐	☐	☐	☐	☐

Helps me relax	☐	☐	☐	☐	☐
Keeps me awake/alert	☐	☐	☐	☐	☐
Cheers me up	☐	☐	☐	☐	☐
Makes me feel good	☐	☐	☐	☐	☐
Is easy to prepare	☐	☐	☐	☐	☐
Can be cooked very simply	☐	☐	☐	☐	☐
Takes no time to prepare	☐	☐	☐	☐	☐
Can be bought in shops close to where I live or work	☐	☐	☐	☐	☐
Is easily available in shops and supermarkets	☐	☐	☐	☐	☐
Smells nice	☐	☐	☐	☐	☐
Looks nice	☐	☐	☐	☐	☐
Has a pleasant texture	☐	☐	☐	☐	☐
Tastes good	☐	☐	☐	☐	☐
Contains no additives	☐	☐	☐	☐	☐
Contains natural ingredients	☐	☐	☐	☐	☐
Contains no artificial ingredients	☐	☐	☐	☐	☐
Is not expensive	☐	☐	☐	☐	☐
Is cheap	☐	☐	☐	☐	☐
Is good value for money	☐	☐	☐	☐	☐
Is low in calories	☐	☐	☐	☐	☐
Helps me control my weight	☐	☐	☐	☐	☐
Is low in fat	☐	☐	☐	☐	☐
Is what I normally eat	☐	☐	☐	☐	☐
Is well-known	☐	☐	☐	☐	☐
Is like the food I ate when I was a child	☐	☐	☐	☐	☐
Comes from countries I approve of politically	☐	☐	☐	☐	☐
Has the country of origin clearly marked	☐	☐	☐	☐	☐
Is packaged in an environmentally friendly way	☐	☐	☐	☐	☐

Page 7: Section 3: Gene-based personalised advice

12. Please give your position on the following statements. *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 5 answer(s).

	Agree	Neither disagree/nor agree	Disagree
I only want gene-based personalised advice about predisposition of curable diseases.	☐	☐	☐
I only want gene-based personalised advice about a disease if I can prevent this disease.	☐	☐	☐
Concerning genetic advice, I want gene-based personalised advice about my risk of developing cardiovascular disease.	☐	☐	☐
Concerning genetic advice, I want gene-based personalised advice about my risk of developing type II diabetes.	☐	☐	☐
Concerning genetic advice, I want gene-based personalised advice about my risk of developing obesity.	☐	☐	☐

13. Please indicate the extent to which the following potential outcomes would increase the likelihood of you adopting gene-based personalised nutrition or physical activity advice: *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 10 answer(s).

	Not increase it at all	Increase it slightly	Increase it moderately	Increase it strongly	Increase it extremely
Knowing what foods are best for me	☐	☐	☐	☐	☐
Losing weight	☐	☐	☐	☐	☐
Gaining weight	☐	☐	☐	☐	☐
Fitness	☐	☐	☐	☐	☐
Improving my family's health	☐	☐	☐	☐	☐
Improving my health	☐	☐	☐	☐	☐
Improving my quality of life	☐	☐	☐	☐	☐
Improving my sports performance	☐	☐	☐	☐	☐
Preventing a future illness	☐	☐	☐	☐	☐
Preventing the expression of a hereditary illness	☐	☐	☐	☐	☐

13.a. Other, please specify:

The following questions use a rating scale with 7 places; please select the number that best describes your opinion. For example, if you were asked to rate 'the weather in London' on such a scale, the 7 places would be interpreted as follows:

Example: The weather in London is:

good	1	2	3	4	5	6	7	**bad**
	extremely	quite	slightly	neither	slightly	quite	extremely	

If you think the weather in London is extremely good, then you would select number 1.

If you think the weather in London is quite bad, then you would choose number 6.

