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The NOW Trial: A Pragmatic Randomized Controlled Trial of Personalized, Genetic-Based Lifestyle Advice

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Health and Rehabilitation Sciences

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The NOW Trial: A Pragmatic Randomized Controlled Trial of Personalized, Genetic-Based Lifestyle Advice

Abstract

Background: The impact of nutrigenomics and lifestyle genomics interventions on health outcomes and behaviours remains controversial and under-explored.

Objectives: To determine the short-term (3-month), moderate-term (6-month) and long-term (12-month) impact of providing personalized, genetic-based lifestyle information and advice on anthropometric measures, as well as dietary intake and adherence.

Methods: The nutrigenomics, overweight/obesity and weight management trial (NOW Trial) is a pragmatic randomized controlled trial that was incorporated into the Group Lifestyle Balance™ (GLB) program ($N=140$). Inclusion criteria: overweight or obesity ($BMI \geq 25 \text{ kg/m}^2$), ≥ 18 years of age, English-speaking, having access to internet at least one day per week, willing to undergo genetic testing, and not seeing another healthcare provider outside of the study for weight-loss advice. Exclusion criteria: Pregnancy and lactation. Twelve-month GLB weight management program groups were randomized 1:1 to receive either the standard GLB program or a modified nutrigenomics-based GLB program (GLB+NGx). Data collection occurred at baseline, 3-, 6- and 12-month follow-up. The predetermined primary outcome was change in body fat percentage (BFP). Dietary intake and adherence were secondary outcome measures.

Statistical Analysis: Statistical tests conducted using SPSS (version 26.0) included: repeated measures analyses of variance (ANOVAs), split-plot ANOVAs, two-way ANOVAs, chi-square

and Fisher's exact tests and logistic regression. Key components of the Theory of Planned Behaviour were considered in the dietary intake analyses.

Results: After 3- and 6-month follow-up, the GLB+NGx group improved (reduced) their BFP to a significantly greater extent ($p<0.05$) than the standard GLB group. There were no statistically significant differences in BFP between groups after 12 months. Furthermore, the GLB+NGx group significantly reduced their total fat intake after 12 months; the standard GLB group did not. Dietary adherence to saturated fat and total fat recommendations were significantly ($p<0.05$) greater in the GLB+NGx group compared to the standard GLB group at 12 months.

Conclusion: Genetically-tailored lifestyle advice can lead to improvements in body composition over the short-term and moderate-term, and motivate long-term dietary changes and adherence to nutrition recommendations. Biological mechanisms may challenge long-term weight loss, even with genetically-tailored advice that motivates long-term dietary changes.

Keywords: nutrigenomics, nutritional genomics, nutrigenetics, lifestyle genomics, genetics, nutrition, overweight, obesity, Theory of Planned Behaviour, Theory of Planned Behavior

Summary for Lay Audience

Nutrigenomics is a science that explores how our genes impact the way our bodies respond to the foods, beverages and nutrients we consume. For example, one person may lose more weight by following a lower saturated fat nutrition plan compared to someone else. Nutrigenomics can be used to provide more personalized nutrition advice. Some studies have shown that giving personalized, genetic-based information and advice can help motivate individuals to make dietary changes. Very few studies have assessed the effectiveness of nutrigenomics-based weight loss interventions. Therefore, the studies included in this dissertation aimed to build upon past research and provide new insights into whether providing people with genetic-based lifestyle advice results in improvements in dietary intake, weight and body fat. To study this, we randomly assigned people to receive either standard advice for weight management or genetic-based advice for weight management and then followed up with them after 3, 6 and 12 months. The study participants also participated in a 12-month intervention. Overall, people who received the genetic-based advice experienced a decrease in body fat, more so than the people who received the standard advice after 3 and 6 months. After 12 months, there was no major difference in body fat between these two groups. When we looked at changes to their nutritional intake, people who received the genetic-based advice significantly reduced their overall intake of dietary fat after 12 months, whereas those who received the standard advice did not. Additionally, after 12 months, people who received the genetic-based advice better adhered to the recommendations for total fat and saturated fat compared to those who received the standard intervention. Overall, we found that nutrigenomics interventions can motivate long-term (12-month) dietary changes and can lead to improvements in body fat over the short-term (3-month) and moderate-term (6-month) to a greater extent than standard advice. Previous research shows that over time, the body tries to compensate for weight loss with physiological mechanisms promoting weight regain. This may help to explain why we found that after 12 months, the group receiving the standard advice had lost a similar amount of body fat as the group receiving genetic-based advice, despite the genetic intervention group improving their diet to a greater extent.

Statement of Co-Authorship

The following dissertation includes six integrated articles, three of which have been published, and three of which have been submitted for publication. For published manuscripts, reference formatting, sub-heading numbers, spelling (Canadian) table numbers and figure numbers have been revised for consistency with the present dissertation. In addition, acknowledgments have been removed from the individual chapters and are included in the proceeding Acknowledgments section of this dissertation. Co-authorship details for each of the six articles are as follows:

Chapter 2 (published):

Horne J, Madill J, Gilliland J. 2017. “Incorporating the ‘Theory of Planned Behavior’ into personalized healthcare behavior change research: a call to action.” *Personalized Medicine* 14(6): 521-29.

This article was conceptualized and written by Horne with guidance from Madill and Gilliland. Horne conducted the literature search, conceptualized the presented ideas, wrote and revised manuscript, and formatted and submitted the article to the journal *Personalized Medicine*. Horne also completed all recommended revisions resulting from the journal’s peer-review process. Madill and Gilliland advised on the revisions and approved the final manuscript.

Chapter 3 (published):

Horne J, Madill J, O’Connor C, Shelley J, Gilliland J. 2018. “A systematic review of genetic testing and lifestyle behaviour change: Are we using high-quality genetic interventions and considering behaviour change theory?” *Lifestyle Genomics*. 11(1): 49-63.

Horne designed the review protocol with guidance from Gilliland, piloted data collection forms with Gilliland, critically appraised articles, trained a student volunteer to conduct searches, took the lead on data entry, critically appraised all included articles, conducted analyses, interpreted results, wrote and revised the manuscript, and formatted and submitted article to the journal *Lifestyle Genomics*. Madill, O’Connor, Shelley and Gilliland provided guidance throughout the research process, and revised and approved the final manuscript.

Chapter 4 (submitted):

Horne J, Gilliland J, Madill J. “Assessing the effectiveness of actionable nutrigenomics and lifestyle genomics interventions for weight management: A critical, scoping review with directions for future research.”

Horne completed the literature search, reviewed, summarized, and critiqued the included articles, conceptualized the presented ideas, wrote, revised, formatted and submitted the manuscript to the journal. Gilliland and Madill reviewed and approved the final manuscript.

Chapter 5 (published):

Horne J, Gilliland J, O'Connor C, Seabrook J, Hannaberg P, Madill J. 2019. "Study protocol of a pragmatic randomized controlled trial incorporated into the Group Lifestyle Balance™ Program: The Nutrigenomics, Overweight/Obesity and Weight Management Trial (The NOW Trial)." *BMC Public Health* 19(1): 310.

Horne took a leadership role in designing the study with feedback from Madill, Gilliland, Seabrook and O'Connor. Horne helped register the clinical trial, helped to obtain ethics approval, recruited participants, collected data, ran the interventions, entered data in database, wrote and revised the manuscript, and formatted and submitted a version of the manuscript to *BMC Public Health*. Seabrook advised on the sample size calculation and statistical analysis plan. Gilliland and Madill further contributed to the supervision of this project. Gilliland, O'Connor, Seabrook, Hannaberg and Madill revised manuscript drafts and approved the final manuscript.

Chapter 6 (submitted):

Horne J, Gilliland J, O'Connor C, Seabrook J, Madill J. "Enhanced long-term dietary change and adherence in a nutrigenomics-guided lifestyle intervention program compared to a population-based (GLB/DPP) lifestyle intervention for weight management: Results from the NOW randomized controlled trial."

Horne was responsible for assisting with registering the clinical trial and obtaining ethics approval. She was further responsible for recruiting participants, collecting data, running the interventions, entering data in the database, writing and revising the manuscript and submitting it to the journal for peer-review. Gilliland, O'Connor, Seabrook and Madill reviewed and revised drafts and approved the final manuscript draft. Seabrook also advised on the statistical analyses. Gilliland and Madill further contributed to the supervision of this project.

Chapter 7 (submitted):

Horne J, Gilliland J, Seabrook J, O'Connor C, Madill J. "Change in weight, BMI, and body composition after 3, 6 and 12 months in a population-based intervention vs. genetic-based intervention: Results from the NOW randomized controlled trial."

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List of Abbreviations

ACE: angiotensin converting enzyme
ACTN3: alpha-actinin-3
ADRB3: adrenergic receptor beta 3
ANOVA: analysis of variance
APOA2: apolipoprotein A-II
BFP: body fat percentage
BIA: bioelectrical impedance analysis
BMI: body mass index
CD: cannot determine
CDHQII: Canadian Diet History Questionnaire II
COI: conflict of interest
DHA: docosahexaenoic acid
DNA: deoxyribonucleic acid
DPP: Diabetes Prevention Program
DTC: direct-to-consumer
EEFHT: East Elgin Family Health Team
EPA: eicosapentaenoic acid
FTO: fat-mass and obesity-associated
GLB: Group Lifestyle Balance™
GLB+NGx: Group Lifestyle Balance™ + nutrigenomics
GSTP1: glutathione S-transferase pi 1
HCP: healthcare provider
IL6: interleukin 6
MC4R: melanocortin 4 receptor
MUFA: monounsaturated fatty acid
NA: not applicable
NFIA-AS2: nuclear factor I A antisense RNA 2
NIH: National Institutes of Health
NOS3: nitric oxide synthase 3
NOW: Nutrigenomics, Overweight/Obesity and Weight Management
NR: not reported
NRF2: nuclear factor erythroid 2-related factor 2
NS: not stated
PA: physical activity
PBC: perceived behavioural control
PHBC: personalized healthcare behaviour change
PLI: personalized lifestyle intervention
PPAR γ 2: peroxisome proliferator-activated receptor gamma 2
PUFA: polyunsaturated fatty acid
RAA: reasoned action approach
RAAS: renin-angiotensin-aldosterone system
RCT: randomized controlled trial
RD: registered dietitian

rs: reference SNP
SD: standard deviation
SFA: saturated fatty acid
SLI: standard lifestyle intervention
SNP: single nucleotide polymorphism
TCF7L2: transcription factor 7 like 2
TNF α : tumor necrosis factor alpha
TPB: Theory of Planned Behaviour
UCP1: uncoupling protein 1
WC: waist circumference
3DFR: 3-day food record
%kcal: percent of calories

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CHAPTER 1: INTRODUCTION

1.1 Introduction

Nutrigenomics is a science that seeks to explore interactions between genetic variation, nutritional intake, and subsequent health outcomes (Gibney and Walsh 2013). The terms *nutrigenomics* and *nutritional genomics* are often used interchangeably. Recently, the more broad definition *lifestyle genomics* has been coined, which is used to describe the study of interactions between genetic variation, lifestyle habits (such as nutrition, physical activity, smoking, etc.) and subsequent health and disease outcomes (Karger 2019). Table 1.1 provides an overview of key terms and definitions which appear throughout this dissertation and are related to the field of genetics.

Table 1.1: Key terms and definitions

Term	Definition
Gene	A section of DNA, which forms part of the chromosome. It is the functional unit of heredity. Everyone has the same genes, but individuals differ in their genetic variants (see definition below).
Variant (Genotype)	A set of two alleles, typically making a single nucleotide polymorphism (SNP) (e.g. a “TT” variant/genotype). Variants/genotypes can also exist in the form of copy number variants.
SNP	When one allele is replaced by a different allele (e.g. a “T” replacing an “A”). This is the most common type of variation within the genetic code.
Allele	One of two variant forms of a genotype (e.g. a “T” allele).
rs#	A number used to identify a specific location on a gene. The letters “rs” stand for Reference SNP.
Linkage Disequilibrium	The association between alleles in different locations on the genome, whereby having a specific genetic variant at one location, predicts a strong likelihood of having a certain genetic variant at another, nearby genetic location.
Nutrigenomics (Nutritional Genomics, Nutrigenetics)	Terms used to describe the study of the interaction between genetic variation, nutritional intake, and subsequent health outcomes.
Lifestyle Genomics	The study of the interaction between genetic variation, lifestyle habits (e.g. physical activity, sleep, smoking, nutrition, etc.), and subsequent health outcomes.

From a weight management perspective, lifestyle genomics and nutrigenomics help to explain why some individuals lose more weight or improve their body composition to a greater extent than others, even when they are following the same nutrition and physical activity plan.

1.2 Research Purpose, Objectives and Hypotheses

The overarching aim of this dissertation is to provide new insights into whether providing people with genetic-based nutrition advice can improve nutrition- and health-related outcomes. Overall, it is hypothesized that when patients enrolled in a genetically-tailored weight management program receive genetic-based lifestyle information and advice, this will reduce weight and positively impact body composition, dietary intake, and dietary adherence to a greater extent than population-based lifestyle information and advice over the short-term (3 months), moderate-term (6 months) and long-term (12 months).

Objectives:

- To review and summarize the literature on the impact of providing genetic-based lifestyle information and advice on weight-related outcomes and lifestyle changes
- To determine if the provision of genetic-based lifestyle information and advice is more effective than population-based lifestyle advice for improving: 1) anthropometric measures [body fat percentage (BFP) as the predetermined primary outcome; weight and BMI as predetermined secondary outcomes], 2) dietary intake, and 3) dietary adherence.
- To compare the short-term (3 month), moderate-term (6 month) and long-term (12 month) impact of providing personalized lifestyle advice on: 1) anthropometric measures, 2) dietary intake, and 3) dietary adherence.

1.3 The Science of Nutrigenomics and Lifestyle Genomics

1.3.1 Background Information

There are numerous examples of gene-diet-health outcome interactions reported in the literature (Zhang et al. 2012; Grau et al. 2010; Corella et al. 2009; Cornelis et al. 2006). At the same time, consumer interest in nutrigenetic testing continues to grow. In response, genetic testing companies now offer several different nutrigenetic and lifestyle genomics tests to consumers. While systematically reviewing the quality of the evidence to support the information included in commercially available consumer nutrigenetic tests is beyond the scope of this dissertation, a brief summary of nutrigenomics and lifestyle genomics interactions relevant to the present dissertation is provided below. Details on how this science can be translated and incorporated into clinical practice is further outlined in Chapter 5 (section 5.4.12 and Supplementary Table 5.4).

1.3.2 Nutrigenomics and Lifestyle Genomics Examples

Genetic-based information and/or recommendations which are related to weight management can be provided to patients for: calories, protein, total fat, monounsaturated fat, polyunsaturated fat, saturated fat, appetite, and physical activity. The goal of providing these personalized lifestyle recommendations and information is to motivate health behaviour change and/or optimize health outcomes by providing advice that is tailored towards the individual. As such, several consumer genetic testing services offer information related to one or more of these gene-nutrient interactions (Nutrigenomix 2019; Athletigen 2018; MyDNA 2019). Genes included in these consumer tests include, but are not limited to: UCP1, FTO, TCF7L2, APOA2,

PPAR γ 2, MC4R, ADRB3, NRF2, GSTP1, NFIA-AS2 and ACTN3. Each of these will be further discussed below.

UCP1 and Calories

The uncoupling protein 1 (UCP1) gene plays a role in separating oxidative phosphorylation from ATP synthesis, while producing heat as a result of this metabolic process (Gene Cards n.d.). This particular gene is expressed almost exclusively in brown adipose tissue, which is more metabolically active than white adipose tissue (Jorge et al. 2017). Research has demonstrated that individuals with GG or GA genotype at UCP1 rs1800592 have lower metabolic rates than those with the AA genotype (Nagai et al. 2011) and therefore calorie intake can be targeted based on individual genetic variation. In addition, the presence of at least one G allele has also been associated with obesity (Hayakawa et al. 1999; Heilbronn et al. 2000; Ramis et al. 2004).

FTO and Protein

Common variants within the fat-mass and obesity-associated (FTO) gene have been consistently linked to overweight and obesity whereby A allele carriers are at an increased risk of obesity and obesity-related conditions (Yang et al. 2017). FTO genetic variation is associated with differences in hunger/satiety and food intake, likely caused by FTO genetic variation affecting leptin and ghrelin levels. There does not appear to be a link between resting energy expenditure and FTO variation (Speakman 2015). In terms of weight loss, results from a 2-year randomized controlled trial (RCT) demonstrated that individuals with the risk allele of FTO rs1558902 (in strong linkage disequilibrium with rs9939609) had greater improvements in body composition and greater weight loss when following a higher protein diet (25% of calories from

protein) (Zhang et al. 2012). This protective effect of protein intake on obesity in high-risk FTO genotypes was recently replicated in a cross-sectional study (Merritt et al. 2018).

TCF7L2 and Total Fat

Transcription factor 7 like 2 (TCF7L2) plays an important role in the synthesis of glucagon-like peptide 1, which contributes to body weight via appetite, adipose tissue metabolism and insulin signalling (Flint et al. 1998; Verdich et al. 2001; Azuma et al. 2008; Boschmann et al. 2009; Gao et al. 2007). The release of glucagon-like peptide 1 is stimulated differently by fat and carbohydrate whereby there is a greater release after ingesting dietary fat, therefore altering intakes in these dietary components could impact weight-loss response (Eller et al. 2008; Paniagua et al. 2007). Results from a 2-year RCT found that consuming a diet lower in total fat (20% of calories) can reduce body adiposity in those with high-risk genetic variants in TCF7L2 rs12255372 (Mattei et al. 2012) [in strong LD with rs7903146 in some ethnicities (Humphries et al. 2006)]. Another RCT demonstrated the effectiveness of following a dietary pattern low in total fat (20-25% of calories) for weight loss in individuals with the TT genotype of TCF7L2 rs7903146 (Grau et al. 2010).

APOA2 and Saturated Fat

Apolipoprotein A-II (APOA2) is a major component of high-density lipoprotein particles and regulates both triglyceride and postprandial metabolism (Delgado-Lista et al. 2018; Julve et al. 2010). There is an association between APOA2 genetic variation, saturated fat intake, and obesity. Individuals who carry the CC variant of the APOA2 gene (rs5082) are at an increased risk of obesity when their intake of saturated fat is high. Consuming a diet low in saturated fat (<22 g per day) is associated with a lower body mass index (BMI) in individuals with the risk

variant (Corella et al. 2010; Corella et al. 2011). While the mechanism for this nutrigenomics interaction is not well-understood, individuals with the CC variant of APOA2 (rs5082) have demonstrated low ghrelin levels when consuming a low saturated fat diet, thus demonstrating a proposed mechanism for the association between saturated fat intake, obesity, and APOA2 genetic variation via regulation of a hormone involved in hunger signalling (Smith et al. 2012).

FTO, Saturated and Unsaturated Fat

As indicated above, FTO genetic variation is linked to risk of obesity and obesity-related conditions (Yang et al. 2017), likely due to the effects on leptin and ghrelin levels leading to differences in hunger/satiety and food intake (Speakman 2015). FTO genetic variation at rs9939609 impacts individual responses to dietary unsaturated fat intake whereby a diet high in saturated fat ($\geq 15.5\%$ of calories) and low in polyunsaturated fat (polyunsaturated fat: saturated fat ratio < 0.38) accentuates the risk of obesity (Phillips et al. 2012). Another study found that A allele carriers following a hypocaloric diet high in polyunsaturated fat (6% of calories; 7 grams omega-6; 2 grams omega-3 per day) had a lower BMI, weight and fat mass compared to individuals with TT genotypes following the same dietary pattern (De Luis et al. 2015).

PPAR γ 2 and Monounsaturated Fat

The peroxisome proliferator-activated receptor gamma 2 (PPAR γ 2) plays an important role in regulating adipogenesis – a process in which pre-adipocytes become adipocytes (fat cells, which make up adipose tissue) (Memisoglu et al. 2003). Memisoglu et al. (2003) were the first to discover an interaction between PPAR γ 2 genetic variation, monounsaturated fat intake, and body mass index BMI (Memisoglu et al. 2003). Later research discovered that a higher intake of monounsaturated fat (comprising approximately 50% of total fat) was associated with

significantly lower body fat and BMI in individuals with high risk genotypes of PPAR γ 2 (Garaulet et al. 2011).