14. My adoption of gene-based advice to modify dietary or physical activity behaviour would be *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
good								bad

15. Most people who are important to me would approve of my adoption of gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

16. My adoption of gene-based advice to modify dietary or physical activity behaviour would be

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unpleasant								pleasant

17. I would consider adopting gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
agree								disagree

18. Most people like me would adopt of gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
likely								unlikely

19. My adoption of gene-based advice to modify dietary or physical activity behaviour would be

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
worthless								valuable

20. I am definitely going to adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
agree								disagree

21. For me to adopt gene-based advice to modify dietary or physical activity behaviour would be

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
easy								difficult

22. My friends would approve of my adoption of gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

23. My adoption of gene-based advice to modify dietary or physical activity behaviour would be

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
interesting								boring

24. My friends would adopt of gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

25. I am confident that I can adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
true								false

26. My adoption of gene-based advice to modify dietary or physical activity behaviour is up to me

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

27. I intend to adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
agree								disagree

28. For me to adopt gene-based advice to modify dietary or physical activity behaviour is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
impossible								possible

Please take a few minutes to tell us what you think about the possibility of adopting gene-based advice to modify dietary or physical activity behaviour. There are no right or wrong responses; we are merely interested in your personal opinion. In response to the questions below, please list the thoughts that come immediately to mind.

29. What do you see as the advantages of adopting gene-based advice to modify dietary or physical activity behaviour? *Required*

30. What do you see as the disadvantages of adopting gene-based advice to modify dietary or physical activity behaviour? *Required*

31. What positive feelings do you associate with adopting gene-based advice to modify dietary or physical activity behaviour? *Required*

32. What negative feelings do you associate with adopting gene-based advice to modify dietary or physical activity behaviour? *Required*

When it comes to you adopting gene-based advice to modify dietary or physical activity behaviour, there might be individuals or groups who would think you should or should not perform this behaviour.

33. Please list the individuals or groups who would approve or think you should adopt gene-based advice to modify dietary or physical activity behaviour? *Required*

34. Please list the individuals or groups who would disapprove or think you should not adopt gene-based advice to modify dietary or physical activity behaviour? *Required*

35. Sometimes when we are not sure what to do, we look to see what others are doing. Please list the individuals or groups who are most likely to adopt gene-based advice to modify dietary or physical activity behaviour. *Required*

36. Please list the individuals or groups who are least likely to adopt gene-based advice to modify dietary or physical activity behaviour. *Required*

37. Please list any factors or circumstances that would make it easy or enable you to adopt gene-based advice to modify dietary or physical activity behaviour. *Required*

38. Please list any factors or circumstances that would make it difficult or prevent you from adopting gene-based advice to modify dietary or physical activity behaviour. *Required*

Page 8: Section 4: Feedback

We are very interested in your opinion of our survey. The following questions are to gain your feedback on completing the survey:

39. How long did it take you to complete the survey?

40. Did you understand the definition of gene-based personalised nutrition? *Required*

41. Were the instructions for each section clear? *Required*

42. Where there any questions that you found difficult to answer? If so which? *Required*

43. Were you happy with the order in which questions were asked? *Required*

44. Do you have any other comments? *Required*

45. Please provide your date of birth: *Required*

Dates need to be in the format 'DD/MM/YYYY', for example 27/03/1980.

(dd/mm/yyyy)

46. If you would like to be entered into a draw to win a £50 voucher of your choice please provide your email address.

Page 9: Thank you!

If you would like to receive the overall findings from this research please send an email to Alexandra King: alexandra.king@stmarys.ac.uk

Thank you very much for your time.

Appendix 14: Final survey

Personalised advice survey

Page 1: Page 1

Hello,

Thank you for your interest in taking part in our survey, before you agree to take part please read the information provided on the next page and then check the consent form.

If you would like to be entered into a draw to win a £50 voucher of your choice please provide your email address at the end of the survey.

Thank you for your time.

PS. This survey contains a completion code for SurveySwap.io

Page 2: Information about the survey

Section A: The Research Project

Project Title: Investigation of factors that influence young adults intention to adopt gene-based personalised diet and physical activity advice.

On the one hand, the nutrients we consume can affect the way our genes are expressed; on the other, our genes are able to influence how our bodies respond to these nutrients. Personalised nutrition is looking at the complex interaction between nutrients and genes to create tailored diets which complement a person's unique genetic profile. Not only will personalised nutrition optimise the health of the individual, but it may also work on a larger scale to help prevent society-wide diseases such as obesity, Type 2 diabetes, cardiovascular disease, cancer, and malnutrition.