ACE and Sodium

The angiotensin-converting enzyme (ACE) is part of the renin-angiotensin-aldosterone system (RAAS), which plays a role in blood pressure regulation. Within the RAAS system, ACE is responsible for cleaving angiotensin I to form angiotensin II (Lifton 1996). It is postulated that salt-sensitive individuals experience a blunted RAAS response to high dietary sodium, thus increasing the risk of salt-sensitive hypertension (Poch et al. 2007). Salt-sensitive hypertension can be measured by monitoring ambulatory blood pressure following high sodium intake. Research demonstrates that individuals with high-risk genetic variants in the ACE gene are more prone to high blood pressure when consuming a high intake of sodium (approximately 2300 mg daily). Those with low-risk genetic variants are less likely to present with high blood pressure in response to a high sodium intake (Poch et al. 2007; Giner et al. 2012).

MC4R and Snacking (Appetite)

Individual genetic variation can also have an impact on eating behaviours. The melanocortin 4 receptor (MC4R) gene codes for a receptor found in the hypothalamus region of the brain where hunger and appetite are controlled (Adan et al. 2006). Studies have demonstrated that individuals with the CC or CT variant (C allele carriers) of MC4R (rs17782313) are more likely to eat more frequently during the day and have an intensified appetite (Stutzmann et al. 2009). On the contrary, those with the TT variant are less likely to eat frequently through the day (Stutzmann et al. 2009). Research further demonstrates that individuals with the CC or CT variant at rs17782313 of the MC4R gene are more likely to be overweight/obese (Srivastava et

al. 2014; Loos et al. 2008; Zobel et al. 2009). MC4R variants have also been linked to higher intakes of calories and fat, binge eating, excessive hunger, hyperphagia, and food-seeking behaviours (Adan et al. 2006; Qi et al. 2008; Branson et al. 2003).

FTO and Physical Activity

While dietary strategies exist to mitigate obesity-risk associated with FTO genetic variation, it has also been well-established that physical activity can attenuate the obesity-associated effects in high risk FTO genotypes. Numerous studies have demonstrated this association and results from the current body of literature have been highly consistent (Sonestedt et al. 2011; Q. Yang et al. 2017; Celis-Morales et al. 2016; Andreasen et al. 2008; Zou et al. 2015; Speakman 2015; Corella et al. 2012; Lee et al. 2010; Kilpeläinen et al. 2011; Sonestedt et al. 2009; Ahmad et al. 2010; Rampersaud et al. 2008; Vimalleswaran et al. 2009; Scott et al. 2010; Xi et al. 2011; Zhu et al. 2014). The attenuating effects of physical activity on FTO-related overweight and obesity provide an example of a lifestyle genomics interaction.

ADRB3, NRF2, GSTP1, NFIA-AS2 and Endurance

Several genes have been demonstrated to impact genetic predisposition to excel at endurance/aerobic-based activities. Studies have assessed associations between certain genetic variants and elite endurance performance, running economy, maximal oxygen uptake, and maximum ventilation. The following genes appear to play a significant role in this endurance athletic predisposition: adrenergic receptor beta 3 (ADRB3), nuclear factor erythroid 2-related factor 2 (NRF2), glutathione S-transferase pi 1 (GSTP1), and nuclear factor I A antisense RNA 2 (NFIA-AS2) (Santiago et al. 2011; He et al. 2007; Zarebska et al. 2014; Ahmetov et al. 2015).

ACTN3 and Strength

The alpha-actinin-3 (ACTN3) gene encodes for a protein that is expressed almost exclusively in type 2 (fast twitch) muscle fibres (North et al. 1999). The CC and TC genotypes in the ACTN3 gene (rs1815739) have been significantly associated with speed and power phenotypes across numerous studies (Ahmetov et al. 2011; Kikuchi et al. 2016; N. Yang et al. 2003; Ma et al. 2013; Eynon et al. 2009). As such, ACTN3 has been referred to as “a gene for speed” (Pickering and Kiely 2017).

In summary, there are several lifestyle genomics interactions relevant to weight management and available through consumer genetic testing services. It is plausible that personalizing weight management strategies through genetically-guided nutrition and physical activity advice could result in improved health-related outcomes.

1.4 Consumer Nutrigenetic and Lifestyle Genomics Testing

1.4.1 The Current State of the Canadian Industry

Canadians have expressed great interest in nutrigenetic testing (Nielsen et al. 2014; Vallée Marcotte et al. 2019). With increasing scientific knowledge, coupled with significant consumer interest in genetic testing for personalized nutrition, there are several companies offering nutrigenetic testing services to consumers. Many of these companies offer information and advice related to both physical activity and nutrition, based on the results of their genetic test. Questions have been raised about the scientific validity and clinical utility of such tests, given the lack of regulatory industry oversight (San-Cristobal et al. 2013; Grimaldi et al. 2017). Indeed, there is variable scientific validity and clinical utility among currently available consumer genetic tests, and this has led researchers to develop proposed guidelines to assess the

scientific validity of such tests (Grimaldi et al. 2017). Overall, the current Canadian industry allows for the widespread consumer availability of nutrigenetic and lifestyle genomics testing to those willing and/or able to pay between approximately \$90 - \$450 CDN (23andMe n.d.; MyDNA 2019; Pathway Genomics n.d.; Nutrigenomix Inc n.d.). Consumers can purchase such tests via direct-to-consumer (DTC) services, or through a healthcare provider.

1.4.2 The Nutrigenetic and Lifestyle Genomics Testing Process

The complete nutrigenetic testing process moves from science through to consumers (Horne et al. 2020). Scientific knowledge provides the basis for developing consumer genetic tests and reports. Industry's responsibilities include reviewing and interpreting science and collaborating with genetic testing laboratories for the genetic analyses. Consumers provide a saliva sample or buccal swab to the company [or to the healthcare provider (HCP) offering the services], which is sent to the laboratory for analysis. In DTC genetic testing, the company sends the genetic report directly to the consumer. When such testing is offered through a HCP, the genetic testing company sends the genetic report to the HCP, who then sets up a meeting with the patient to review their report. Notably, the vast majority of companies offer their genetic testing services to consumers via DTC pathways; it is less common for a company to offer their services exclusively through HCPs (Horne et al. 2020). It has been suggested that many ethical concerns exist with DTC genetic testing (Trent 2013) and as such, offering genetic testing exclusively through a HCP could be superior to DTC genetic testing. Because of widespread ethical concerns, several American states have banned DTC genetic testing altogether (Hogarth et al. 2008). The process for genetic testing via DTC services and via a HCP are outlined in Figures 1.1 and 1.2, respectively.

Figure 1.1: The DTC process for genetic testing

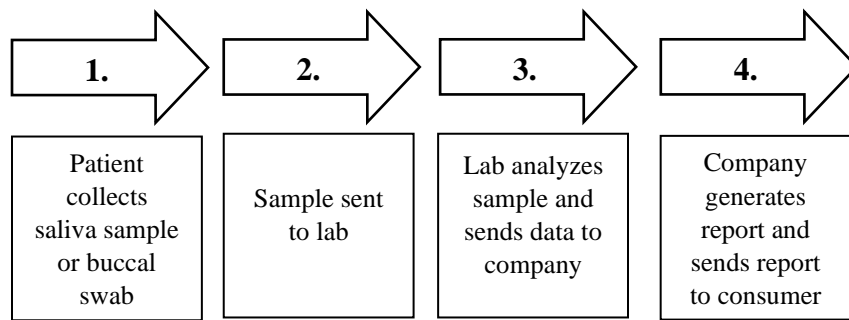
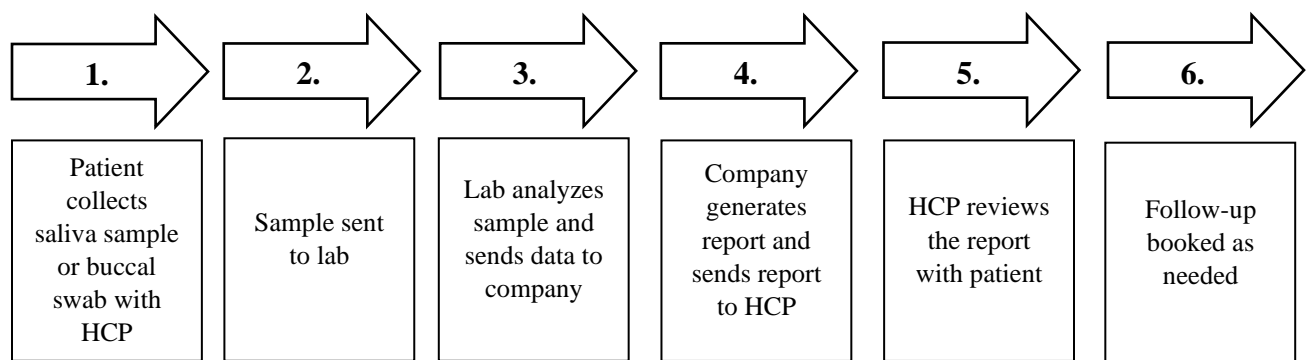


Figure 1.2: The process for genetic testing through a HCP



1.5 The Missing Link Between Science and Consumer Services

There is scientific evidence to support several gene-lifestyle-health outcome interactions (Zhang et al. 2012; Stutzmann et al. 2009; Phillips et al. 2012; Yang et al. 2017; Corella et al. 2010; Grau et al. 2010; Ma et al. 2013). With advancing scientific knowledge, consumer genetic testing companies are offering personalized nutrition and physical activity recommendations to consumers. Given that consumers express great interest in DNA-based personalized nutrition (Nielsen et al. 2014; Vallée Marcotte et al. 2019), and some studies demonstrate that patients are more motivated to change health behaviours when they receive personalized, DNA-based dietary advice (Vernarelli et al. 2010; Egglestone et al. 2013; Nielsen and El-Soehy 2014; Hietaranta-Luoma et al. 2014; Kaufman et al. 2012), nutrigenomics and lifestyle genomics certainly warrant

further investigation. To date, minimal research has assessed the impact of the pragmatic incorporation of personalized, genetic-based weight management interventions in clinical practice, yet such interventions are used by numerous HCPs globally. Furthermore, significant methodological flaws limit the small body of knowledge that exists in this area; this is further discussed in Chapter 4. More broadly, research on the effectiveness of the variety of consumer lifestyle genomics tests available on the market is lacking. With respect to lifestyle changes resulting from genetic testing, several studies have been conducted, but there has been minimal consideration of established behaviour change theories within the existing body of literature (Horne et al. 2018); Chapter 3 provides more detail on this. Thus, there are several important research gaps to be filled in this niche area of personalized nutritional sciences and human behaviour.

1.6 Outline of Dissertation

This dissertation is organized into an integrated manuscript format. As such, there may be some repetition among the chapters. Additionally, abstract formatting varies throughout this dissertation as each abstract style is specific to the journal that the manuscript was published in, or that the manuscript was submitted to.

The purpose of this introductory chapter was to provide a brief overview of the science of nutrigenomics and lifestyle genomics, including a review of genetic variants that were used on the Nutrigenomics, Overweight/Obesity and Weight Management (NOW) trial intervention. An overview of consumer nutrigenetic and lifestyle genomics testing was also presented. Moreover,

this chapter introduced the overarching objectives and hypotheses of the present dissertation, which are further detailed in later chapters.

Chapter 2 presents a call to action for personalized healthcare behaviour change researchers to incorporate the Theory of Planned Behaviour (TPB) into their work. This chapter additionally provides a thorough overview of the TPB and proposes a possible theoretical expansion to include *personalization* in the model. This manuscript has been published in the journal *Personalized Medicine*.

In Chapter 3, we systematically reviewed and summarized the current body of literature on the impact of genetic testing on lifestyle behaviour change. This chapter further assesses the quality of the genetic interventions provided to participants and whether researchers have considered established theories of human behaviour in their work. This manuscript has been published in the journal *Lifestyle Genomics*.

Chapter 4 critically reviews and summarizes the literature on the effectiveness of pragmatic lifestyle genomics interventions on weight management. This manuscript has been submitted for publication.

Following the literature review chapters, Chapter 5 provides a detailed overview of the study design for the NOW trial, which builds on past research. This chapter has been published in the journal *BMC Public Health*.

The results chapters start with Chapter 6, which gives an overview of dietary change and adherence in the NOW trial, and then moves to Chapter 7, which details the resulting weight and body composition outcomes. Chapter 6 provides an analysis and summary of the dietary intake and adherence results from the NOW trial, and is followed by Chapter 7, which provides an analysis and summary of weight-related outcomes of the NOW trial. These chapters have been submitted for publication.

Finally, Chapters 8 and 9 wrap up the dissertation with an integrated discussion and conclusion on the key findings of the NOW trial. These chapters discuss how the NOW trial findings relate to past work and how the results can be used to inform future research endeavours.

**CHAPTER 2: THE THEORY OF PLANNED BEHAVIOUR AND
PERSONALIZED HEALTHCARE BEHAVIOUR CHANGE
RESEARCH**

As published* in *Personalized Medicine*:

Horne J, Madill J, Gilliland J. 2017 “Incorporating the ‘Theory of Planned Behavior’ into personalized healthcare behavior change research: A call to action.” *Personalized Medicine* 14(6): 521-29.

*Reference formatting, table numbers, spelling (Canadian) and figure numbers have been revised for consistency with the present dissertation.

2.1 Title: Incorporating the ‘Theory of Planned Behaviour’ into personalized healthcare behaviour change research: A call to action

2.1.1 Abstract

The ‘Theory of Planned Behaviour’ (TPB) has been tested and validated in the scientific literature across multiple disciplines and is arguably the most widely accepted theory among behaviour change academics. Despite this widespread acceptability, the TPB has yet to be incorporated into personalized healthcare behaviour change (PHBC) research. Several prominent personalized healthcare researchers suggest that personalizing healthcare recommendations have a positive impact on changes in lifestyle habits. However, research in this area has demonstrated conflicting findings. We provide a scientific and theoretical basis to support a proposed expansion of the TPB to include personalization and call to action personalized healthcare behaviour change researchers to test this expansion. Specific recommendations for study designs are included.

2.1.2 Background

The ‘Theory of Reasoned Action’, developed in the late 1960s, focused on attitudes and subjective norms as key predictors of human behaviour. In 1991, Ajzen published a seminal text in *Organizational Behavior and Human Decision Processes* where he proposed an important expansion of Ajzen and Fishbein’s ‘Theory of Reasoned Action’ (Ajzen 1991). He coined this new expanded theory, the ‘Theory of Planned Behaviour’ (TPB; see Figure 2.2) (Ajzen 1991).

The TPB posits that there are three main factors contributing to one’s *intention* to perform a behaviour, as well as the resulting *actual* behaviour. These three independent factors

include: attitudes, subjective norms and perceived behavioural control (Figure 2.2). The reasoned action approach (RAA) (Fishbein and Ajzen 2010) further breaks down these main categories into more descriptive subcategories. Attitudes can be classified as either experiential attitudes or instrumental attitudes. The former refers to affective attitudes such as pleasant–unpleasant, whereas the latter refers to cognitive attitudes such as health–unhealthy (Mceachan et al. 2016). Subjective norms refer to perceived social pressures to perform a behaviour, as well as the individual’s weighting on the importance of the opinions of others, which leads to behavioural intention through social reward/punishment. This is referred to as the subcategory of injunctive norms. Descriptive norms is the second subcategory for this key construct, and simply refers to the perceived behaviours of others (Mceachan et al. 2016). Perceived behavioural control refers to the perceived extent to which an individual has access to the appropriate resources and opportunities to perform a given behaviour and comprises the subcategories of capacity and autonomy. Capacity refers to the perceived ease/difficulty of a given behaviour, whereas autonomy refers to one’s perception of control over a given behaviour (Mceachan et al. 2016). An individual’s intention (motivation) to perform a behaviour is central to the TPB and can be influenced by these three independent factors and six related subcategories (Ajzen 1991; Fishbein and Ajzen 2010; Mceachan et al. 2016). Overall, the TPB/RAA identifies key proximal determinants of behaviour change, which should be considered in intervention studies aimed toward assessing behaviour change.

Ajzen’s work has been distinguished as having the highest scientific impact score of all Canadian and American social psychology research (Ajzen 2011). Meta-analyses have found that the TPB can be used to predict behaviours from behavioural intention or perceived behavioural

control with mean correlations ranging from 0.4 to 0.53 (Rivis and Sheeran 2003; Armitage and Conner 2001). Meta-analyses have further found that attitudes, subjective norms and/or perceived behavioural control can be used to predict intentions with mean multiple correlations ranging from 0.59 to 0.66 (Rivis and Sheeran 2003; Armitage and Conner 2001; Cheung and Chan 2000; McEachan et al. 2011; Notani 1998; Schulze and Wittmann 2003). Moreover, with the exception of autonomy, all subcategories of the RAA (outlined above) were found to be significant predictors of behavioural intention in recently completed regression analyses (Mceachan et al. 2016). Meta-analyses of the TPB in relation to specific health-related behaviours including alcohol consumption, diet, sexual health behaviours and treatment adherence in chronic illness have also been recently conducted (Cooke et al. 2016; Andrew et al. 2016; Rich et al. 2015; Mcdermott et al. 2015). Notably, the vast majority of these meta-analyses consistently demonstrated medium to large associations between the key constructs of the TPB and behavioural intention as well as actual behaviour engagement, with the exception of treatment adherence in chronic illness whereby intention-behaviour effect sizes were small (Cooke et al. 2016; Andrew et al. 2016; Rich et al. 2015; Mcdermott et al. 2015). While the TPB has proven to be a strong predictor of behaviour change, and is widely used by behaviour change researchers, it is clear that there are other factors contributing to behaviour change that have not yet been identified and validated within the context of this theory.

With recent advances in personalized healthcare technology, there has been a considerable increase in research pertaining to personalization of healthcare information and recommendations. Personalized healthcare, for the purposes of this paper, refers to healthcare information and recommendations, based on an individual's blood work results and/or individual

genetic profile. Several prominent researchers in the field of personalized healthcare suggest that individualizing lifestyle recommendations based on genetics or blood work could have a favorable impact on motivation (behavioural intention) and behaviour change (Nielsen, Shih, and El-Sohemy 2014; Nielsen and El-Sohemy 2014; Celis-Morales et al. 2015). To date, changes in several behaviours have been studied in personalized healthcare research including alcohol, nutrition, physical activity, smoking and health-screening behaviours (Nielsen and El-Sohemy 2014; Hendershot et al. 2010; Marsaux et al. 2016; Hishida et al. 2010; Bloss, Schork, and Topol 2011; Roke et al. 2017). Despite the widespread validation and acceptance of the TPB among academics, the use of this theory in personalized healthcare research is lacking. Notably, a PubMed search of ([‘Theory of Planned Behavior’ AND ‘personaliz*’ AND ‘health’] OR [‘Theory of Planned Behavior’ AND ‘personalis*’ AND ‘health’] OR [‘Theory of Planned Behaviour’ AND ‘personaliz*’ AND ‘health’] OR [‘Theory of Planned Behaviour’ AND ‘personalis*’ AND ‘health’]), conducted in April 2017 yielded only two results, neither of which would be considered personalized healthcare research (Middlemass et al. 2012; Denison et al. 2015).

Based on the current state of knowledge pertaining to behaviour change and personalized healthcare, this paper calls to action PHBC researchers for the incorporation of the TPB into scientific research methods. Furthermore, this paper is the first of its kind to propose a potential expansion of the TPB, based on *personalization*. It is recommended that this expansion be tested in robust personalized healthcare research to determine if the TPB should be revised to incorporate personalization as a significant predictor of behavioural intention and actual behaviour, alongside attitudes, subjective norms and perceived behavioural control. In particular,

within the TPB, it is hypothesized that personalization will have a significant impact on attitudes and subjective norms (Figure 2.2).

2.1.3 Attitudes Towards Personalized Healthcare

Prior to delving further into PHBC research conducted to date, it is important to understand the attitudes of healthcare professionals, students in post-secondary health programs and consumers toward personalized healthcare, as these individuals will largely affect the uptake and acceptability of personalized healthcare in society. Most studies assessing attitudes toward personalized healthcare have focused on personalization based on genotyping.

A recent randomized clinical trial found that consumers had favorable attitudes toward participating in genetic testing for personalized healthcare, and those who underwent genetic testing were more likely to recommend it to friends and family (Kattel et al. 2017). Another recent study found that ‘perceived personalization benefit’ played a larger role in consumers’ intention to utilize personalized nutrition services than ‘perceived personalization risk’ suggesting that attitudes toward personalized healthcare based on genetics were overall positive (Berezowska et al. 2014). Additionally, a review article concluded that extensive research has demonstrated consumers’ keen interest to undergo genetic testing for personalized healthcare (Gibney and Walsh 2013). Given these findings, it is not surprising that significant economic growth of genetic testing has been predicted (Vickery and Cotugna 2005).

For healthcare professionals and students in health programs (many of whom will become healthcare professionals), attitudes have been variable with some expressing skepticism

and others expressing more positive attitudes toward genetic testing (Bouwman, Molder, and Hiddink 2009; Collins et al. 2013; Cormier et al. 2014; Horne, Madill, and O'Connor 2016). Overall, the availability of genetic testing in clinical practice is growing rapidly (Downie, Donoghue, and Stutterd 2017). With increasing uptake in clinical practice, the question of whether or not personalized healthcare impacts behaviour change is an important one to consider and is proving to be a priority area of research, with at least four review articles published on this topic over the past year alone (O'Donovan et al. 2017; Li et al. 2016; Hollands et al. 2016; French et al. 2017).

2.1.4 Current State of PHBC Research

Over the past decade, there has been a considerable amount of research conducted examining the impact of providing personalized healthcare recommendations on motivation and behaviour change. One of the largest projects currently underway is the 'Food4Me' project, which commenced its research activities in 2011. 'Food4Me' is a EU funded, large-scale research initiative, which aims to improve scientific knowledge pertaining to personalized healthcare, including motivation and behaviour change resulting from the provision of personalized nutrition and physical activity recommendations (Food4Me 2011). We reviewed the 29 peer-reviewed publications posted on the 'Food4Me' website (Food4Me n.d.) and found eight unique articles pertaining to the impact of personalized nutrition and physical activity recommendations on one or more of the following components of the TPB: attitudes and behaviour (Berezowska et al. 2014; Marsaux et al. 2016; Fallaize et al. 2013; Marsaux et al. 2015; Poinhos et al. 2014; Stewart-Knox et al. 2013; Stewart-Knox et al. 2009). However, none of the eight manuscripts specifically referred to the TPB, therefore, it is possible that one or more

components of the TPB were included unintentionally. No study from the ‘Food4Me’ project was designed based upon the TPB specifically.

Despite the lack of consideration of the TPB in the ‘Food4Me’ project and other personalized healthcare research projects assessing behaviour change, several components of the TPB can be found within PHBC research methods. Of the 29 articles published on the ‘Food4Me’ website, five studies assessed attitudes related to genetic testing and personalized healthcare, which tended to be positive (Berezowska et al. 2014; Fallaize et al. 2013; Poinhos et al. 2014; B. Stewart-Knox et al. 2013; Stewart-Knox et al. 2009). Two ‘Food4Me’ studies analyzed behaviour change, and each article found no significant impact on behaviour change with the provision of personalized healthcare reports and/or recommendations (Marsaux et al. 2016, 2015). While these studies did not find an impact on behaviour change, a recent randomized controlled trial (RCT) found significantly greater reductions in sodium intake when individuals were provided with personalized nutrition advice based on genetics, in comparison to those who were provided with population-based health recommendations (Nielsen and El-Sohemy 2014). Similarly, a study assessing changes in lifestyle following a genetic-based hypertension intervention also found significant changes in sodium intake among participants provided with DNA-based advice (Taylor and Wu 2010). Furthermore, an RCT found that the provision of personalized nutrition advice enhances motivation (behavioural intention) to change lifestyle behaviours (Nielsen and El-Sohemy 2014).

The inconsistent findings of PHBC research suggest that there are confounding factors influencing behaviour change, which are not being considered in the scientific methods. This is

likely due to the minimal use of validated theoretical underpinnings to inform study design. While the current body of knowledge appears to have unintentionally addressed one or more components of the TPB, a more comprehensive and intentional approach to the incorporation of the TPB in study design and methodology is required. This would allow for an improved understanding of the extent to which personalized healthcare recommendations, based on genetics and/or blood work, may affect behavioural intention and actual behaviour performance. Studies assessing motivation and behaviour change should include an analysis of attitudes, subjective norms, perceived behavioural control and actual behavioural control to determine how these factors may alter study outcomes.

2.1.5 A Call to Action for PHBC Research

It is well known that nutrition, physical activity and wellness strategies can be used to improve health and well-being and decrease the risk for chronic disease, but despite this knowledge, rates of obesity and chronic disease continue to climb (Arena et al. 2017). Behaviour change (or lack thereof) is a key contributor to the increasing rates of obesity and chronic disease despite our increased knowledge of methods to improve health through lifestyle modification (Arena et al. 2017). As such, innovative strategies are needed to enhance both intention to change lifestyle habits as well as actual change in lifestyle habits, and personalized healthcare is garnering considerable attention as an innovative healthcare strategy to help combat current global health crises. This paper calls to action PHBC researchers to test the potential expansion of the TPB to include ‘personalization’ as a possible novel component of the TPB (Figure 2.2). We propose that personalization may have a significant impact on attitudes and normative beliefs and therefore has the potential to significantly influence behaviours.

In order to incorporate the TPB into personalized healthcare research, it is first important to understand the different components of the theory, including attention to key constructs such as behavioural beliefs, attitude toward the behaviour, normative beliefs, subjective norms, control beliefs, perceived behavioural control, actual behavioural control, intention and behaviour (Figure 2.1). In brief, in the TPB, behavioural beliefs are seen to influence attitudes, normative beliefs to influence subjective norms and control beliefs to influence perceived behavioural control. Attitudes, subjective norms and perceived behavioural control all have a significant impact on one's behavioural intention and actual behaviour. However, it is also important to note that factors influencing actual behavioural control, such as the social determinants of health (Public Health Agency of Canada, 2016), strongly predict behaviours regardless of attitudes and subjective norms. Describing each component of the TBP in detail is beyond the scope of this paper and has been accomplished elsewhere (Ajzen 1991, 2006; Fishbein and Ajzen 2010). Several key resources and seminal texts provide a solid background for deepening understanding of the TPB (Ajzen 1991, 2006; Fishbein and Ajzen 2010).

We contend that this theoretical background could be translated into a more practical application to inform the development of assessment tools with theoretical and practical utility for research in the field. Instructions on completing a TPB questionnaire are available on the University of Massachusetts website (Ajzen 2006). This resource provides a step-by-step guideline to develop a TPB questionnaire, which includes defining the behaviour, specifying the research population, formulating items for direct measures and administering a pilot questionnaire. Sample TPB questionnaires are also available on the website and can be used for

guidance in the development of assessment tools to be used in the field (Ajzen 2006). Ajzen suggests that multiple regression or structural equation modeling analyses can be used to establish the extent to which attitudes, subjective norms and perceived behavioural control may have contributed to intentions. These methods of statistical analyses can also be used to determine the extent to which intentions and perceived behavioural control may have predicted actual behaviour(s) (Ajzen 2006).

To test the proposed addition of personalization within the TPB, we further advise that an assessment of attitudes toward genetic testing and/or blood work (depending on the method of personalization within the study) be included within the TPB questionnaire. Attitudes toward personalization can be measured on a Likert scale, similar to other questions on Ajzen's sample TPB questionnaire (Ajzen 2006). Ideally, a randomized clinical intervention trial study design could be used for this research, whereby participants are randomly selected to either receive personalized healthcare advice or general population-based healthcare advice. While blinding typically enhances the quality of an RCT, for PHBC research blinding may actually diminish the quality of the results; knowing that one's recommendations are based on their genetics or blood work could influence several aspects of the TPB including behavioural beliefs, attitudes, normative beliefs and subjective norms, thus impacting behavioural intention and behaviours. Therefore, we do not recommend the blinding of participants. Through the use of repeated measures analysis of variance and multiple regression, comparisons can then be made within and between groups to determine the extent to which personalized healthcare advice may have impacted attitudes and subjective norms, and thus behavioural intention as well as actual behaviour. To further enhance study design, consideration of the social determinants of health

(Public Health Agency of Canada, 2016) could additionally be incorporated within the study questionnaire to determine if factors such as income, education level, housing and employment, for example, influenced perceived behavioural control and thus behavioural intention and actual behaviour.

In addition to testing the proposed expansion of the TPB, several hypotheses could be tested in PHBC research, which incorporate the key constructs of the TPB. Perhaps receiving genetic testing or blood work results could lead to more positive attitudes toward a behaviour such as exercising. This may translate into greater intentions to participate in physical activity and actual engagement in physical activity. Or rather, perhaps personalized healthcare only has a significant impact on behaviour change in those with a baseline negative attitude toward the behaviour of interest; personalized healthcare may significantly alter attitudes and thus lead to greater behaviour change but only in those with baseline negative attitudes. These hypotheses have yet to be tested in PHBC research, and should be tested in future studies to advance our understanding of determinants of behaviour change in relation to personalized healthcare.

Furthermore, it would be beneficial to conduct a systematic review of PHBC research with a focus on assessing how the (likely unintentional) incorporation of components of the TPB may have impacted the findings of studies conducted to date. While several reviews have been published on the topic of behaviour change resulting from personalized healthcare, no review has evaluated studies within the context of the TPB (O'Donovan et al. 2017; Li et al. 2016; Hollands et al. 2016; French et al. 2017). Based on the information presented in this paper, it is evident that there is a need for researchers in the field of personalized healthcare and behaviour change

to incorporate the TPB into their work as a key theoretical underpinning of study design. Past research in other disciplines can be used to guide research methods (McEachan et al. 2011; Cooke et al. 2016; Andrew et al. 2016; Rich et al. 2015; Mcdermott et al. 2015).

2.1.6 Conclusion

The lack of consideration of validated theory in the design of studies assessing PHBC can have a significant impact on the results, as these studies fail to consider key factors that have been shown to affect behaviour change. This paper calls to action PHBC researchers to incorporate the TPB in their methods in order to provide a more accurate and thorough assessment of whether personalized healthcare advice, based on genetics and/or blood work, has a significant impact on behaviour change. This paper suggests that the next expansion of Ajzen's TPB may be the addition of personalization (Figure 2.2). Future research should seek to test the addition of personalization within the TPB through robust research methods such as RCTs. This call to action is timely in light of the increased focus on innovative healthcare strategies to address the myriad of health concerns arising globally, whereby interventions facilitating behaviour change could have a significant impact on global health.

2.1.7 Future Perspective

Based on the current body of knowledge, in addition to the authors' clinical and academic experience, we predict that testing the proposed expansion of the TPB will yield positive findings toward personalization of healthcare recommendations significantly impacting behaviour change within some limits. While we predict that personalization will significantly influence behaviour change, the ability to change one's behaviour must still remain within the

individual's actual and perceived behavioural control. In addition, we predict that the method of communicating genetic information will play into one's likelihood of changing, whereby the use of gain-framed messages and actionable advice may have a more favorable impact on one's likelihood of altering their lifestyle habits. Comprehension of the results of personalized healthcare testing and recommendations will also play into likelihood of behaviour change. As an example, the results of a nutrigenomics test may inform an individual that they have an increased risk for cardiovascular disease, but by limiting caffeine intake this elevated risk could be reduced. This personalized genetic result and consequent gain-framed, actionable recommendation will likely alter one's attitudes toward changing the behaviour. If the individual was to inform their family and/or friends about the results of the genetic test, it is likely that they would feel pressure from their social circle to abide by the recommendation. While personalization of healthcare will likely impact attitudes and subjective norms, it is unlikely that it will be a strong enough force to impact perceived and actual behavioural control. If the pressures of work and home life do not allow for adequate sleep and lead to increased stress, one may continue to consume a high quantity of caffeine, regardless of their genetic test. Thus, perceived and actual behavioural controls remain unchanged. It is for this reason that Figure 2.2 depicts an influence of personalization on attitudes and subjective norms, but not perceived behavioural control. Considering the above-mentioned points, if the individual was sleeping adequately and consumed caffeine for the simple enjoyment of the taste of the caffeinated beverages, the results of the genetic test would likely motivate them to stop drinking caffeinated beverages.

It is further predicted based on clinical experience and our review of the literature that specific aspects of personalized healthcare interventions facilitate behaviour change to a greater extent than others. For example, providing genetic testing through a trained healthcare professional rather than using direct-to-consumer methods will likely facilitate behaviour change to a greater extent. Moreover, providing actionable recommendations rather than disease risk estimates is likely to result in greater behaviour change. We posit that future research will be able to identify similar factors in PHBC research that have been shown to facilitate behaviour change and will use this knowledge to design an algorithm for effective personalized healthcare results and recommendations. To our knowledge, this hypothesis has yet to be tested in scientific research.

Overall, we predict that personalization of healthcare will be added to the TPB as a key factor influencing attitudes and subjective norms and thus intention and behaviour. Achieving behaviour change when it comes to lifestyle habits is arguably one of the most challenging aspects of clinical practice. We further predict that the field of genetic testing will continue to grow as more robust PHBC research is conducted and published. These predictions stem from clinical and academic experience, our review of the literature and theoretical perspectives.

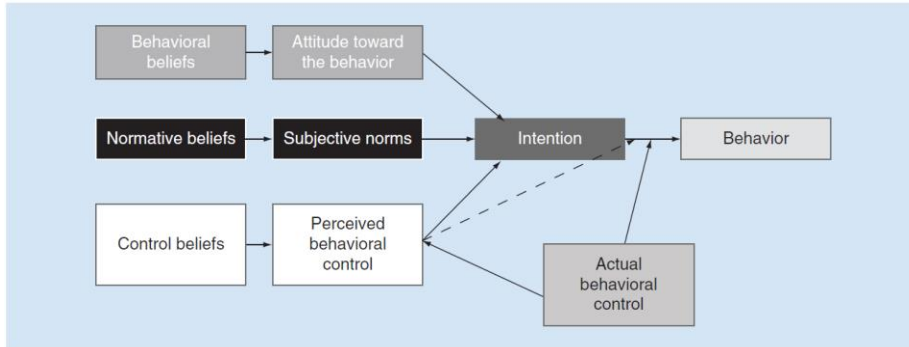
Financial & Competing Interests Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options,

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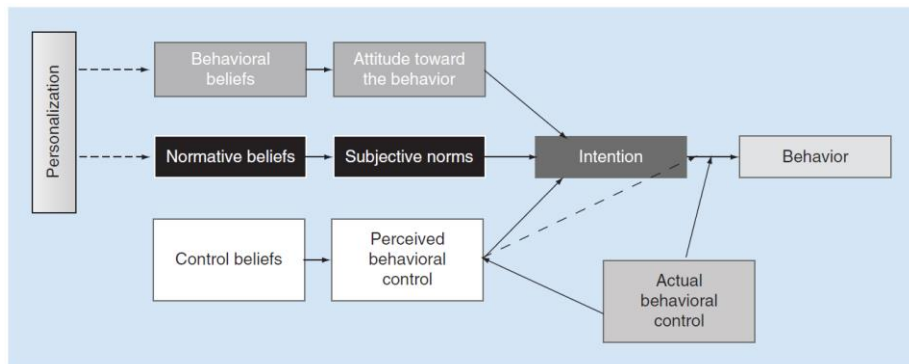
2.1.8 Figures and Executive Summary

Figure 2.1: The ‘Theory of Planned Behaviour’



‘Theory of Planned Behavior’. Solid arrows indicate a direct relationship. The dashed arrow indicates a potential direct relationship, which warrants further investigation. Adapted with permission from [2].

Figure 2.2: Personalization: A proposed expansion of the ‘Theory of Planned Behaviour’



Personalization: a proposed expansion of the ‘Theory of Planned Behavior’. Solid arrows indicate a direct relationship. Dashed arrows indicate a potential direct relationship, which warrants further investigation. The present manuscript proposes ‘personalization’ as a potential future expansion of the ‘Theory of Planned Behavior’. Adapted with permission from [2].

Figure 2.3: Executive summary

Executive summary

The ‘Theory of Planned Behaviour’ (TPB)

- The TPB is a widely accepted and validated behaviour change theory, which suggests that there are three main factors contributing to behaviour change: attitudes, subjective norms and behavioural control (perceived and actual).

Consideration of theory in personalized healthcare behaviour change research

- To date, consideration of theory (especially the TPB) is limited in personalized healthcare behaviour change (PHBC) research.
- This lack of consideration of theory helps to explain the heterogeneity of current PHBC research findings.

Predictions for the future

- We predict that robust research will demonstrate that personalization will significantly influence behaviour change and thus personalization will be added to the TPB.
- The impact of personalization on behaviour change will be limited to a significant influence on attitudes and subjective norms.

Call to action

- This paper calls to action PHBC researchers to test the proposed expansion of the TPB to include personalization.

Conclusion

- Present research demonstrates a lack of consideration of theoretical underpinnings to inform study design, yet the results of several articles demonstrate that personalization is likely a key component to be added to behaviour change theory.
- Future research should seek to inform study design using the TPB and determine the extent to which personalization influences key components of the TPB.

CHAPTER 3: A SYSTEMATIC REVIEW OF GENETIC TESTING AND LIFESTYLE BEHAVIOUR CHANGE

As published* in *Lifestyle Genomics*:

Horne J, Madill J, O'Connor C, Shelley J, Gilliland J. 2018 "A systematic review of genetic testing and lifestyle behaviour change: Are we using high-quality genetic interventions and considering behaviour change theory?" *Lifestyle Genomics* 11(1): 49-63.

*Reference formatting, table numbers and figure numbers have been revised for consistency with the present dissertation.

3.1 Title: A systematic review of genetic testing and lifestyle behaviour change: Are we using high-quality genetic interventions and considering behaviour change theory?

3.1.1 Abstract

Background: Studying the impact of genetic testing interventions on lifestyle behaviour change has been a priority area of research in recent years. Substantial heterogeneity exists in the results and conclusions of this literature, which has yet to be explained using validated behaviour change theory and an assessment of the quality of genetic interventions. The theory of planned behaviour (TPB) helps to explain key contributors to behaviour change. It has been hypothesized that personalization could be added to this theory to help predict changes in health behaviours.

Purpose: This systematic review provides a detailed, comprehensive identification, assessment, and summary of primary research articles pertaining to lifestyle behaviour change (nutrition, physical activity, sleep, and smoking) resulting from genetic testing interventions. The present review further aims to provide in-depth analyses of studies conducted to date within the context of the TPB and the quality of genetic interventions provided to participants while aiming to determine whether or not genetic testing facilitates changes in lifestyle habits. This review is timely in light of a recently published “call-to-action” paper, highlighting the need to incorporate the TPB into personalized healthcare behaviour change research.

Methods: Three bibliographic databases, one key website, and article reference lists were searched for relevant primary research articles. The PRISMA Flow Diagram and PRISMA Checklist were used to guide the search strategy and manuscript preparation. Out of 32,783 titles retrieved, 26 studies met the inclusion criteria. Three quality assessments were conducted and

included: (1) risk of bias, (2) quality of genetic interventions, and (3) consideration of theoretical underpinnings – primarily the TPB.

Results: Risk of bias in studies was overall rated to be “fair.” Consideration of the TPB was “poor,” with no study making reference to this validated theory. While some studies ($n = 11$; 42%) made reference to other behaviour change theories, these theories were generally mentioned briefly, and were not thoroughly incorporated into the study design or analyses. The genetic interventions provided to participants were overall of “poor” quality. However, a separate analysis of studies using controlled intervention research methods demonstrated the use of higher-quality genetic interventions (overall rated to be “fair”). The provision of actionable recommendations informed by genetic testing was more likely to facilitate behaviour change than the provision of genetic information without actionable lifestyle recommendations. Several studies of good quality demonstrated changes in lifestyle habits arising from the provision of genetic interventions. The most promising lifestyle changes were changes in nutrition.

Conclusions: It is possible to facilitate behaviour change using genetic testing as the catalyst. Future research should ensure that high-quality genetic interventions are provided to participants, and should consider validated theories such as the TPB in their study design and analyses. Further recommendations for future research are provided.