Gene-based personalised advice is healthy eating and physical activity advice that is tailored to suit an individual based on their own personal health status, lifestyle and genetics. There are a number of benefits to personalised advice based on genetics compared to general health advice. The advice provided may be more precise and effective for you as an individual, risk of diet and physical activity related diseases may be communicated at a younger age to encourage behaviour change and prevent subsequent health problems.

The aim of this survey is to understand factors that influence intention to adopt gene-based personalised nutrition in a young population. This may enable a greater understanding of how gene-based advice can be utilised as a preventative public health tool in young adults.

You are invited to take part in an online survey to investigate the factors that influence the attitude and intention of young adults to utilise gene-based personalised advice for diet and physical activity. The survey is organised by Alexandra King as part of her PhD under the supervision of Dr Yiannis Mavrommatis and Dr Leta Pilic. The results of the study will be analysed and presented as part of a PhD and may also be published in a peer reviewed academic journal or presented at an academic conference. The research is funded by St Mary's University.

For further information please contact Alexandra King (alexandra.king@stmarys.ac.uk).

Supervisors contact details: Yiannis Mavrommatis (yiannis.mavrommatis@stmarys.ac.uk)

Leta Pilic (leta.pilic@stmarys.ac.uk)

Section B: Your Participation in the Research Project

You have been invited to take part in the study because you are a young adult (18 -25 years of age), living in the UK, are not pregnant, lactating, following a restricted diet or have a diagnosed eating disorder. You are under no obligation to take part in the survey.

The survey will take approximately 20 minutes to complete, you will be asked questions about your attitude and intention to adopt gene-based advice for your diet and physical activity. To understand factors that influence your attitude and intention you will also be asked questions about your perception of your health, food choice, body weight, physical activity and characteristics. You will not be asked to provide your name or date of birth so your survey response will be anonymous. This means once you have completed the survey your response will not be identifiable or able to be withdrawn. If you would like a copy of this information or the findings of the survey, please email Alexandra King (alexandra.king@stmarys.ac.uk).

Page 3: Consent

Project Title: Investigation of factors that influence young adults intention to adopt gene-based personalised advice for diet and physical activity.

Main investigator and contact details: Alexandra King alexandra.king@stmarys.ac.uk

Members of the research team:

Yiannis Mavrommatis yiannis.mavrommatis@stmarys.ac.uk

Leta Pilic leta.pilic@stmarys.ac.uk

- I agree to take part in the above research. I have read the Participant Information section. I understand what my role will be in this research, and all my questions have been answered to my satisfaction.
- I understand that I am free to withdraw from the research at any time before completion of the survey, for any reason and without prejudice. After which I understand my response will not be able to be identified and therefore withdrawn.
- I have been informed that the confidentiality of the information I provide will be safeguarded.
- I am free to ask any questions at any time by emailing the main investigator.
- I am 18 -25 years of age, living in the UK, not pregnant, lactating, following a restricted diet or have a diagnosed eating disorder

Data Protection: I agree to the University processing personal data which I have supplied. I agree to the processing of such data for any purposes connected with the Research Project as outlined to me.

1. Please read the statement below and check if you agree: *Required*

I agree with all statements above and provide my informed consent to take part in the study.

Page 4: Introduction

Hello,

Thank you for agreeing to take part in our survey. The survey will ask a series of questions about your attitude towards and intention to adopt gene-based personalised diet and physical activity advice.

Before you start we would like to provide a definition of gene-based personalised diet and physical activity advice:

“healthy eating and physical activity advice that is tailored to suit an individual based on their own personal health status, lifestyle and genetics’’

As described in the information section: There are a number of benefits to personalised advice based on genetics compared to general health advice. The advice provided may be more precise and effective for you as an individual, risk of diet and physical activity related diseases may be communicated at a younger age to encourage behaviour change and prevent subsequent health problems.

In this survey we are interested in your opinions, there are no right or wrong answers. All answers are anonymous.

There is no option to save the survey so please make sure you complete all questions in one go, it should take about 20 minutes to complete.

Thanks again!