3.1.2 Background

Since decoding the entire human genome in 2003 (National Institutes of Health 2015), there have been considerable advances in genetic research and the clinical utility of genetic testing. The terms *nutrigenomics* or *nutritional genomics* describe the study of how genes

interact with the foods, beverages, and supplements consumed to influence health outcomes (Gibney and Walsh 2013). Currently, there are no generally accepted or standardized terms describing the study of how genes interact with physical activity, sleep, or smoking to influence subsequent health outcomes. These gene-lifestyle interactions can be referred to using the broad term *lifestyle genomics*. Despite the lack of a standardized terminology, research pertaining to nutrigenomics and other emerging genomic sciences continues to advance. Specifically, behaviour change guided by genetic testing results or other personalized healthcare information is emerging as a priority area of research, with several reviews on this topic published in recent years (Hollands et al. 2016; French et al. 2017; O'Donovan et al. 2017).

Genetic testing is increasingly used in clinical practice to provide personalized information and recommendations about health risks and lifestyle habits at a relatively low cost (Caulfield and McGuire 2012). However, studies assessing whether or not genetic testing promotes changes in lifestyle habits have conflicting findings (Egglestone, Morris, and O'Brien 2013; Hietaranta-Luoma et al. 2014; Nielsen and El-Soheby 2014; Marsaux et al. 2016). Given that chronic diseases can often be managed through lifestyle interventions alone, or a combination of lifestyle interventions and medication (Knowler et al. 2002; Roth et al. 2017; CDC 2016), genetic tests providing personalized lifestyle recommendations hold considerable promise.

Behaviour change is a multifactorial, complex area of research and clinical practice. The theory of planned behaviour (TPB) is arguably the most widely accepted behaviour change theory in academia (Ajzen 2011). This theory posits that attitudes, subjective norms, and

perceived behavioural control are key constructs that can be used to predict behaviours. Actual behavioural control, which typically refers to factors such as income, educational level, and other social determinants of health for the purposes of healthcare research, further contributes to one's likelihood of performing a behaviour (Ajzen 2011, 1991). It is important for genetic testing behaviour change research to consider validated theories in order to control for a number of confounding factors that could significantly influence the results of a study.

Despite the complexity of behaviour change, genetic testing behaviour change studies do not often use any theoretical underpinnings to inform their study design, or for the analysis and interpretation of their data. This is concerning, as it implies that these studies did not report whether they considered the many confounding factors impacting behaviour change, including but not limited to attitudes, subjective norms, and perceived and actual behavioural control (Ajzen 2006). Consideration of such factors could help explain why some studies conclude that genetic testing facilitates health behaviour change, while others conclude that it does not. For example, a study may find that genetic testing has a positive influence on attitudes and subjective norms, but it is only when behavioural control is high (for example, with a higher income or education level) that genetic testing facilitates health behaviour change. The importance of such considerations has been highlighted in a recent call to action for personalized healthcare behaviour change research, which recommended the completion of a systematic review with perspective from the TPB as an important next step in advancing knowledge in personalized healthcare behaviour change literature (Horne, Madill, and Gilliland 2017).

Systematic reviews and meta-analyses are typically considered the highest quality of scientific evidence and, notably, often guide clinical practice (West et al. 2002). When it comes to systematic reviews assessing behaviour change as a result of genetic testing interventions, a simple risk-of-bias assessment is not sufficient to develop the most meaningful conclusions; yet it is often the only quality assessment conducted in this type of work (Hollands et al. 2016; French et al. 2017; Li et al. 2016). It is further important to consider the delivery of a health/genetic intervention (such as considering the provision of disease risk estimates vs. actionable behaviour change recommendations) and to consider behaviour change theories (Horne, Madill, and Gilliland 2017). Therefore, the development of more comprehensive methods for reviewing and compiling the primary research articles conducted to date related to genetic testing behaviour change is needed.

The present review provides an in-depth analysis and summary of the current body of knowledge, thus presenting the most robust and comprehensive review of genetic testing behaviour change research conducted to date. Overall, the purpose of this comprehensive systematic review is to use these novel perspectives to answer the following research questions: Are we considering validated behaviour change theory (particularly the TPB) in genetic testing behaviour change research? Are we using high-quality genetic interventions in genetic testing behaviour change research? What is the impact of genetic testing on behaviour change pertaining to four lifestyle factors: nutrition, physical activity, smoking, and/or sleep? These four lifestyle factors were chosen as they have all been shown to have a significant impact on chronic disease management (Audrain et al. 1997; Dean and Söderlund 2015; Walker et al. 2010; Zhu et al. 2017; Wu, Zhai, and Zhang 2014). Behaviour change is challenging, and it is important to find

strategies that effectively facilitate beneficial lifestyle changes related to nutrition, physical activity, smoking, and/or sleep. Genetic tests may provide information on disease risk, which can be mitigated through specific alterations in lifestyle habits such as improving nutrition, optimizing physical activity habits, quitting smoking or smoking less, and engaging in healthful sleep-related behaviours.

3.1.3 Methods

Search Strategy

The systematic review protocol that was used to guide this review is detailed elsewhere (Petticrew and Roberts 2006). In brief, the search strategy was guided by the PRISMA Flow Diagram (Moher et al. 2009). From February to April 2017, the following databases were searched for relevant articles: *PubMed*, *Scopus*, and *Nursing and Allied Health*. Publications posted on the Food4Me website (Food4Me n.d.), as well as the reference lists of 4 recent review articles published on topics similar to those of the present review (Hollands et al. 2016; O'Donovan et al. 2017; French et al. 2017; Li et al. 2016), were also screened for articles relevant to the research questions. After the number of records had been condensed through title and abstract screening, the full-text articles were reviewed to assess each one for eligibility according to predetermined inclusion and exclusion criteria. The complete search terms and search strategy were developed and approved by all authors, and they are detailed in Figure 3.1 and Figure 3.2, respectively.

Selection Criteria

To capture a comprehensive summary of the research conducted to date, the present review was not limited to a single, specific study design. We included primary research articles published in English in peer-reviewed journals from all years which assessed the impact of genetic testing on one or more of the four lifestyle habits of interest (nutrition, physical activity, smoking, and/or sleep). Both qualitative and quantitative studies were included. Studies were excluded if there was not at least one group of participants who underwent genetic testing and/or if the study did not provide follow-up data related to one or more of the lifestyle habits of interest after the participants had received the results of a genetic test. One author (JH) completed data extraction using piloted forms (The Cochrane Collaboration 2011), which were tested on 4 studies, reviewed by another author (JG), and modified during the piloting process by two authors (JH and JG).

Analysis

The National Institutes of Health (NIH) Study Quality Assessment Tools were used to conduct a risk-of-bias assessment in quantitative research (National Institutes of Health n.d.). The Critical Appraisal Skills Programme Qualitative Research Checklist (Critical Appraisal Skills Programme 2017) was used to assess risk of bias in qualitative research. The quality of the genetic intervention was also assessed. To our knowledge, there currently is no tool available for assessing the quality of a genetic intervention. As such, we developed the first assessment tool for evaluating the quality of a genetic intervention provided to subjects (Supplementary Table 3.4). The quality rating and general outline for this new tool was based on the format of the NIH Study Quality Assessment Tools (National Institutes of Health n.d.). The questions included were developed from a review of previously identified critiques and concerns related to genetic

testing and health risk messages (Nielsen and El-Sohehy 2014; Fenech 2008; Katsanis and Katsanis 2016; Witte, Meyer, and Martell 2001; Hall, Weinman, and Marteau 2004; Legenthal et al. 1997; Bloss, Schork, and Topol 2011; Bloss et al. 2013; Ferguson and Barnett 2012).

Consideration of the main components of the TPB (attitudes towards a behaviour, subjective norms, behavioural control, and intention) (Ajzen 2006), as well as consideration of theory more generally, was assessed using deductive content analysis of the manuscripts (Elo and Kyngäs 2008). The deductive content analyses of consideration of the TPB and its key components in each study was then translated into a rating, based on the rating system generated in the NIH Study Quality Assessment Tools, whereby “good” indicates a robust consideration of the main components of the TPB, “fair” indicates intermediate consideration of the main TPB components, and “poor” represents little to no consideration of the main TPB components. An overall quality score was assigned to each article based on a point system, where “good” ratings were awarded 3 points, “fair” ratings were awarded 2 points, and “poor” ratings were awarded 1 point. The maximum possible overall quality rating was 9/9, upon consideration of all three assessments.

3.1.4 Results

The comprehensive electronic literature search returned a total of 32,783 results, with 26 studies meeting the predetermined inclusion criteria. In these 26 studies, the following outcomes were assessed: nutrition ($n = 18$), physical activity ($n = 16$), and smoking ($n = 12$) (Figure 3.2), with 14 articles assessing more than one lifestyle habit of interest to this review. The vast majority of the literature has been published over the past decade, with a large spike in

publications recently in 2015 (Supplementary Figure 3.3). Consistent with recommendations for systematic reviews (Petticrew and Roberts 2006), our review was analytic and descriptive in nature and included: (a) a tabulation of the study characteristics and findings (Table 3.1); (b) a thorough and robust quality assessment (Table 3.2); and (c) a narrative synthesis. Research conducted thus far has focused on a variety of genes, as outlined in (Table 3.3). It is concerning to note that 12 studies (46%) did not report whether or not the authors had a conflict of interest (COI). The vast majority of the literature has focused on genetic testing for determining the risk of developing certain diseases or conditions (88%; $n = 23$), while only a small number of studies have focused on nutrient metabolism (12%; $n = 3$), which indirectly affects the risk of developing diseases or conditions (Siscovick et al. 2017; Cornelis et al. 2006; Hietaranta-Luoma et al. 2014). The three separate quality assessments completed on each study are summarized in Table 3.2. Risk of bias was overall rated as “fair.”

Are We Using High-Quality Genetic Interventions?

Although some risk of bias is apparent, the ratings for the quality of the genetic interventions were more concerning, since overall the ratings were “poor” and only 6 of the 26 studies (23%) received a “good” rating. Thus, it is clear that the studies did not provide high-quality interventions to their participants, which helps to explain why the majority of studies did not report that genetic interventions facilitated lifestyle behaviour change.

Are We Considering Validated Behaviour Change Theory?

Consideration of the TPB and/or one or more of the theory’s three key components had made overall ratings of “poor.” The deductive content analyses of the theoretical underpinnings mentioned in the studies are summarized in Supplementary Table 3.5. Fifteen studies (58%) did not make reference to any specific behaviour change theory or model within the text. When a

theory was included, it was generally only briefly mentioned and was not thoroughly incorporated into the study design, or expanded upon in the discussion. No study specifically referred to the TPB, suggesting that researchers have yet to consider this important theory in their study design or interpretation of findings. Several studies incidentally considered certain aspects of the TPB in the development of their scientific methods or within the text, such as the consideration of *behavioural control* by assessing one or more social determinants of health, such as income (Public Health Agency of Canada 2016). Overall, behaviour change theory is not being thoroughly incorporated into genetic testing behaviour change research.

Does Genetic Testing Impact Changes in Nutrition, Physical Activity, and/or Smoking Behaviour?

Overall. Given the heterogeneity of the literature and complexity of genetics-based behaviour change research, a cause-and-effect relationship between genetic testing and health behaviour change cannot be identified. Notably, it appears that it is unlikely that genetic testing has a “fatalistic” or negative impact on health behaviour change related to nutrition, physical activity, and smoking, since no study found that genetic testing negatively impacted the health behaviours of interest to the present review. Interestingly, 78% of the studies with health-promoting lifestyle behaviour change findings provided their participants with a genetics-based intervention that included actionable health behaviour recommendations. Examples of actionable recommendations provided to participants for each lifestyle factor included recommendations to reduce sodium intake (nutrition) (Nielsen and El-Sohemy 2014), incorporate exercise into one’s daily routine (physical activity) (Meisel et al. 2015), and quit smoking (smoking) (Audrain et al. 1997). Conversely, only 50% of the studies with null findings provided their participants with actionable health behaviour recommendations. Since an overarching cause-and-effect statement

about the impact of genetic testing on behaviour change cannot be made, a best evidence synthesis is provided below.

Nutrition. Of the 18 articles that assessed a nutrition-related outcome, 6 (33%) showed a positive, health-promoting effect of genetic testing on behaviour change at one or more time points (both short term and long term, as further outlined in Tables 3.1 and 3.2). While this does not indicate that the majority of studies positively influenced nutrition, multiple studies of good quality ($n = 6$) have demonstrated that it is possible to facilitate healthier nutritional behaviours through the provision of genetic testing (Egglestone, Morris, and O'Brien 2013; Hietaranta-Luoma et al. 2014; Nielsen and El-Sohehy 2014; Voils et al. 2015; Kaufman et al. 2012; Vernarelli et al. 2010).

Physical Activity. The provision of genetic testing to facilitate physical activity behaviour change does not appear to be as promising as behaviour change related to nutrition. Of the 16 studies that analyzed physical activity-related outcomes independently, only 2 (13%) found positive influences of genetic testing on physical activity (Egglestone, Morris, and O'Brien 2013; Kaufman et al. 2012), with follow-up periods ranging from 2 to 8 months in one study (Kaufman et al. 2012) and the periods not indicated in the other study (follow-up varied for each participant) (Egglestone, Morris, and O'Brien 2013). However, these articles rated poorly in their overall quality assessment, with "poor" to "fair" quality ratings of 3 (Egglestone, Morris, and O'Brien 2013) and 4 (Kaufman et al. 2012).

Smoking. Similar to nutrition, 4 (33%) of the 12 genetic intervention studies had a positive influence on smoking-related behaviours. However, improvements in smoking-related behaviours were generally only sustained over a short-term period. The overall quality of these studies was “fair.”

Sleep. It is clear that sleep is an understudied area of genetic testing and behaviour change research, since our comprehensive search did not yield a single study that assessed sleep (sleep quality, hours of sleep, etc.) as a behaviour change outcome.

Pooled Analyses. Two studies completed pooled analyses of changes in more than one lifestyle factor. Chao et al. did not find significant changes in nutrition or physical activity on their own, but when pooled together, there were significantly greater changes to nutrition and physical activity in the high-risk genetic testing group than in the non-risk and control groups (Chao et al. 2008). Additionally, in a pooled analysis of changes to nutrition, physical activity, or smoking, Egglestone et al. (Egglestone, Morris, and O’Brien 2013) found significant changes between the genetic testing group and the control group. However, their results should be interpreted with caution, as this study was awarded the lowest overall quality rating of 3 (Table 3.2).

Results from Controlled Intervention Trials

While it is important to be comprehensive and consider all studies conducted on the topic of interest regardless of the research methods chosen, controlled interventions should be further highlighted and reviewed separately from other study designs given that this is the highest possible level of evidence for the original research included in the present review.

In total, 15 controlled intervention trials have been conducted over the past two decades. Approximately half of these studies ($n = 7$; 47%) found significant changes in nutrition and/or physical activity or in smoking at 1–3 time points included in the study. Consistent with the overall analysis, the controlled interventions found that nutrition was the most promising area of behaviour change, followed by smoking (short-term only).

The genetic interventions in the controlled intervention trials overall ranked “fair,” demonstrating that in comparison to the result of the pooled analysis of all study designs, these studies provided their participants with higher-quality genetic interventions. This may help explain why 47% of the controlled intervention studies found significant changes in lifestyle habits resulting from the genetic intervention, compared to 36% of the studies using other study designs. The overall ranking of these studies was “fair,” with a mean rating of 5.6 out of the highest possible score of 9. Risk of bias overall was “fair” and consideration of the TPB was rated to be “poor,” which is consistent with the results of the analysis of all study designs combined.

3.1.5 Discussion

Given that decoding the entire human genome was the primary focus of genetic research until 2003 (National Institutes of Health 2015), it is not surprising to find that the majority of studies included in the present review were published after this time, with only 2 studies published before 2003. Since then, much greater focus has been placed on genetic testing behaviour change research pertaining to nutrition, physical activity, and smoking. However,

several studies included in the present review (46%) did not include a COI statement. Future research should ensure the inclusion of a COI statement given this concerning finding and given the increased emphasis in academia on the importance of considering COI in genetic testing and other research.

Improving one or more of the four lifestyle behaviours of interest to this review has been shown to have a beneficial effect on chronic disease management and general health and well-being (Dean and Söderlund 2015; Walker et al. 2010; B. Zhu et al. 2017; Wu, Zhai, and Zhang 2014). The present review indicated that improvements to smoking habits were promising in the short-term. This finding was consistent with that of a previously published systematic review of the impact of genetic notification on smoking cessation (de Viron et al. 2012).

While nutrition, physical activity, and smoking habits have been researched in multiple genetic intervention studies, sleep remains an understudied area of genetics and behaviour change. This is notable considering the substantial impact that sleep has on overall health and well-being. Current systematic reviews demonstrate a significant impact of sleep on cognition and emotion (Krause et al. 2017), glycemic control (Zhu et al. 2017), and overweight or obesity (Wu, Zhai, and Zhang 2014), to name a few. To our knowledge, little is known about the ability of sleep to modify genetic-associated health risks. Thus, future research should seek to first determine gene-sleep interactions that may influence health outcomes using methodologies similar to those of nutrigenomics research, as opposed to a genome-wide association study approach. Upon determining ways in which sleep may mitigate genetics-associated health risks,

future research should then seek to determine if genetic testing helps to motivate healthy sleep-related behaviours.

The considerable heterogeneity in studies (Tables 3.1 and 3.2) can be explained by a number of factors. Notably, the variation of statistical analyses between groups (i.e., genetic testing groups vs. control groups or high-risk genetic result groups vs. non-risk genetic result groups) would have impacted the findings and subsequent conclusions drawn. Consideration of theories in general to inform the study design was poor, and consideration of the TPB was absent, which further helps to explain the heterogeneity of findings, since several possible confounding factors were missed. Additionally, only 3 studies (Hietaranta-Luoma et al. 2014; Nielsen and El-Sohemy 2014; Roke et al. 2017) focused on nutrient metabolism. Therefore, a future focus is needed on genetic interventions related to nutrient metabolism and the subsequent disease risk through genetic testing of modifier genes (genetic risks that can be mitigated through specific lifestyle changes), rather than genetics-based disease risk estimates where there may be no known lifestyle modifications that can alter the genetic risk. It is possible that nutrition was the most promising lifestyle factor for promoting health behaviour change given that genetic testing of modifier genes typically leads to the provision of actionable recommendations [e.g., the recommendation to reduce sodium intake (Nielsen and El-Sohemy 2014)].

It is important to note that our risk-of-bias results are consistent with the previously published literature (Hollands et al. 2016; O'Donovan et al. 2017; French et al. 2017; Li et al. 2016), providing validation for the NIH quality assessment process completed in the current review. Effect sizes were not included in this review due to heterogeneity of the genetic

interventions and study designs of the included articles that would have introduced potential flaws in effect size calculations and any conclusions drawn from such calculations. For randomized controlled trials, effect sizes have recently been presented elsewhere (Hollands et al. 2016, although these should be interpreted with caution due to the significant heterogeneity of treatments (genetic interventions), measurements of outcomes, and populations studied. To our knowledge, we have developed and utilized the first quality assessment tool for evaluating and rating genetic interventions. Future research should seek to utilize this novel tool and significant contribution to the literature to assess the quality of genetic interventions in both primary research and systematic reviews. Furthermore, the components of this tool can be used in future genetic testing behaviour change study designs to improve the quality of genetic interventions provided to participants (Supplementary Table 3.4). Although the genetic intervention quality assessment was based on previously published robust research and critical commentaries (Nielsen and El-Sohemy 2014; Fenech 2008; Katsanis and Katsanis 2016; Witte, Meyer, and Martell 2001; Hall, Weinman, and Marteau 2004; Legenthal et al. 1997; Bloss, Schork, and Topol 2011; Bloss et al. 2013; Ferguson and Barnett 2012), assessing the quality of evidence supporting the genetic tests provided to participants was beyond the scope of the present review. This is an important area of future research and is a notable ethical concern of genetic testing.

This review provides the most comprehensive analysis of genetic testing behaviour change research completed to date. However, some limitations to the present review exist. While this review summarized whether the genetic information was delivered direct to consumer or through a healthcare provider (Table 3.2), the practice of each provider is inevitably distinct. Some may incorporate behaviour change theory into their practice in order to maximally

promote health behaviour change, while others may simply provide an explanation of the genetic results. This limitation further highlights the complexity of genetic testing behaviour change research. Additionally, the TPB was chosen as the key theory of interest given that it is one of the most widely accepted and validated theories of behaviour change, with over 4,500 publications referencing this theory and several meta-analyses finding that the key components of the TPB can be used to predict behavioural intentions with mean multiple correlations ranging from 0.59 to 0.67 (Ajzen 2011; Notani 1998; Ravis and Sheeran 2003; Wittmann 2003; Armitage and Conner 2001; Cheung and Chan 2000; Mceachan et al. 2016). However, a number of other theories have been validated and are frequently used in behaviour change research, such as the transtheoretical model (Prochaska and Velicer 1997).

By improving upon genetic testing behaviour change studies, we anticipate the development of an algorithm that can be used to inform effective genetic testing behaviour change interventions for individuals who might benefit from this more personalized approach to healthcare. Indeed the limitations of genetic testing and the possible risk of harm (NIH: Genetics Home Reference 2018) should be considered prior to an individual's decision to undergo genetic testing, especially in situations where one may learn about their risk of developing a disease, where actionable strategies for mitigating the risk are currently unknown (NIH: Genetics Home Reference 2018). Given that behaviour change is complex and multifactorial and studies have yet to robustly incorporate validated theory and high-quality genetic interventions into their methods, we cannot conclude with a broad statement about the impact of genetic testing on behaviour change. However, it is clear that it is possible to facilitate behaviour change through the provision of high-quality genetic interventions. Incorporating behaviour change theory into

future research is an important consideration to enhance our knowledge in this field. Specific recommendations for study design have recently been published elsewhere (Horne, Madill, and Gilliland 2017). An interdisciplinary research team with expertise in genomics as well as behaviour change may be the optimal approach given the complexities of this field of study. Considerable future research is needed in this promising and exciting area of lifestyle behaviour change research.

3.1.6 Conclusion

The use of validated theory to inform a robust study design (Horne, Madill, and Gilliland 2017) and the provision of actionable, high-quality, genetic-based information and advice is recommended to test a behaviour change hypothesis in genetics research. Rather than using the traditional systematic review process of assessing solely risk of bias, we have demonstrated that factors beyond risk of bias influence research outcomes related to genetic testing and behaviour change. As more robust literature continues to be published, allowing for the determination of key components of genetic interventions that best facilitate behaviour change, lifestyle genomics behaviour change research has the potential to make a substantial impact on global health and well-being through the facilitation of personalized, health-promoting lifestyle behaviour change.

3.1.7 Tables and Figures

Table 3.1: Summary of study characteristics and behaviour change findings

First author et al. date	Participants (n baseline; n follow-up)	Intervention group(s)	Comparison group(s)	Target diseases/ conditions (genes tested)	Follow-up	Lifestyle habits assessed	Outcomes (p values); conclusions	Ranking of study design ¹	COI
Roke et al. 2017	Young female adults (n = 57; n = 56)	Genetic testing	No genetic testing	Health effects related to omega-3 intake (FADS1)	3 months	Nutrition (omega-3: EPA and DHA)	NS change in omega-3 intake in the genetic testing group compared to the control group (no genetic testing)	1	No
Marsaux et al. 2016	Adults (n = 265; n = 130)	High-risk genetic result	Non-risk genetic result	Overweight/ obesity (FTO)	6 months	Physical activity	NS change in subjective or objective physical activity with provision of FTO genotype risk info	3	Yes
Meisel et al. 2015	Young adults (n = 1,016; n = 279)	Genetic testing	No genetic testing	Obesity (FTO)	1 month	Nutrition (adherence to a variety of eating behaviours) and physical activity	NS changes in nutrition and physical activity (pooled) between groups	1	No
Boeldt et al. 2015	Adults working at health and technology companies (NR; n = 2,037)	Genetic testing	None	23 conditions including heart attack, Alzheimer disease, type 2 diabetes, obesity, colon cancer, and cervical cancer (NR)	5.6±2.4 months	Nutrition (dietary fat) and physical activity	NS (significance level NR) change in nutrition and physical activity following genetic testing ²	4	No
Hietaranta-Luoma et al. 2014	Adults (n = 122; n = 113 at 12 months)	Genetic testing and High-risk genetic result	No genetic testing and Non-risk genetic result	Cardiovascular disease (apoE)	2 weeks 6 months 12 months	Nutrition (fat quality, and consumption of vegetables, berries, fruits, and fatty and sugary foods) and physical activity	Improved dietary fat quality in the high-risk genetic result group vs. the control group at 2 weeks (p < 0.05) and 6 months of follow-up (p < 0.05); decreased intake of high-fat, high-sugar foods in the non-risk genetic result group vs. the control group at 12 months (p < 0.05)	1	No

Voils et al. 2015	Veterans (<i>n</i> = 601; <i>n</i> = 506 at 3 months, <i>n</i> = 472 at 6 months)	Genetic testing	No genetic testing	Type 2 diabetes (TCF7L2, PPARγ, and KCNJ11)	3 months 6 months	Nutrition (calories, carbohydrates, protein, fat, saturated fat, MUFA, and PUFA) and physical activity	Reduced calories and fat (MUFA and PUFA) in the genetic testing group vs. the no-genetic-testing group (<i>p</i> < 0.05) at 3 months; NS changes in nutrition between the groups at 6 months; NS changes in physical activity at either time point	1	Yes
Marsaux et al. 2016	Adults (<i>n</i> = 1,607; <i>n</i> = 1,233 with subjective data at 6 months, <i>n</i> = 730 with objective data at 6 months)	Genetic testing	No genetic testing	Overweight/obesity (FTO)	3 months 6 months	Physical activity	NS changes in physical activity with the addition of genetic information	1	Yes
Nielsen et al. 2014	Adults (<i>n</i> = 138; <i>n</i> = 130 at 3 months, <i>n</i> = 123 at 12 months)	High-risk genetic result and Non-risk genetic result	No genetic testing	Caffeine metabolism (CYP1A2), vitamin C utilization (GSTT1 and GSTM1), sweet taste perception (TAS1R2), and sodium sensitivity (ACE)	3 months 12 months	Nutrition (caffeine, vitamin C, added sugar, and sodium)	The high-risk genetic result group (for the ACE gene) had reduced sodium intake to a greater extent than the control group by the 12-month follow-up (<i>p</i> = 0.008); NS changes in caffeine, vitamin C, and added sugar intake at each follow-up time point; NS changes in sodium intake at the 3-month follow-up	1	Yes
Egglestone et al. 2013	Adults who had purchased a DTC genetic test or were considering purchasing a test or who were awaiting their results (<i>n</i> = 275)	Genetic testing	No genetic testing	NR (NR)	Varied	Nutrition (healthier diet, vitamins/supplements, caffeine, fibre, salt, fat, and fruits/vegetables), physical activity, and smoking	Greater health behaviour scores in the genetic testing group vs. the control group (<i>p</i> = 0.02 for pooled nutrition, physical activity, and smoking); the most common changes were "healthier diet," "more exercise," and "taking vitamins or supplements"; more often reported "sufficient fruit and vegetable intake" in the genetic testing group (<i>p</i> = 0.03); NS changes in smoking individually	2	NR

Bloss et al. 2013	Adults working at health and technology companies ($n = 3,639$; $n = 2,037$ at 3 months, $n = 1,325$ at 14 ± 1.3 months)	Genetic testing	None	Deep vein thrombosis, melanoma, sarcoidosis, haemochromatosis, lactose intolerance, breast cancer, prostate cancer + 20 other conditions not listed (variable)	3 months 14 ± 1.3 months	Nutrition (dietary fat) and physical activity	NS changes in nutrition or physical activity at 3 months (significance level NR) or 14 ± 1.3 months	4	No
Kaufman et al. 2012	Adult customers of DTC genetic testing companies ($n = 3,167$; $n = 1,048$)	Genetic testing and High-risk genetic result	Non-risk genetic result	Variable (variable)	2–8 months	Nutrition (change diet) and physical activity	The participants who considered themselves at high risk of colon cancer were significantly more likely to change their diet ($p = 0.02$) and start exercising more ($p = 0.01$) than those who considered themselves at low risk of colon cancer; 10% of all participants reported they changed a supplement, 33% reported being more careful about their diet, and 14% reported exercising more	2	NR
Hollands et al. 2012	Adults with 1st-degree relatives with Crohn's disease ($n = 497$; $n = 426$)	Genetic testing and High-risk genetic result	No genetic testing and Non-risk genetic result	Crohn's disease (NOD2)	6 months	Smoking	NS changes in smoking cessation between the genetic testing and the non-genetic-testing group; NS changes in smoking cessation between the high-risk and the non-risk genetic result group (significance level NR)	1	No
Bloss et al. 2011	Adults working at health and technology companies ($n = 3,639$; $n = 2,037$)	Genetic testing	None	23 conditions including breast and prostate cancer (NR)	5.6 ± 2.4 months	Nutrition (dietary fat) and physical activity	NS changes in nutrition and/or physical activity following genetic testing	4	NR
Vernarelli et al. 2010	Adults with at least one parent who developed Alzheimer disease ($n = 279$; $n = 272$)	High-risk genetic result	Non-risk genetic result	Alzheimer disease (apoE)	6 weeks	Nutrition (dietary supplement use) and physical activity	The high-risk genetic result group was more likely to take supplements than the non-risk genetic result group ($p = 0.0001$)	3	No

Hishida et al. 2010	Adult smokers ($n = 562$; $n = 533$)	Genetic testing	No genetic testing	Lung and oesophageal cancer (L-myc)	12 months	Smoking	NS changes in smoking cessation between the genetic testing and the no-genetic-testing group	1	No
Quach et al. 2009	Adults with a personal and/or family history of breast and/or ovarian cancer ($n = 120$; NR)	Genetic testing	None	Breast and ovarian cancer (BRCA1/2)	6 months	Nutrition (healthy diet and vitamin use) and physical activity	NS changes in nutrition, vitamin use, or physical activity after genetic testing (significance level NR)	4	NR
O'Neill et al. 2008	Adult females (NR; $n = 115$ at 1 month and 6 months)	High-risk genetic result	Uninformative genetic result and Non-risk genetic result	Breast cancer (BRCA1/2)	1 month 6 months	Nutrition (saturated fat, fruit/vegetables) and physical activity	NS differences between groups in nutrition or physical activity at baseline and 1 month or 6 months following genetic testing	3	NR
Chao et al. 2008	Adult with parent who developed Alzheimer disease ($n = 162$; $n = 147$)	Genetic testing and High-risk genetic result	No genetic testing and Non-risk genetic result	Alzheimer's disease (apoE)	12 months	Nutrition (changes in diet, changes in vitamin/supplement use) and physical activity	The high-risk genetic result group was more likely to report a nutrition or physical activity change than the non-risk genetic result group ($p = 0.003$) and the no-genetic-testing group ($p = 0.03$); most common was a change in medication/supplement use (specifically vitamin E)	1	NR
Sanderson et al. 2008	Adult smokers (NR; $n = 61$)	Genetic testing and High-risk genetic result	No genetic testing and Non-risk genetic result	Lung cancer (GSTM1)	1 week 2 months	Smoking	Fewer cigarettes smoked ($p = 0.009$) and greater quit rates ($p = 0.009$) at the 1-week follow-up in the high-risk genetic result group than in the no-genetic-testing group; NS differences at the 2-month follow-up between the groups for cigarettes smoked and quit rates	1	No
Rees et al. 2007	Adult females ($n = 23$)	Genetic testing	None	Breast cancer (BRCA1/2)	Varied – up to 18 months	Nutrition (dietary changes), physical activity, and smoking	Few women reported a significant impact on nutrition, physical activity, and/or smoking as a result of receiving genetic testing results and counselling (significance level N/A)	Qualitative	NR

Rief et al. 2007	Adults ($n = 294$)	Genetic testing and consultation	No genetic testing – consultation only and No genetic testing and no consultation	Obesity (NR)	6 months	Nutrition (restraint eating)	NS changes to restraint eating in the genetic testing group compared to the no-genetic-testing groups	1	No
Carpenter et al. 2007	Adult smokers ($n = 729$; $n = 199$)	High-risk genetic result	Non-risk genetic result	Emphysema (AAT)	3 months	Smoking	Those with high-risk genetic results made significantly greater quit attempts than the non-risk genetic result group ($p = 0.004$)	3	NR
Ito et al. 2006	Adult smokers ($n = 697$; $n = 369$ with data for baseline, 3 and 9 months)	Genetic testing	No genetic testing	Lung and oesophageal cancer (<i>L-myc</i>)	3 months 9 months	Smoking	NS differences in smoking cessation between groups at 3 months (significance level NR) or 9 months	1	NR
Marteau et al. 2004	Adult probands and their adult relatives with familial hypercholesterolaemia ($n = 341$; $n = 275$)	Genetic testing	No genetic testing	Familial hypercholesterolaemia (NR)	6 months	Nutrition (total fat and unsaturated fat), physical activity, and smoking	NS impact on nutrition, physical activity, or smoking with genetic testing	1	NR
Mcbride et al. 2002	Adult smokers ($n = 557$; $n = 412$ at 6 months, $n = 356$ at 12 months, $n = 487$ with data from all 3 time points)	Genetic testing	No genetic testing	Lung cancer (GSTM1)	6 months 12 months	Smoking	Greater smoking cessation in the genetic testing group than in the no-genetic-testing group ($p < 0.006$) at 6 months; NS smoking cessation rates at 12 months	1	NR
Audrain et al. 1997	Adult smokers ($n = 550$; $n = 426$)	Genetic testing	No genetic testing	Lung cancer (CYP2D6)	12 months	Smoking	Greater likelihood of quit attempts in the genetic testing group than in the no-genetic-testing group ($p = 0.02$); NS change in 30-day cessation between groups	1	NR

Table 3.1 Legend: COI, conflict of interest; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; NS, not statistically significant ($p > 0.05$ unless otherwise stated); NR, not reported; DTC, direct to consumer; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid. ¹The rank of the study design is as follows, based on the categories of the NIH Quality Assessment Tools (NIH, 2014) in combination with consideration of the hierarchy of evidence (Evans et al. 2003): 1 = controlled intervention study; 2 = observational cohort/cross-sectional study; 3 = case-control study; 4 = pre-post study with no control group. ²Note: significance levels for this group of participants are reported in Bloss et al. 2011.

Table 3.2: Summary of quality assessment ratings and impact of genetic testing on lifestyle factor(s) of interest

Ranking of study design ¹	First author, year	Quality assessment rating				overall quality score	Key findings: impact of genetic testing on lifestyle factor(s) of interest				Source of genetic information	Specific lifestyle factors with significant improvement
		methods	genetic info	TPB			nutrition	PA	smoking	nutrition & PA		
1	Roke et al. 2017	Good	Fair	Fair	7	⚠					Other	N/A
1	Hietaranta-Luoma et al. 2015	Fair	Good	Poor	6	√ ^a (2 weeks) √ ^b (6 months) √ ^c (12 months)	⚠				HCP	Improved dietary fat quality (high-risk genotype vs. control at 2 weeks and baseline to 6-month follow-up in high-risk genotype group); decreased intake of high-fat, high-sugar foods (in low-risk genotype vs. control at 12 months)
1	Marsaux et al. 2015	Fair	Fair	Poor	5		⚠				DTC	N/A
1	Meisel et al. 2015	Poor	Fair	Fair	5	⚠	⚠				DTC	N/A
1	Voils et al. 2015	Fair	Good	Poor	6	√ ^d (3 months) ⚠ (6 months)	⚠				HCP	Reduced calories and fat (MUFA and PUFA)
1	Nielsen et al. 2014	Good	Fair	Poor	6	⚠ (3 months) √ ^a (12 months)					DTC	Reduced sodium intake
1	Hollands et al. 2012	Good	Good	Poor	7		⚠				Other	N/A
1	Hishida et al. 2010	Poor	Poor	Poor	3		⚠				HCP	N/A

1	Chao et al. 2008	Fair	Poor	Poor	4	△	△	√ ^{a, e}	HCP	General improvements to nutrition and PA; vitamin E supplementation was the most common change reported	
1	Sanderson et al. 2008	Poor	Fair	Fair	5			√ ^a (1 week) △ (2 months)	HCP	Fewer cigarettes smoked and greater smoking cessation	
1	Rief et al. 2007	Fair	Good	Poor	6	△			HCP	N/A	
1	Ito et al. 2006	Poor	Good	Fair	6		△		Other	N/A	
1	Marteau et al. 2004	Fair	Fair	Fair	6	△	△	△	HCP	N/A	
1	McBride et al. 2002	Poor	Good	Fair	6			√ ^d (6 months) △ (12 months)	Other	Greater smoking cessation	
1	Audrain et al. 1997	Fair	Fair	Fair	6			√ ^d (quit attempts) △ (30-day cessation)	HCP	Greater likelihood of quit attempts	
Summary² (n = 15)		Fair	Fair	Poor	5.6	3/8	0/6	3/7	1/1		
2	Egglestone et al. 2013	Poor	Poor	Poor	3	√ ^d	√ ^d	△	√ ^d	DTC	Greater health behaviour scores; the most common changes were “healthier diet,” “more exercise,” and “taking vitamins or supplements”; more often reported “sufficient fruit and vegetable intake”
2	Kaufman et al. 2012	Fair	Poor	Poor	4	√ ^e	√ ^e			DTC + optional HCP	“Changed their diet” and “started exercising more”
Summary² (n = 2)		Fair – poor	Poor	Poor	3.5	2/2	2/2	0/1	1/1		
3	Marsaux et al. 2016	Fair	Fair	Poor	5		△		DTC	N/A	
3	Vernarelli et al. 2010	Good	Poor	Poor	5	√ ^e	△		HCP	Greater changes in supplement use; vitamin E, vitamin C, botanicals, multivitamins, vitamin B, and fish oil/omega were the most common changes reported	
3	O’Neill et al. 2008	Good	Poor	Poor	5	△	△		HCP	N/A	
3	Carpenter et al. 2007	Fair	Fair	Poor	5			√ ^e	DTC + optional HCP	Greater 24-h quit attempts	
Summary² (n = 4)		Good – fair	Fair – poor	Poor	5.0	1/2	0/3	1/1			
4	Boeldt et al. 2015	Fair	Poor	Fair	5	△	△		DTC + optional HCP	N/A	

4	Bloss et al. 2013	Fair	Poor	Fair	5	⚠	⚠	DTC + optional HCP	N/A
4	Bloss et al. 2011	Fair	Poor	Poor	4	⚠	⚠	DTC + optional HCP	N/A
4	Quach et al. 2009	Fair	Poor	Fair	5	⚠	⚠	HCP	N/A
Summary² (n = 4)		Fair	Poor	Fair	4.8	0/4	0/4		
Qualitative	Rees et al. 2007	Good	Poor	Poor	5	⚠	⚠	HCP	N/A
Summary² (n = 1)		Good	Poor	Poor	5.0	0/1	0/1		
Summary of all studies (n = 26)		FAIR	POOR	POOR	5.2	Nutrition: 6/18 (33%) PA: 2/16 (13%) Smoking: 4/12 (33%)		Studies with significant beneficial health behaviour change(s): 7/9³ (78%) provided actionable recommendations Studies with null findings: 7/14 (50%) provided actionable recommendations	

“Other” sources of genetic information: Roke et al. 2017, used a researcher; McBride et al. 2002, used “trained counsellors”; Ito et al. 2006, used a “trained interviewer”; Hollands et al. 2012, used a “trained research counsellor.” No studies found a detrimental effect of genetic testing on lifestyle change. Statistically significant beneficial behaviour change(s); ⚠, no statistically significant behaviour change(s); blank cells, lifestyle factor(s) of interest was/were not assessed; N/A, not applicable; TPB, theory of planned behaviour; PA, physical activity; HCP, genetic intervention offered through a healthcare provider; DTC, genetic intervention offered direct to consumer; Other, another method was used to deliver the genetic intervention to the participants; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid. ¹ The rank of the study design is as follows, based on the National Institutes of Health Quality Assessment Tools (National Institutes of Health n.d.) and the hierarchy of evidence pyramid (Evans 2003): 1 = controlled intervention study; 2 = observational cohort/cross-sectional study; 3 = case-control study; 4 = pre-post study with no control group. ² n = x indicates the total number of studies included in the summary; modes are reported for each of the three quality assessment ratings; x/x indicates the number of beneficial behaviour change findings/the total number of studies (note: several studies included multiple analyses such as those with more than one follow-up time point, and those assessing more than 1 lifestyle factor of interest); the overall quality score is represented as a mean. ³ Three studies did not provide information about whether or not actionable recommendations were provided. ^a High-risk genotype vs. control group. ^b Baseline to 6-month follow-up in high-risk genotype group. ^c Non-risk genotype vs. control group. ^d Genetic testing group vs. control group. ^e High-risk genotype group vs. non-risk genotype group.