Page 5: Section 1: About You

6. What gender do you identify as? *Required*

- [ ] Male
- [ ] Female
- [ ] Other
- [ ] Prefer not to say

3. Please state your age in years *Required*

4. Please specify your ethnicity *Required*

- ○ Asian or Asian British
- ○ Black, Black British, Caribbean or African
- ○ Mixed or multiple ethnic groups
- ○ White
- ○ Other ethnic group

6. Where is your home located? *Required*

- ○ England
- ○ Wales
- ○ Scotland
- ○ Northern Ireland

7. What is the highest degree or level of education you have completed? *Required*

- ○ Secondary School (GCSE or equivalent)
- ○ Further Education (A Level or equivalent)
- ○ Bachelor's Degree
- ○ Master's Degree
- ○ Ph.D. or higher
- ○ Prefer not to say

8. How healthy do you consider yourself? *Required*

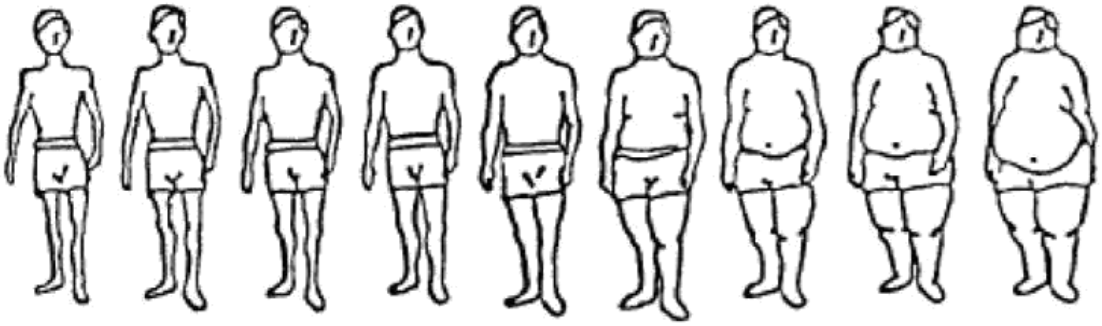
- Very unhealthy
- Unhealthy
- Moderately unhealthy
- Healthy
- Very Healthy

9. 'In the past week, on how many days have you done a total of 30 min or more of physical activity, which was enough to raise your breathing rate? This may include sport, exercise, and brisk walking or cycling for recreation or to get to and from places, but should not include housework or physical activity that may be part of your job.' *Required*

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7

9.

MALE Body Types



01 ☐ 02 ☐ 03 ☐ 04 ☐ 05 ☐ 06 ☐ 07 ☐ 08 ☐ 09 ☐

FEMALE Body Types

10 ☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18 ☐

Please select the figure that you believe most closely resembles your body image: *Required*

○ 1	2	○	3 ○
○ 4	5	○	6 ○
○ 7	8	○	9 ○
○ 10	11	○	12 ○
○ 13	14	○	15 ○
○ 16	17	○	18 ○

Page 6: Section 2: Your health

11. Please indicate the extent to which you agree or disagree with the following statements: *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 6 answer(s).

	Completely disagree	Disagree	Neither disagree/nor agree	Agree	Completely agree
I can be as healthy as I want to be	☐	☐	☐	☐	☐
I am in control of my health	☐	☐	☐	☐	☐
I can pretty much stay healthy by taking care of myself	☐	☐	☐	☐	☐
Efforts to improve your health are a waste of time	☐	☐	☐	☐	☐
I am bored by all the attention that is paid to health and disease prevention	☐	☐	☐	☐	☐
What's the use of concerning yourself about your health you'll only worry yourself to death	☐	☐	☐	☐	☐

12. Please give your position on the following statements. It is important to me that the food I eat on a typical day: *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 36 answer(s).

	Not at all important	A little important	Moderately Important	Very Important	Extremely important
Contains a lot of vitamins and minerals	☐	☐	☐	☐	☐
Keeps me healthy	☐	☐	☐	☐	☐
Is nutritious	☐	☐	☐	☐	☐
Is high in protein	☐	☐	☐	☐	☐
Is good for my skin/teeth/hair/nails etc.	☐	☐	☐	☐	☐
Is high in fibre and roughage	☐	☐	☐	☐	☐
Helps me cope with stress	☐	☐	☐	☐	☐
Helps me to cope with life	☐	☐	☐	☐	☐