Table 3.3: Frequencies of genes tested in genetic interventions and their reported associated health outcomes

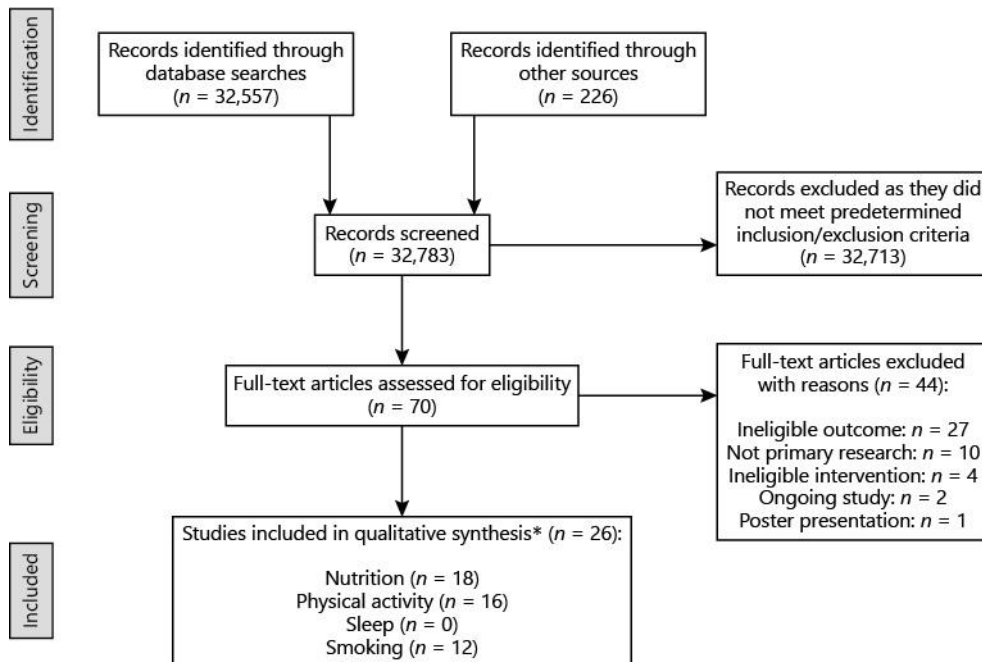
Gene	Frequency	Health outcomes reported to be associated with the gene
AAT	1	Emphysema
ACE	1	Salt sensitivity
apoE	3	Alzheimer disease Cardiovascular disease
BRCA1	3	Breast cancer Ovarian cancer
BRCA2	3	Breast cancer Ovarian cancer
CYP1A2	1	Caffeine metabolism
CYP2D6	1	Lung cancer
FADS1	1	Omega-3 metabolism
FTO	3	Overweight/obesity
GSMT1	3	Lung cancer Vitamin C utilization
GSTT1	1	Vitamin C utilization
KCNJ11	1	Type 2 diabetes
<i>L-myc</i>	2	Lung cancer Oesophageal cancer
NOD2	1	Crohn's disease
PPAR γ	1	Type 2 diabetes
TAS1R2	1	Sweet taste preference
TCF7L2	1	Type 2 diabetes

Of the studies that reported the specific genes tested in the genetic intervention, single nucleotide polymorphisms in 16 unique genes were tested, with apoE, BRCA1/2, FTO, and GSTM1 having the highest frequencies of use in the genetic intervention.

Figure 3.1: Search terms

nutrigenetic* OR nutrigenomic* OR DNA OR "nutritional genomic*" OR gene OR genes OR genetic* OR genom* OR "personalized nutrition" OR "personalised nutrition"
AND
behavior* OR behaviour* OR habit* OR smoking OR smoke* OR diet OR nutrition OR "physical activity" OR exercise OR sleep
AND
change OR changes OR effect OR effects OR impact OR impacts OR modif*
AND
information OR recommendation* OR advice OR intervention OR program* OR counsel*

Figure 3.2: Search strategy



*Several articles assessed behaviour change related to >1 lifestyle factor of interest; therefore, the total number of records included in the systematic review does not match the total number of articles by lifestyle category.

Supplementary Table 3.4: Quality assessment tool for genetic interventions

Criteria	Yes	No	Other (CD, NR, NA)*
1. Were the results of the genetic test interpreted and explained by a trained healthcare professional?			
2. Was a copy of the genetic testing report provided to the participants?			
3. Were the results of the genetic test communicated to participants on more than one occasion (i.e. was there follow-up provided after the initial communication of the results)?			
4. Were the results provided in the report, or discussed in the genetic counselling session actionable (i.e. did the report contain specific recommendations or did the genetic counsellor communicate specific recommendations)?			
5. Were the participants provided with an opportunity to ask questions about their results?			

Other Comments: _____

Overall Rating: _____ (Good, Fair, Poor; if Poor state reasons)

*CD, cannot determine; NA, not applicable; NR, not reported

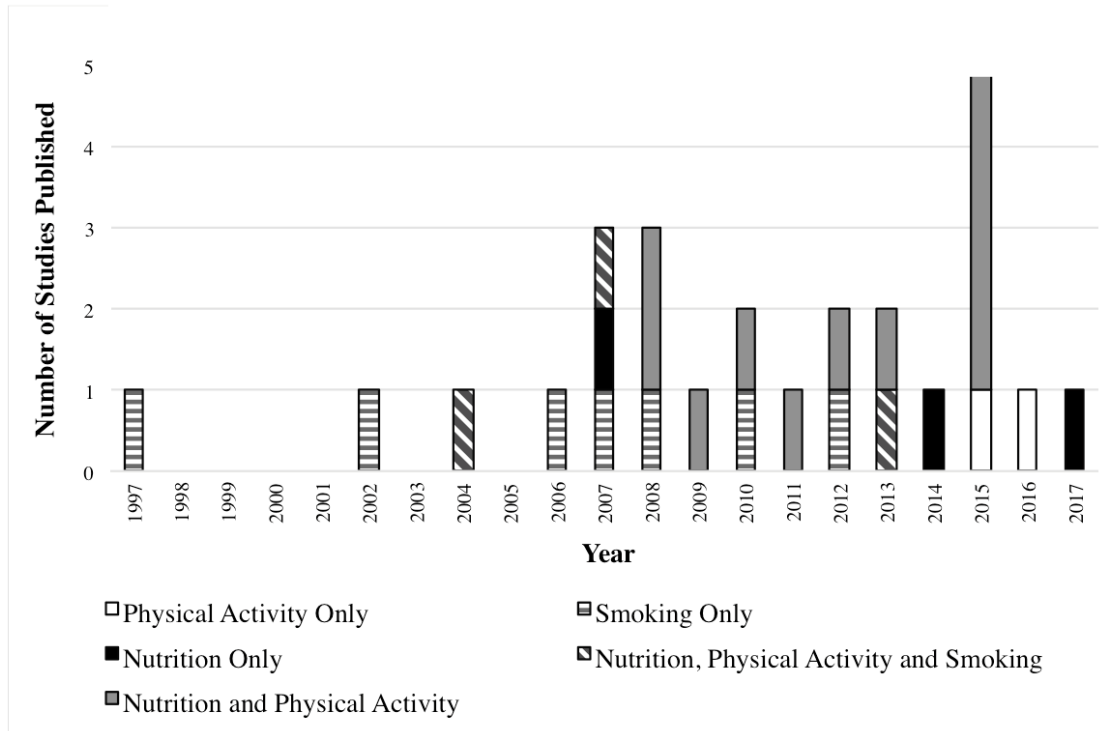
Supplementary Table 3.5: Summary of behaviour change theories and models included in genetic intervention behaviour change research manuscripts

Author (Year)	Was reference made to the TPB?	Was reference made to another behaviour change theory or model?	Other Comments
Roke (2017)	No	Yes – Parallel Process Model*	
Marsaux (2016)	No	No	
Meisel (2015)	No	No	
Boeldt (2015)	No	Yes – Health Belief Model and Parallel Process Model*	
Hieteranta-Luoma (2015)	No	No	
Voils (2015)	No	No	Referred to “behaviour theories” in general
Marsaux (2015)	No	No	
Nielsen (2014)	No	No	
Egglestone (2013)	No	No	
Bloss (2013)	No	No	
Kaufman (2012)	No	No	
Hollands (2012)	No	No	- Referred generally to “theories of attitude change”
Bloss (2011)	No	No	
Vernarelli (2010)	No	No	
Hishida (2010)	No	Yes – Transtheoretical Model**, Extended Parallel Process Model	
Quach (2009)	No	Yes – Self-Regulation Model	
O’Neil (2008)	No	Yes – Transtheoretical Model**	
Chao (2008)	No	No	
Sanderson (2008)	No	Yes – Extended Parallel Process Model	
Rees (2007)	No	Yes – Transtheoretical Model**	- Discussed that interventions based on behaviour change theories are more effective - Referenced a meta-analysis of Protection Motivation Theory - Referenced an article which referred to several theoretical perspectives including the TPB and Theory of Reasoned Action
Rief (2007)	No	No	
Carpenter (2007)	No	Yes – Transtheoretical Model**	
Ito (2006)	No	Yes – Transtheoretical Model**	
Marteau (2004)	No	No	Referenced a meta-analysis of Protection Motivation Theory
McBride (2002)	No	Yes – Transtheoretical Model** and Social Cognitive Theory	
Audrain (1997)	No	Yes – Transtheoretical Model**	

*The *Parallel Process Model* is often referred to as *The Common Sense Model*

**The *Transtheoretical Model* is often referred to as *The Stages of Change*

Supplementary Figure 3.3: Number of studies published annually by category



*Full bar represents total number of studies published in the given year

**CHAPTER 4: A CRITICAL, SCOPING REVIEW OF GENETIC-
BASED INTERVENTIONS FOR WEIGHT MANAGEMENT**

4.1 Title: Assessing the effectiveness of actionable nutrigenomics and lifestyle genomics interventions for weight management: A critical, scoping review with directions for future research

4.1.1 Abstract

The use of nutrigenomics and lifestyle genomics in clinical practice has the potential to optimize weight-related outcomes for patients. A scoping review was conducted to summarize and evaluate the current body of knowledge related to the effectiveness of providing DNA-based lifestyle advice on weight-related outcomes, with the aim of providing direction for future research. Primary studies were included if they were written in English, evaluated weight-related and/or body composition outcomes, and provided participants with an actionable genetic-based lifestyle intervention. Interventions that only provided information on genetic risk for diseases/conditions were excluded. Data were extracted from each article meeting inclusion criteria (n=3) and the studies were critically appraised for methodological quality. Research in this area is promising, but limited. One study demonstrated that a nutrigenetic intervention resulted in greater long-term weight loss compared to a standard intervention, while another found no significant improvements in weight-related outcomes with genetically-tailored advice. The third study found that individuals with high-risk FTO genotypes had greater changes in markers of adiposity compared to a group receiving standard/non-personalized advice, but no differences were observed between the genetic group and groups receiving other levels of personalization that did not include the provision of genetic information and advice. With limited existing research, the effectiveness of nutrigenomics and lifestyle genomics interventions for weight management in clinical practice cannot yet be conclusively determined. Recommendations for future research are detailed in the present manuscript.

4.1.2 Background

Consumers have expressed considerable interest in nutrigenetic testing (Vallée Marcotte et al. 2019; Nielsen and El-Sohemy 2014). As a result, many companies are offering personalized DNA-based lifestyle advice, most of which provide specific recommendations to optimize weight management practices (Nutrigenomix Inc., n.d.; MyDNA 2019; Pathway Genomics, n.d.; 23andMe n.d.). With increasing epidemiological and interventional research demonstrating relationships between genetics, nutrition and physical activity, and weight-related outcomes (Garaulet et al. 2011; Phillips et al. 2012; Zhang et al. 2012; Corella et al. 2009), personalized lifestyle recommendations based on genetics are beginning to be established. For example, evidence from a 2-year randomized controlled trial (RCT) reported that variation in the FTO gene at rs9939609 can predict weight loss response to a lower vs. higher protein diet (Zhang et al. 2012).

Weight loss continues to be a priority for the general public (Sui et al. 2019). As such, nutrigenomics and lifestyle genomics testing for weight management are attractive tools, as they promote more personalized strategies for individuals to optimize their weight loss response to a particular dietary plan (Garaulet et al. 2011; Phillips et al. 2012; Zhang et al. 2012; Corella et al. 2009). While the scientific evidence for personalized weight management strategies continues to grow, long-term behaviour change and weight management remains a challenge and weight loss outcomes in clinical practice often do not satisfy the wants or needs of patients (Soleymani, Daniel, and Garvey 2016; Field, Camargo, and Ogino 2013; Rogerson, Soltani, and Copeland 2016). Moreover, weight loss is often followed by weight regain above and beyond baseline weight. Research has demonstrated that such weight “yo-yoing” (the constant and recurring

decrease and increase in weight over time) could be more harmful to health than maintenance of a higher body mass index (BMI) (Rhee 2017).

Research demonstrates that individual responses to nutritional intake for weight management differ based on genetic variation (Garaulet et al. 2011; Phillips et al. 2012; Zhang et al. 2012; Corella et al. 2009). Some studies have also shown that individuals are more motivated to follow nutrition advice when it is based on their genetics (Nielsen and El-Sohemy 2014; Horne et al. 2018; Kaufman et al. 2012). Thus, it is possible that the provision of nutrigenomics and lifestyle genomics interventions could be used as tools to support long-term weight management. However, multiple factors beyond genetics, nutrition, and physical activity contribute to the development and management of obesity including the social determinants of health, built environment, food access and availability, medications, certain diseases/conditions such as polycystic ovarian syndrome, sleep, stress and others (Moore et al. 2010; Finkelstein, Ruhm, and Kosa 2005; Seabrook and Avison 2010; Gilliland et al. 2012; Naderpoor et al. 2015; Maina et al. 2004). Thus, managing overweight and obesity is multi-factorial. Nutritional genomics and lifestyle genomics are not the only considerations of weight management, but they remain important components of the overall picture, alongside other factors.

With the robust and growing research foundation on the science of nutrigenomics, lifestyle genomics, and differing weight loss responses to the same nutrition plans, this review aims to summarize and evaluate the current body of knowledge related to the effectiveness of providing DNA-based lifestyle advice on weight-related outcomes, with the aim of providing direction for future research.

4.1.3 Methods

A scoping review was conducted with guidance from Arksey and O'Malley's methodological framework (Arksey and O'Malley 2005). The purpose of this review was to identify, summarize and review the existing literature on the efficacy of using genetic-based lifestyle interventions to enhance weight loss and/or improve body composition. Furthermore, we aimed to use these results to provide direction for future research. English articles assessing the impact of providing genetic-based lifestyle advice on weight-related, BMI and/or body composition outcomes were included. Non-English articles, and articles assessing the impact of providing information on genetic risk (i.e. without actionable lifestyle advice) were excluded. To capture studies only assessing the pragmatic use of genetic-based lifestyle interventions, articles were also excluded if they aimed to identify or replicate gene-nutrient-health outcome/weight interactions. *PubMed* and *Google Scholar* were searched for relevant studies using different combinations of the following search terms: nutrigenomics, nutrigenetics, nutritional genomics, lifestyle genomics, weight, BMI, body composition, intervention, nutrition, lifestyle, and/or physical activity. Reference lists of included articles were reviewed for relevant articles.

The following data from each study were charted: author(s), year of publication, intervention type and comparator, duration of intervention, study population, methods, relevant outcome measures, single nucleotide polymorphisms (SNPs) included in genetic reports, genetic testing company (where applicable), and relevant results related to the effectiveness of genetic-based weight management interventions. Each article was critically appraised for key limitations

of the employed scientific methods to determine gaps in the existing literature and provide direction for future research.

4.1.4 Results

A summary of studies meeting the inclusion criteria ($n=3$) is presented in Table 4.1. This review found that overall research in this area is minimal, with only three studies assessing the practical impact of providing actionable genetic-based lifestyle information on weight-related and/or body composition outcomes. While two RCTs have been conducted, one was a feasibility study (Frankwich et al. 2015), which has not yet been followed up with a larger, adequately powered trial and in the other, change in a weight-related outcome was not the primary outcome of interest (Celis-Morales et al. 2017; Newcastle University 2016).

The retrospective chart review by Arkadianos et al. (2007) was an informative first step for this body of knowledge. The authors concluded that individuals receiving the nutrigenomics intervention were more likely to maintain weight loss and experienced significantly greater BMI reductions over the long-term, compared to individuals who were advised to follow a low glycemic-index, Mediterranean diet. However, several methodological limitations should be noted. First, due to the nature of the study methods (retrospective chart review), cause and effect relationships cannot be drawn. Furthermore, the nutrition recommendations provided to participants were not specific to weight management; rather, they provided recommendations for general health and wellbeing. For example, SNPs in tumor necrosis factor alpha (TNF α), interleukin 6 (IL6) and nitric oxide synthase 3 (NOS3) were tested to provide nutrition

recommendations such as “*Add supplement Omega 3 (700-1400 mg). Make sure weekly diet contains portions of oily fish*” (Arkadianos et al. 2007). Additionally, intervention durations were not standardized and therefore varied substantially in both total length and the amount of follow-up. Of note, income was not considered as a confounding factor, and given that patients either chose to purchase a nutrigenetic test (out of pocket) or did not purchase a nutrigenetic test in this study, it is plausible that income levels differed significantly between groups. This is an important confounding factor to consider given that income is a well-established social determinant of health (Government of Canada 2019; Seabrook and Avison 2012). The authors noted several other limitations including the lack of placebo, modest sample ($n=93$) size, and a sample consisting of Caucasian individuals from Greece with a history of difficulty losing weight, thus limiting generalizability (Arkadianos et al. 2007).

Frankwich and colleagues conducted the first RCT in this area (Frankwich et al. 2015). This was a feasibility RCT. Feasibility trials are distinguished by their focus on assessing the viability or capability of conducting a larger trial, rather than assessing effectiveness or efficacy of an intervention with adequate power (Eldridge et al. 2016). The percent of participants achieving 5% weight loss was the primary outcome, and this study found that there was no significant difference between groups in the percent of participants achieving 5% weight loss (Frankwich et al. 2015). However, typically estimates of participant outcomes such as weight loss would be reported as estimates with 95% confidence intervals (without p-values) given that feasibility trials are not adequately powered to assess the effectiveness of an intervention (Eldridge et al. 2016). In fact, the authors noted limitations related to the small sample size ($n=32$), and determined that a sufficiently powered trial would require 336 participants per group

using a sample size calculation with 80% power and an alpha-level of 0.05 (Frankwich et al. 2015).

Finally, Celis-Morales et al. (2017) conducted the second RCT on this topic, which was a sub-study within the larger Food4Me RCT. This was a significant contribution to the body of knowledge in this area. In total, participants were provided with information and advice related to five gene-lifestyle-health outcome interactions (FTO, physical activity and weight; FADS1 omega-3 and cardiovascular health; TCF7L2 dietary fat and weight; ApoE(e4), saturated fat and cholesterol/cardiovascular health; MTHFR, folate and cardiovascular health). This study compared weight and waist circumference (WC) outcomes between a control group and different levels of personalized advice (as outlined in Table 4.1), and further compared risk and non-risk FTO genotype groups (Celis-Morales et al. 2017). Participants randomized to receive FTO genetic information/advice were informed that “A specific variation of this gene is associated with a greater need to maintain a healthy body weight and engage in physical activity. A healthy weight combined with exercise may provide added health benefits for these individuals.” Carriers of the high-risk FTO allele were further advised to “[reduce their] body weight and waist circumference to a healthy normal range because [they] have a genetic variation that can benefit by reducing these two obesity-related markers.” Furthermore, participants randomized to receive genetic-based advice were provided with weight-related information and advice according to a variant within the TCF7L2 gene. They were informed that “a specific variation of this gene is associated with improved weight loss when consuming a low-fat diet compared with the effect of other weight-loss diets” and that “reducing dietary fat may enhance weight loss in these individuals” (Celis-Morales et al. 2017). While the RCT was well-designed and is

reflective of direct-to-consumer (DTC) lifestyle genomics testing, there are some considerable limitations to note. First, the height, weight, and waist circumference (WC) data were all self-reported. While the authors point out that these measures are reliable (Celis-Morales et al. 2015), certainly measured data would still have improved validity and reliability. Another notable limitation of this study was that the FTO-related advice provided to participants was borderline actionable. Given the complexity of weight management (Moore et al. 2010; Finkelstein, Ruhm, and Kosa 2005; Seabrook and Avison 2010; Gilliland et al. 2012; Naderpoor et al. 2015; Maina et al. 2004), simply advising individuals to “maintain a healthy body weight” does not provide specific direction on how to achieve this aside from a broad statement advising individuals to exercise. While the TCF7L2-related advice to consume a low-fat diet was actionable, the exact amount of dietary fat was not well-defined and only individuals with the high-risk genotype of TCF7L2 received an actionable recommendation. Therefore, it is not surprising that individuals provided with genetic-based information/advice did not reduce their weight or WC to a greater extent than those receiving other forms of personalized advice (Table 4.1). The authors do mention this as a limitation, stating that the feedback was “only a positive reinforcement” (Celis-Morales et al. 2017). Lastly, a weight-related outcome was not the predetermined primary outcome of this study and therefore it is possible that the statistical power for this study was inadequate, which is also noted by the authors (Celis-Morales et al. 2017).