Helps me relax	☐	☐	☐	☐	☐
Keeps me awake/alert	☐	☐	☐	☐	☐
Cheers me up	☐	☐	☐	☐	☐
Makes me feel good	☐	☐	☐	☐	☐
Is easy to prepare	☐	☐	☐	☐	☐
Can be cooked very simply	☐	☐	☐	☐	☐
Takes no time to prepare	☐	☐	☐	☐	☐
Can be bought in shops close to where I live or work	☐	☐	☐	☐	☐
Is easily available in shops and supermarkets	☐	☐	☐	☐	☐
Smells nice	☐	☐	☐	☐	☐
Looks nice	☐	☐	☐	☐	☐
Has a pleasant texture	☐	☐	☐	☐	☐
Tastes good	☐	☐	☐	☐	☐
Contains no additives	☐	☐	☐	☐	☐
Contains natural ingredients	☐	☐	☐	☐	☐
Contains no artificial ingredients	☐	☐	☐	☐	☐
Is not expensive	☐	☐	☐	☐	☐
Is cheap	☐	☐	☐	☐	☐
Is good value for money	☐	☐	☐	☐	☐
Is low in calories	☐	☐	☐	☐	☐
Helps me control my weight	☐	☐	☐	☐	☐
Is low in fat	☐	☐	☐	☐	☐
Is what I normally eat	☐	☐	☐	☐	☐
Is well-known	☐	☐	☐	☐	☐
Is like the food I ate when I was a child	☐	☐	☐	☐	☐
Comes from countries I approve of politically	☐	☐	☐	☐	☐
Has the country of origin clearly marked	☐	☐	☐	☐	☐
Is packaged in an environmentally friendly way	☐	☐	☐	☐	☐

12. Please indicate the extent to which you agree or disagree with the following statements:

Please don't select more than 1 answer(s) per row.

Please select at least 3 answer(s).

	much lower than average	lower than average	slightly lower than average	average	slightly higher than average	higher than average	much higher than average
Your chances of getting cardiovascular disease in the future compared with those of the average adult of your age and sex are	☐	☐	☐	☐	☐	☐	☐
Your chances of getting type 2 diabetes in the future compared with those of the average adult of your age and sex are	☐	☐	☐	☐	☐	☐	☐
Your chances of becoming obese in the future compare with those of the average adult of your age and sex are	☐	☐	☐	☐	☐	☐	☐

Page 7: Section 3: Gene-based personalised advice

14. Please give your position on the following statements. *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 5 answer(s).

	Agree	Neither disagree/nor agree	Disagree
I only want gene-based personalised advice about predisposition of curable diseases.	☐	☐	☐
I only want gene-based personalised advice about a disease if I can prevent this disease.	☐	☐	☐
Concerning genetic advice, I want gene-based personalised advice about my risk of developing cardiovascular disease.	☐	☐	☐
Concerning genetic advice, I want gene-based personalised advice about my risk of developing type II diabetes.	☐	☐	☐
Concerning genetic advice, I want gene-based personalised advice about my risk of developing obesity.	☐	☐	☐

16. Please indicate the extent to which the following potential outcomes would increase the likelihood of you adopting gene-based personalised nutrition or physical activity advice: *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 10 answer(s).

	Not increase it at all	Increase it slightly	Increase it moderately	Increase it strongly	Increase it extremely
Knowing what foods are best for me	☐	☐	☐	☐	☐
Losing weight	☐	☐	☐	☐	☐
Gaining weight	☐	☐	☐	☐	☐
Fitness	☐	☐	☐	☐	☐
Improving my family's health	☐	☐	☐	☐	☐
Improving my health	☐	☐	☐	☐	☐
Improving my quality of life	☐	☐	☐	☐	☐
Improving my sports performance	☐	☐	☐	☐	☐
Preventing a future illness	☐	☐	☐	☐	☐
Preventing the expression of a hereditary illness	☐	☐	☐	☐	☐

14.a. Other, please specify:

The following questions use a rating scale with 7 places; please select the number that best describes your opinion. For example, if you were asked to rate 'the weather in London' on such a scale, the 7 places would be interpreted as follows:

Example: The weather in London is:

bad	1	2	3	4	5	6	7	**good**
	extremely	quite	slightly	neither	slightly	quite	extremely	

If you think the weather in London is extremely good, then you would select number 7.