Overall, study limitations in the current body of knowledge are related to study design, the nature of the recommendations provided to participants, small (underpowered) sample sizes, the use of self-reported weight-related data, and lack of consideration of important confounding factors.

Table 4.1: Summary of studies meeting inclusion criteria

Author, year	Methodology	Intervention Duration (data collection follow-ups)	Intervention Type and Comparator	Study Population (number of participants completing study)	Information on Genes, SNPs, Dietary/Lifestyle Advice Provided, and Company (where applicable)	Outcome*	Results Related to the Effectiveness of Genetic-Based Interventions for Weight Management
Arkadianos et al. 2007	Retrospective Chart Review	90 to >365 days (duration differed by patient)	Nutrigenetic-guided diet vs. low glycemic-index, Mediterranean diet	Patients with history of unsuccessful weight loss attempts (n=93)	24 variants in 19 genes to provide advice for: folic acid, vitamin B6, vitamin B12, cruciferous vegetables, vitamin A, vitamin C, vitamin E, caffeine, dairy, vitamin D, calcium, omega-3, exercise	Weight, BMI	<ul style="list-style-type: none"> Nutrigenetic diet group was more likely to have maintained some weight loss Nutrigenetic diet group had significantly greater BMI reduction long-term (>300 days)
Frankwich et al. 2015	RCT (feasibility trial)	24 weeks (follow-up at 8 weeks and 24 weeks)	Nutrigenetic-guided diet vs. standard balanced diet	U.S. veterans (n=32)	Balanced, low-carbohydrate, low-fat or Mediterranean based on SNPs of 7 genes (APOA2 rs5082, ADIPOQ rs17300539, FTO rs9939609, KCTD10 rs10850219, LIPC rs1800588, MMAB rs2241201, and PPARG rs1801282) used in Pathway FIT®'s proprietary algorithm	Weight*, BMI	<ul style="list-style-type: none"> Nutrigenetic intervention did not enhance weight loss Adherence to nutrigenetic intervention was correlated with weight loss (adherence to standard diet was not)
Celis-Morales et al. 2017	RCT	6 months (follow-up at 3 and 6 months)	Diet + phenotype + genotype vs. diet + phenotype vs. diet vs. control; and FTO high-risk genotype vs. FTO non-risk genotype	Overweight/obese individuals from 7 European countries (n=583)	Individuals with high-risk FTO genotype advised to engage in physical activity and reduce weight and waist circumference to maintain a healthy body weight; individuals with high-risk TCF7L2 genotype advised to consume a low-fat diet	Weight, WC	<ul style="list-style-type: none"> High-risk FTO genotype group had greater reductions in weight and WC compared to the control group (standard, non-personalized lifestyle advice) No significant differences in weight loss and WC reductions between diet + phenotype + genotype group and different levels of personalized advice (i.e. diet + phenotype group that received advice based on weight, diet, physical activity level, blood work and WC; and diet only group that received advice based on weight, diet and physical activity level)

*denotes primary outcome indicated in manuscript

4.1.5 Discussion

To our knowledge, this is the first review that summarized and assessed the current body of knowledge related to the impact of providing patients with genetic-based lifestyle interventions for managing weight, BMI and/or body composition. It is clear that significant gaps exist in the literature.

Critically analyzing the level of evidence available to support the genes tested and subsequent dietary advice provided was beyond the scope of this review. However, it should be noted that the lack of regulation in the genetic testing industry allows for tests to go to market without any accountability to base such tests on robust or any level of scientific evidence (Caulfield and McGuire 2012); as such, guidelines have been developed to assess the scientific validity and evidence for various nutrigenomics interactions (Grimaldi et al. 2017). It is interesting to note that one of the three conducted studies provided genetic-based recommendations for following low-carbohydrate nutrition plans for weight loss, when the evidence to support such genetic-based advice has been scrutinized. Recent research has assessed whether genetic-based alignment to low-carbohydrate nutrition plans is effective for predicting weight loss outcomes. These studies (Coletta et al. 2018; Gardner et al. 2018) do not assess the effectiveness of providing patients/consumers with genetic-based lifestyle advice and therefore were not included in the present review. However, based on the results from these two studies, it is clear that our knowledge of using genetics to predict weight loss response to low-carbohydrate diets is lacking as both studies concluded that dietary alignment to the particular genetic profiles did not correlate with greater weight loss outcomes (Coletta et al. 2018; Gardner et al. 2018).

This simply demonstrates that the genes tested, and genetic-based nutrition advice provided were not based on robust evidence; it does not necessarily imply that all nutrigenomics interventions will be ineffective at reducing weight and/or improving body composition. Until further research provides better insights for tailoring carbohydrate intake based on genetics, it remains inappropriate to use nutrigenetic testing to provide information in response to low-carbohydrate nutrition plans for weight loss. While we work towards improving knowledge in this area, perhaps interventions providing genetically-tailored weight management advice should be focused on other nutrients such as protein and saturated fat (Zhang et al. 2012; Casas-Agustench et al. 2013; Corella et al. 2009).

From a consumer genetic testing perspective, with the current lack of industry regulation, companies are free to provide any genetically-guided advice regardless of the level of scientific evidence (Caulfield and McGuire 2012). Until regulation catches up with industry practices, the development of clinical practice guidelines in nutrigenomics would help to provide guidance to researchers and clinicians for incorporating evidence-based nutrigenomics advice into research and clinical practice. Ultimately, this would enhance the potential for nutrigenomics to improve health outcomes for the general public.

Overall, weight management remains a challenging area of clinical practice. Research evaluating the effectiveness of genetic-based weight management interventions has been minimal, and results have been variable thus far. While there were some promising findings by Arkadianos et al. (2007), this study had significant methodological flaws. Similarly, while

Frankwich et al. (2015) completed the first RCT in this area, this was a feasibility RCT, which has not yet been followed up with a larger, adequately powered clinical trial. Lastly, Celis-Morales (2017) completed a second RCT, but the genetic-based advice provided to participants was minimal, and borderline actionable, and the study may not have been adequately powered statistically.

Based on this review, future research should seek to use evidence-based nutrigenetic interventions, employ an RCT methodology, be adequately powered to detect significant differences for a predetermined weight-related primary outcome, consider important confounding factors, be at least 12 months in duration, and follow established processes for clinical trials such as the SPIRIT and CONSORT guidelines (Chan et al. 2013; Zwarentein et al. 2008). Furthermore, this future work should provide a genetic-based intervention that is likely to facilitate behaviour change; a quality assessment tool for genetic-based interventions has been developed and should be used to help researchers design appropriate interventions (Horne et al. 2018). This work should also use previously developed study quality assessment tools to inform study design and reduce any risk of bias (National Institutes of Health n.d.).

4.1.6 Conclusion

Research assessing the impact of providing genetically-tailored information and advice on weight management outcomes is minimal. Notable limitations exist in the study methods employed in the current body of knowledge. Future research should address these limitations

before we can thoroughly answer the important research question: *Can the use of nutrigenomics and lifestyle genomics interventions enhance weight-related outcomes?*

CHAPTER 5: STUDY DESIGN

As published* in *BMC Public Health*:

Horne J, Gilliland J, O'Connor C, Seabrook J, Hannaberg P, Madill J. 2019. "Study protocol of a pragmatic randomized controlled trial incorporated into the Group Lifestyle Balance™ Program: The Nutrigenomics, Overweight/Obesity and Weight Management Trial (The NOW Trial)." *BMC Public Health* 19(1): 310.

*Sub-heading numbers, table/figure numbers and reference formatting have been modified for consistency with the present dissertation.

5.1 Title: Study Protocol of a pragmatic randomized controlled trial incorporated into the Group Lifestyle Balance™ Program: The Nutrigenomics, Overweight/Obesity and Weight Management Trial (The NOW Trial)

5.2 Abstract

Background: The nutrigenomics, overweight/obesity and weight management trial (NOW Trial) is a pragmatic randomized controlled trial of community-dwelling adults recruited from the Group Lifestyle Balance™ (GLB) Program. The GLB Program (formerly referred to as the Diabetes Prevention Program) is an evidence-based, intensive weight management program, which was offered to overweight/obese patients ($BMI \geq 25.0 \text{ kg/m}^2$) in a rural Ontario community.

Methods: Patients enrolled in the GLB Program were invited to participate in this study. GLB groups were randomized 1:1 to receive either the standard GLB program + population-based lifestyle advice for weight management, or a modified GLB program + personalized, genetic-based lifestyle advice for weight management. The purpose of this study is to determine if the provision of genetic-based lifestyle guidelines is superior to the provision of population-based guidelines in a pragmatic clinical setting to promote changes in: body composition, weight, body mass index, dietary and physical activity habits, as well as attitudes, subjective norms, and behavioural control. The 12-month intervention protocol consists of 23 group-based sessions and 4 one-on-one sessions. Data collection time points include baseline in addition to 3, 6, and 12-month follow up. The comprehensive study design is described in the present manuscript, using

both the extended CONSORT checklist for reporting pragmatic trials and the SPIRIT checklist as guidance during manuscript development.

Discussion: Overall, this study seeks to pragmatically determine if the provision of DNA-based lifestyle advice leads to improved health and lifestyle outcomes compared to the provision of standard, population-based lifestyle advice. The results of this trial can be used to inform clinical and community nutrition practice guidelines.

Trial Registration: This study was registered with clinicaltrials.gov: NCT03015012 on January 9, 2017.

5.3 Introduction

Lifestyle modification of nutrition and physical activity are often recommended to help manage overweight and obesity (Jensen et al. 2014). Despite increased knowledge of beneficial lifestyle strategies for weight management, rates of overweight and obesity continue to climb among adults in Canada and the United States (Devito, French, and Goldacre 2018; Statistics Canada 2014). The Group Lifestyle Balance™ (GLB) program is one of the most successful lifestyle-based weight management programs and is currently offered in over 80 primary care settings in the United States and is now becoming increasingly prevalent in Canada (University of Pittsburgh, c2017). The GLB program was originally intended only for individuals with prediabetes and was formerly referred to as The Diabetes Prevention Program (DPP). In patients with prediabetes, the DPP lifestyle intervention reduced the risk of progressing to type 2 diabetes by 58%, while the biguanide antihyperglycemic agent, Metformin, reduced the risk of type 2

diabetes by 31% when compared to a placebo pill (Diabetes Prevention Program Research Group 2002). Given the documented success of the DPP, the Ontario Ministry of Health and Long-Term Care encouraged program expansion through broader eligibility criteria (Ontario Ministry of Health and Long-Term Care 2018), and as such some clinics are now offering this program for general weight management (regardless of receiving a prediabetes diagnosis), since overweight and obesity are considered risk factors for the development of type 2 diabetes (Diabetes Canada, c2019).

Although the GLB program has proven to be successful (Kramer et al. 2010; Diabetes Prevention Program Research Group 2002; Piatt et al. 2012), a “one-size fits all” approach to weight management has been critiqued by experts, who argue that this generalized approach yields minimal weight loss outcomes that do not satisfy the wants and needs of clinicians, researchers and patients alike (Field et al. 2013). Genetic testing is an innovative tool, which has the potential to facilitate positive lifestyle changes and enhance patient outcomes, though this has been widely debated in the literature in recent years (Horne et al. 2018; Hollands et al. 2016; O’Donovan et al. 2017; French et al. 2017). A systematic review found that actionable lifestyle recommendations (e.g., “reduce your consumption of sodium”) facilitated behaviour change greater than the provision of simple genetic-based disease-risk estimates, and that nutrition was the most promising lifestyle habit that could be motivated by lifestyle genomics testing (Horne et al. 2018).

A few studies have assessed change in weight from the provision of genetic-based information compared to a standard intervention (Arkadianos et al. 2007; Frankwich et al. 2015;

Celis-Morales et al. 2017). Two studies reported that genetic testing was superior to a standard intervention for changes in weight or BMI (Arkadianos et al. 2007; Celis-Morales et al. 2017), and one study showed that adherence to a genetic-based diet was correlated with greater weight loss, whereas adherence to a standard diet was not (Frankwich et al. 2015).

There have been considerable scientific advancements in knowledge pertaining to nutrition and physical activity recommendations, which can be personalized based on an individual's genetic variation. Nutrigenomics is a science that explores the interaction between nutrition, genetics, and health outcomes (Gibney and Walsh 2013). The science exploring how nutrition and physical activity, alongside other lifestyle components, can impact health outcomes can be referred to as *lifestyle genomics* (Horne et al. 2018). Single nucleotide polymorphisms (SNPs) located within the genes FTO, MC4R, TCF7L2, UCP1, APOA2, and PPARg2 can impact physical activity and dietary approaches to weight management and/or nutritional habits (Corella et al. 2010; Nagai et al. 2011; Zhang et al. 2012; Grau et al. 2010; Mattei et al. 2012; Phillips et al. 2012; Garaulet et al. 2011; Stutzmann et al. 2009; Andreasen et al. 2008). Furthermore, SNPs located within the genes ACTN3, NFIA-AS2, ADRB3, NRF2 and GSTP1 have been shown to impact genetic predisposition to excel in either endurance or strength-based activities (Ma et al. 2013; Ahmetov et al. 2015; Zarebska et al. 2014; He et al. 2006; Santiago et al. 2011). These genetic variants were used in the genetic test provided in the present study as they are currently offered through commercial genetic testing (Nutrigenomix Inc., n.d.), thus optimizing the pragmatic nature of this trial.

While genetics certainly play a role in obesity, there are multiple factors contributing to the current obesity epidemic, including diminished energy expenditure, increased energy intake, rising food costs, the built environment, socioeconomic status, and other social determinants of health (Moore et al. 2010; Eriksson et al. 2003; Finkelstein, Ruhm, and Kosa 2005; Seabrook and Avison 2010; Gilliland et al. 2012; Sarma et al. 2014). Several of these factors can be modified such as energy intake and energy expenditure.

The Theory of Planned Behaviour (TPB) posits that attitudes towards a behaviour, subjective norms, perceived behavioural control and actual behavioural control can be used to predict intentions and behaviours (Ajzen 1991). Although the TPB is one of the most widely-accepted behaviour change theories, it has yet to be incorporated into genetic testing behaviour change research (Horne, Madill, and Gilliland 2017; Horne et al. 2018), despite a recent call to incorporate this theory into personalized healthcare research (Horne, Madill, and Gilliland 2017). By considering this theory, we can account for many contributors impacting behaviour change and therefore account for several confounding factors, which could influence study results. The present randomized controlled trial is the first study to intentionally incorporate the TPB into genetic testing behaviour change research.

The proposed extended CONSORT checklist for reporting pragmatic trials (Zwartein et al. 2008) was used to guide the development of the current manuscript. The complete checklist can be reviewed in Supplementary Table 5.2, with items 1 through 16 being relevant for purposes of this paper.

5.4 Methods/Design

5.4.1 Objectives

The primary objective of this study is to determine if the provision of genetic-based lifestyle advice reduces body fat percentage to a greater extent than the provision of population-based lifestyle advice. Secondary objectives include determining whether the provision of genetic-based lifestyle advice (a) helps to motivate healthful changes to dietary intake and physical activity, (b) leads to greater improvements in anthropometric measures such as weight, BMI, lean mass, fat mass (kg), and water weight, and (c) influences attitudes, subjective norms, behavioural control, and intention to make lifestyle changes. The tertiary objective is to determine if there is a nutrigenomics interaction between ACE rs4343 genetic variation, sodium and water intake, and water weight.

5.4.2 Hypotheses

Compared to the provision of population-based lifestyle advice, providing DNA-based lifestyle advice will lead to significantly greater improvements in: body fat percentage, attitudes and intentions towards behaviour change, the adoption of healthier dietary and physical activity habits, as well as improved weight, and BMI. Furthermore, ACE rs4343 genetic variation will lead to increased water weight when sodium intake is high.

5.4.3 Material and Methods

The flow of the study protocol for this parallel group, superiority randomized controlled trial is outlined in Figures 5.1, 5.2 and 5.3. Further details are provided below.

5.4.4 Sample Size Calculation

Seventy-four participants ($n = 37$ per group) are needed in this study to detect a clinically meaningful difference of 4% in body fat percentage, assuming 80% power, an alpha of 5%, and a standard deviation of 6.1% (Smilowitz et al. 2009). We aimed to recruit 88 participants ($n = 44$ per group) to account for the potential dropout rate of 20%. While minimal research exists outlining a clinically meaningful change in body fat percentage, a 5% change in weight (which would come from fat mass, water weight and/or muscle mass) is often reported to be clinically meaningful (Williamson et al. 2015). Furthermore, clinical experience from the registered dietitians involved in this study helped to determine the clinically meaningful 4% difference mentioned above. This difference has also been supported in published reference standards of body fat percentage in Caucasian adults indicate that a 4% change in body fat percentage is associated with a 1 – 2 decile change on the reference standards charts (Imboden et al. 2017).

5.4.5 Cohort Randomization

A cohort randomization model was used rather than subject randomization to allow all participants in a given GLB group to obtain the same intervention. At the time of randomization, 12 cohorts (GLB groups) were randomized 1:1 to either the personalized lifestyle intervention (PLI) based on genetics, or the standard lifestyle intervention (SLI) based on population-based guidelines. It was anticipated that 12 groups of approximately 7 participants each would be needed to obtain the desired sample size of 88 participants. Prior to obtaining informed consent from participants, randomly permuted blocks were generated using the original generator on an

internet-based randomization program (Dallal 2017). Since participant recruitment was quicker than anticipated and there was an even 1:1 split of a PLI and a SLI group in the last two randomized groups, only 10 of the randomized groups (5 PLI groups, 5 SLI groups) were used, resulting in a total of $N = 140$ participants in the study (mean number of study participants per group \pm SD = 14.0 ± 4.1).

5.4.6 Recruitment

Participants were recruited from the GLB program at the East Elgin Family Health Team (EEFHT). There were two primary methods of recruitment into this program: [1] adults from Elgin and Middlesex Counties in Ontario, Canada were referred to the GLB program by healthcare professionals in the area such as registered dietitians (RDs), physicians, nurses, nurse practitioners, and physical therapists; and [2] adults joined the program through word-of-mouth referrals from members of the community. Participants expressing interest in joining the GLB program were invited to the EEFHT for an in-person meeting to learn about the NOW Trial, and to provide written, informed consent if they decided to take part in the study. Therefore, participants are highly reflective of typical patients in the GLB program. Recruitment occurred from April 2017 until September 2018. This study is registered with clinicaltrials.gov (NCT03015012) and was approved by the Western University Research Ethics Board (108511).

5.4.7 Participants: Screening & Informed Consent

Screening and informed consent were completed in person at The EEFHT during the in-person meeting. Inclusion criteria were as follows: BMI ≥ 25.0 kg/m², ≥ 18 years of age, English-

speaking, willing to undergo genetic testing, having access to a computer with internet at least one day per week, and not seeing another healthcare provider for weight loss advice outside of the study. Pregnancy and lactation were considered exclusion criteria.

5.4.8 Run-In

Upon obtaining written, informed consent, participants were scheduled for in-person baseline data collection, within approximately 14 days (mean \pm SD = 9.3 \pm 5.7) prior to the intervention start date. Participants were not given any lifestyle advice during the run-in period.

5.4.9 Baseline Data Collection

All data were entered into the database using unique study codes for each participant and were securely stored in a locked cabinet, in a locked office. Baseline data consisted of a combination of in-person, online, and telephone data collection methods.