If you think the weather in London is quite bad, then you would choose number 2.

15. My adoption of gene-based advice to modify dietary or physical activity behaviour would be *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
bad								good

17. My adoption of gene-based advice to modify dietary or physical activity behaviour would be

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unpleasant								pleasant

18. My adoption of gene-based advice to modify dietary or physical activity behaviour would be

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
worthless								valuable

.

18. My adoption of gene-based advice to modify dietary or physical activity behaviour would be

Please don't select more than 1 answer(s) per row

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
boring								interesting

20. Most people who are important to me would approve of my adoption of gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

21. Most people like me would adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

22. My friends would approve of my adoption of gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

23. For me to adopt gene-based advice to modify dietary or physical activity behaviour would be

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
difficult								easy

24. I am confident that I can adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
false								true

25. My adoption of gene-based advice to modify dietary or physical activity behaviour is up to me

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

26. For me to adopt gene-based advice to modify dietary or physical activity behaviour is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
impossible								possible

27. I would consider adopting gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

28. I am definitely going to adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

29. I intend to adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

30. gene-based advice to modify dietary or physical activity behaviour will help me to achieve health and fitness goals

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

31. gene-based advice to modify dietary or physical activity behaviour will provide me with motivation to eat healthily and exercise

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

32. gene-based advice to modify dietary or physical activity behaviour will restrict my food choices

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

33. gene-based advice to modify dietary or physical activity behaviour will take effort and time to make changes

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

34. gene-based advice to modify dietary or physical activity behaviour will help me to prevent disease

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

35. gene-based advice to modify dietary or physical activity behaviour will cause me to worry about the risk of developing a disease

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

36. gene-based advice to modify dietary or physical activity behaviour will be expensive

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

37. For me achieving health and fitness goals is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
bad								good

38. For me to prevent the development of disease is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
bad								good

39. For me to be motivated to eat healthily and exercise is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
bad								good

41. For me restriction of my food choices is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
bad								good

42. For me to take effort and time to make changes is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
bad								good

43. For me the expense of gene-based advice is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
bad								good

44. For me to worry about the risk of developing a disease is

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
bad								good

46. My friends would think I should use gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

47. My family would think I should use gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

45. Influencers and people I follow on social media would think I should use gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

46. Health professionals would think I should use gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
unlikely								likely

47. When it comes to matters of health, I want to do what my friends think I should do

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

48. When it comes to matters of health, I want to do what my family think I should do

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

49. When it comes to matters of health, I want to do what influencers and people I follow on social media think I should do

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

50. When it comes to matters of health, I want to do what health professionals think I should do

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

51. How often does lack of time prevent you from eating healthily and or exercising?

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
rarely								frequently

52. How often does lack of clear guidance prevent you from eating healthily and or exercising?

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
rarely								frequently

53. How often does lack of confidence in effectiveness of guidance prevent you from eating healthily and or exercising?

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
rarely								frequently

54. How often does lack of money prevent you from eating healthily and or exercising?

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
rarely								frequently

55. Having enough time would enable me to adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

56. Having enough money would enable me to adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

57. Having confidence in the effectiveness of guidance would enable me to adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

58. Having clear guidance would enable me to adopt gene-based advice to modify dietary or physical activity behaviour

Please don't select more than 1 answer(s) per row.

Please select at least 1 answer(s).

	1	2	3	4	5	6	7	
disagree								agree

Page 8: Section 4: Feedback

59. How long did it take you to complete the survey?

60. Did you understand the definition of gene-based personalised nutrition? *Required*

61. Do you have any other comments? *Required*

62. Please provide your date of birth: *Required*

Dates need to be in the format 'DD/MM/YYYY', for example 27/03/1980.

(dd/mm/yyyy)

63. If you would like to be entered into a draw to win a £50 voucher of your choice please provide your email address.

Page 9: Thank you!

If you would like to receive the overall findings from this research please send an email to Alexandra King:
alexandra.king@stmarys.ac.uk

Thank you very much for your time.

The following code gives you credits that can be used to get free research participants

at SurveySwap.io. Go to: https://surveyswap.io/sr/ND6M-TFPI-9H8C

Or, alternatively, enter the code manually: ND6M-TFPI-9H8C