Trained research assistants collected 3-day food records over the phone using the validated multiple-pass method (Conway et al. 2003). To reduce participant burden, each participant chose to have either three separate phone calls (one for each day of intake), or one phone call (for all three days of intake). One weekend day and two weekdays were collected. In a few cases where research assistants were unable to reach participants over the phone, the food records were collected in-person at the EEFHT. The food records were then analyzed using the Canadian Nutrient File within the nutritional analysis software program *ESHA Food Processor* (version 11.1).

Participants also completed a self-administered past-month, semi-quantitative, online food frequency questionnaire, the *Canadian Diet History Questionnaire II (CDHQII)*. This questionnaire is a modified version of the *United States Diet History Questionnaire* adapted for Canadian data (National Institutes of Health 2018). Most participants completed this questionnaire away from the EEFHT, but in cases where participants did not have internet access at home ($n = 3$), the CDHQII was self-administered at the EEFHT.

In-person baseline data collection included: measured height and weight (to calculate BMI), a BIA assessment to obtain body composition data (using the *Body Stat 1500MDD*; see further detail in methodological Appendix B), a past-week physical activity recall (to calculate metabolic equivalents), a baseline demographic questionnaire, a list of medications, and a TPB questionnaire. To optimize reliability, weight and height measurements were taken on the same *Health O Meter Professional* weigh scale and stadiometer, and body composition was assessed using the same BIA machine. The TPB questionnaire was developed based on Ajzen's Guide to Constructing a TPB Questionnaire (Ajzen 2006). The results for weight, body fat percentage, body fat amount, lean weight, and water weight from the BIA were communicated to participants during their in-person baseline data collection visit.

To assess possible short-term changes in components of the TPB (e.g., attitudes towards nutrition, physical activity, genetic testing, etc.), the TPB questionnaire was administered twice during the baseline assessment period: once during the one-on-one, in-person meeting (pre-

intervention), and once immediately after the group-based intervention was delivered (post-intervention).

5.4.10 Blinding and Allocation Concealment

During informed consent meetings, baseline data collection and the run-in period, participants were blinded to their group assignment. However, participants were not blinded to their group assignment during the administration of the second baseline TPB survey (completed immediately after the first group session in order to assess possible changes short-term in key components of the TPB upon receiving either population-based advice or genetic-based advice). Research assistants collecting and analyzing food intake data were also blinded to the study group of the participants and the statistician will be blinded to the group assignments. Since our outcomes included changes in attitudes related to genetic testing for personalized lifestyle advice, as well as change in nutrition and physical activity habits, it was inappropriate to blind the participants throughout the entire duration of the study. Therefore, participants were informed of their group assignment during the first group intervention meeting, as further outlined in section 5.4.12, below. One author (JH) generated the allocation sequence, enrolled participants, facilitated group and one-on-one interventions, collected data, entered data into the database and scheduled participants, and therefore could not be blinded. Allocation was concealed for the other five co-authors.

5.4.11 Staggered Cohorts

Staggered cohorts have been used to reduce the impact of confounding by indication and have previously been successful in studies comparing active and passive treatment groups

(Blackburn et al. 2017). In the present study, staggered cohorts were pre-planned in order to maximize study efficiency and effectiveness. Seasonality and timing of groups were considered in the planning phase to ensure that there was a similar amount of SLI groups and PLI groups offered during the day and evening. Three SLI groups were offered during the day, and 2 SLI groups were offered in the evenings. Likewise, 3 PLI groups were offered during the day, and 2 PLI groups were offered in the evenings. 1 SLI group began in the spring, 2 in the summer, and 2 in the fall. Similarly, 1 PLI group began in the spring, 2 in the summer, 1 in the fall, and 1 in the winter.

5.4.12 Interventions

Given its previously documented success (Kramer et al. 2010; Diabetes Prevention Program Research Group 2002; Piatt et al. 2012), the GLB program was chosen as the gold standard comparator for this RCT. Furthermore, given that this study is taking place within routine community/clinical practice, it is highly pragmatic with a mean overall PRECIS-2 score of 4.4 (Table 5.1) (Loudon et al. 2015).

Participants joined the GLB group session that best suited their availability, and were blinded to the group intervention assignment at this time. As previously detailed, groups were pre-randomized 1:1 to receive either the standard 12-month GLB Program curriculum + a summary report of population-based lifestyle recommendations (SLI/Control Group), or a modified 12-month GLB Program + a summary report of DNA-based lifestyle recommendations (PLI Group). All participants underwent a group-based weight management program in addition to four one-on-one sessions (one baseline and three follow-up) with a RD. Group sizes ranged

from 7 - 20 participants per group at baseline, with a mean group size of 14 participants. At the three follow-up one-on-one sessions, the RD reviewed the information provided in the summary report (population-based recommendations for the SLI group and DNA-based recommendations for the PLI group; refer to Supplementary Tables 5.3 and 5.4, respectively, for sample reports). One-on-one sessions lasted approximately 30 minutes. The same RD who completed the one-on-one sessions was also the lead trained lifestyle coach for the GLB Program group sessions. This allowed for optimization of intervention reliability in all group and one-on-one sessions. These sessions were highly standardized as outlined in Supplementary Table 5.5. No additional healthcare professionals above and beyond standard practice were hired to run the intervention at the EEFHT. Interventions took place between May 2017 and September 2019.

SLI Group Meetings (Control Group)

The standard GLB Program curriculum involves group-based education on a sustainable healthy lifestyle and a low-fat, calorie-controlled diet as further detailed elsewhere (University of Pittsburgh 2017). Standard GLB group sessions were 1 hour long. The EEFHT expanded the eligibility criteria for this program and offered it to adults with a BMI ≥ 25 kg/m². In addition to the standard GLB Program, participants were provided with an extra 1.5 hour group session (the first session), where they were given an overview of population-based information and recommendations for calories, protein, total fat, saturated fat, total unsaturated fat, monounsaturated fat, polyunsaturated fat, and physical activity. This information is further detailed in Supplementary Table 5.3. Upon completion of the 12-month study, participants in the SLI group were given the results of their lifestyle genomics test if they were interested in receiving it.

PLI Group Meetings (Intervention Group)

The modified GLB Program curriculum is outlined in Supplementary Table 5.5. The modifications allowed participants in this group to follow their DNA-based recommendations, rather than the standard population-based guidelines. For example, if an individual possessed a genetic variant in the FTO gene whereby a moderately high protein diet can enhance weight loss (Zhang et al. 2012), they were given a target for protein, and were taught how to count daily grams of protein (in addition to calories). In comparison, for the standard GLB program, every participant was provided with a target for total fat intake and were taught how to count daily fat grams (in addition to calories). Modified GLB group sessions were 1 hour long. In addition to the modified GLB Program, participants were provided with an extra 1.5 hour group session (the first session), where they were given an overview of personalized DNA-based information and recommendations for calories, protein, total fat, saturated fat, total unsaturated fat, monounsaturated fat, polyunsaturated fat, and physical activity. This information is further detailed in Supplementary Table 5.4. It should be noted that the genetic intervention is rated to be high-quality based on a recently developed genetic intervention quality assessment tool (Horne et al. 2018). The quality assessment is outlined in Supplementary Table 5.6.

5.4.13 Follow-Up Data Collection

Similar to baseline data collection, follow-up data collection involved a combination of in-person, online and telephone data collection methods. All participants were invited to complete follow-up data collection, regardless of their compliance to their intervention's lifestyle recommendation. Complete follow-up data included: BMI, 3-day food records, the CDHQII

past-month online food frequency questionnaire, BIA, a past-week physical activity recall, a follow-up demographic survey and medication list, and a TPB questionnaire. Further details of these measures are indicated above in section 5.4.9. The TPB questionnaire was administered once at each follow-up time point during the one-on-one in-person sessions. In addition, at the 12-month follow-up, participants were asked one open-ended question: *How has your life changed since you started participating in this program/study (if at all)?* Follow-up data collection commenced in August 2017 and is ongoing until September 2019.

5.4.14 Statistical Analysis Plan

We plan to use SPSS Version 23.0 to conduct all statistical analyses, and the data will be analyzed on an intention-to-treat basis. Generalized linear mixed-effects models will be used to test between group differences from baseline to each follow-up period for each outcome indicator. If significant mean differences are detected, a Tukey's post hoc test will be used to compare differences by group. General linear regression models will be used to assess interactions between a given genotype of interest and dietary component of interest on BMI and body composition. General linear regression models will further be used to assess interactions between TPB components, study group, and anthropometric measures of weight and body composition. No interim analyses will be completed.

5.4.15 Outcomes

The primary outcome in this study is change in percent body fat. Secondary outcome measures include changes in: dietary intake (calories, fat, protein, carbohydrates, unsaturated fat

including mono- and poly-unsaturated fat, saturated fat, and sodium), physical activity, attitudes, subjective norms, behavioural control, intention to make lifestyle changes, weight and BMI.

5.4.16 Dissemination

We plan to disseminate the findings from this trial through: a community presentation to the participants involved in the study, presentations at relevant conferences for researchers and healthcare professionals, as well as in peer-reviewed publications.

5.5 Discussion

The overarching aim of this study is to determine if patients have improved health and lifestyle outcomes with the provision of DNA-based lifestyle information and recommendations, compared to the provision of standard, population-based lifestyle advice. Furthermore, it aims to test the aforementioned hypotheses, based on lifestyle genomics weight management advice available to consumers globally through commercial genetic testing. This highlights the pragmatic nature of this trial, and optimizes the potential for knowledge translation on a global-scale.

The NOW Trial protocol differs from previous research in that it was designed pragmatically, using a knowledge translation approach. Furthermore, the NOW Trial aims to compare a DNA-based lifestyle change program to the gold standard, population-based lifestyle change program (the GLB Program), while considering and accounting for major confounding factors of behaviour change. It is also the first lifestyle genomics weight management and

behaviour change study to incorporate the TPB into the study design; this may help target a subset of the population that may benefit most from genetic testing for weight management. This trial is also unique because the genetic information was presented to participants in a group setting, thus demonstrating the feasibility of this more efficient approach to the delivery of genetic information.

Pragmatic clinical trials are distinguished by their focus on informing clinical practice rather than confirming a physiological or clinical hypothesis. Notably, pragmatic trials help to inform real-world research questions that are applicable to broad patient groups (Ford et al. 2016). Given the novel and pragmatic nature of the study, the NOW Trial provides several original contributions to the literature. Overall, the NOW Trial will provide important, innovative health knowledge relevant to researchers, academia, consumers, the genetic testing industry, clinicians and public health authorities.

5.6 Tables and Figures

Table 5.1: PRECIS-2 Scoring Tool

PRECIS-2 Domain	Score [Likert scale 1 (very explanatory) - 5 (very pragmatic)]
1. Eligibility: To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?	5
2. Recruitment: How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?	5
3. Setting: How different are the settings of the trial from the usual setting?	5
4. Organization: How different are the resources, provider expertise, and the organization of care delivery in the intervention arm of the trial from those available in usual care?	4
5. Flexibility (delivery): How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?	4
6. Flexibility (adherence): How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?	4
7. Follow-up: How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?	3
8. Primary outcome: To what extent is the trial's primary outcome directly relevant to participants?	5
9. Primary analysis: To what extent are all data included in the analysis of the primary outcome?	TBD
Mean score:	4.4

Figure 5.1: Flow of study protocol

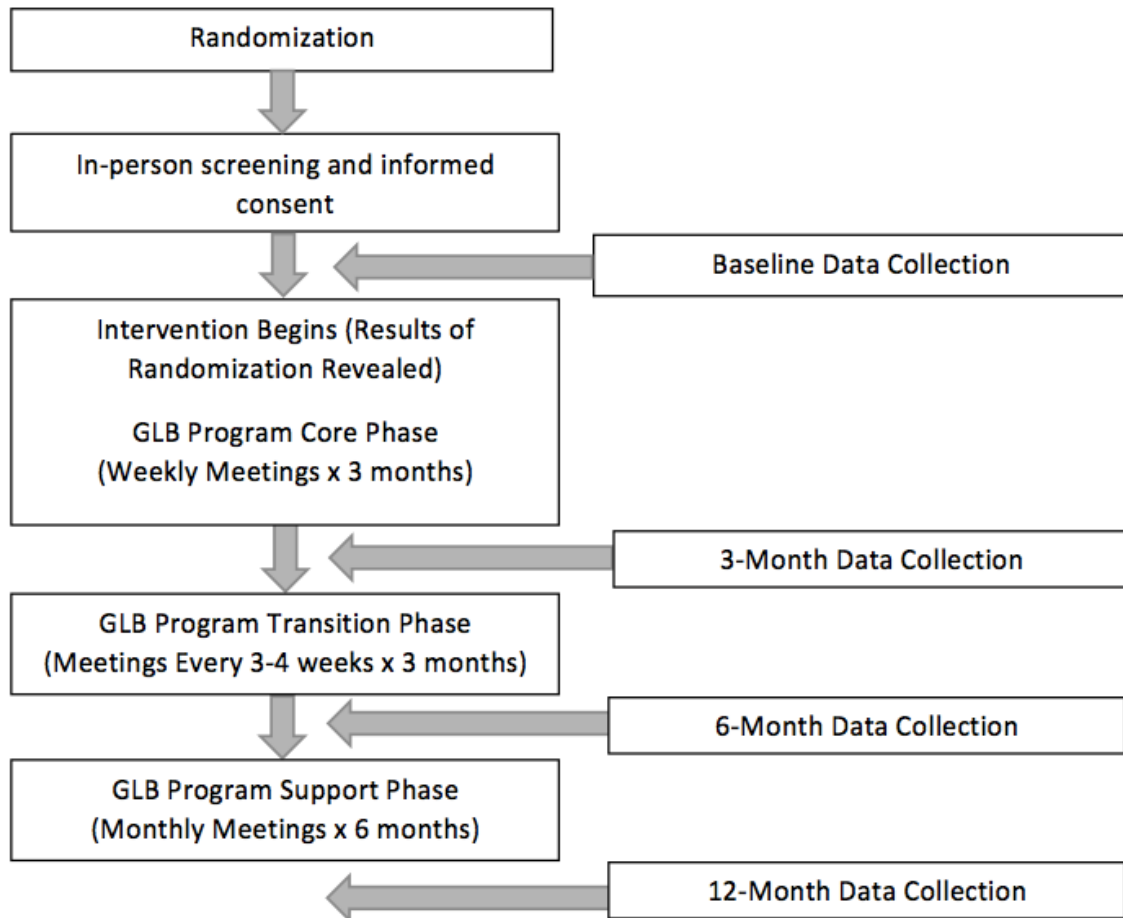


Figure 5.2: CONSORT 2010 Flow Diagram

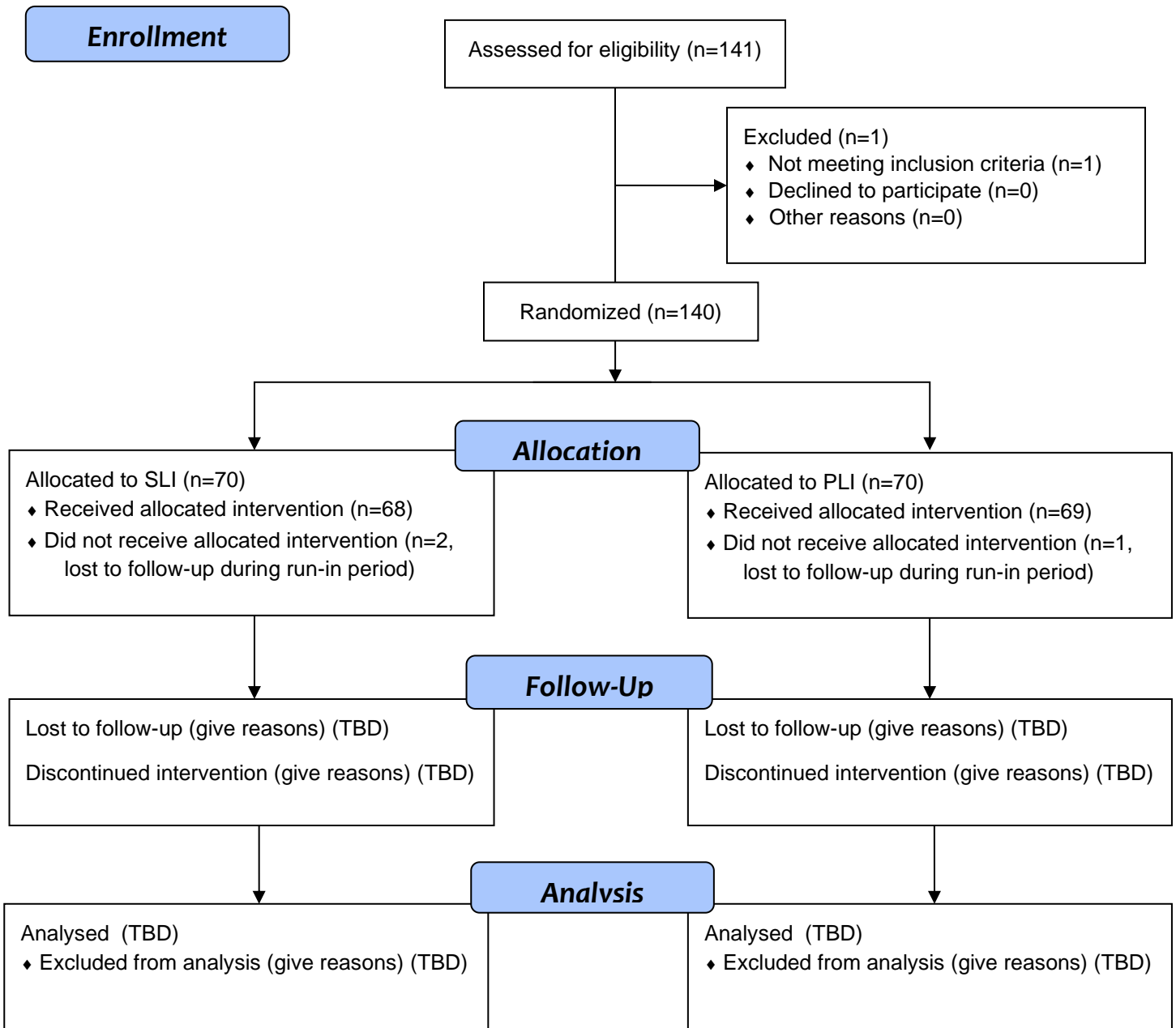


Figure 5.3: SPIRIT flow diagram of the NOW trial study protocol at the EEFHT

TIMEPOINT	STUDY PERIOD						
	Enrolment	Baseline Data Collection	Post-allocation				Close-out
	SE	Run-In	Day 1	3 Mo.	6 Mo.	12 Mo.	12 Mo.
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation Revealed to Participants			X				
INTERVENTIONS:							
<i>Personalized Lifestyle Intervention</i>			←————→				
<i>Standard Lifestyle Intervention (Control)</i>			←————→				
<i>Lifestyle Genomics Results Provided to Control Group</i>							X
ASSESSMENTS:							
<i>Body Composition</i>		X		X	X	X	
<i>Weight/Height/BMI</i>		X		X	X	X	
<i>TPB Survey</i>		X	X	X	X	X	
<i>Demographic Questionnaire + Med List</i>		X		X	X	X	
<i>Past-Week Physical Activity Recall</i>		X		X	X	X	
<i>3-Day Food Records</i>		X		X	X	X	
<i>Past-Month CDHQII</i>		X		X	X	X	
<i>Qualitative Component</i>						X	

SE: study entry Mo: month

Supplementary Table 5.2: Proposed extended CONSORT checklist of items for reporting pragmatic trials

Section	Item	Standard CONSORT description	Extension for pragmatic trials	Checklist
Title and abstract	1	How participants were allocated to interventions (eg, “random allocation,” “randomised,” or “randomly assigned”)		✓
Introduction				
Background	2	Scientific background and explanation of rationale	Describe the health or health service problem that the intervention is intended to address and other interventions that may commonly be aimed at this problem	✓
Methods				
Participants	3	Eligibility criteria for participants; settings and locations where the data were collected	Eligibility criteria should be explicitly framed to show the degree to which they include typical participants and/or, where applicable, typical providers (eg, nurses), institutions (eg, hospitals), communities (or localities eg, towns) and settings of care (eg, different healthcare financing systems)	✓
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	Describe extra resources added to (or resources removed from) usual settings in order to implement intervention. Indicate if efforts were made to standardise the intervention or if the intervention and its delivery were allowed to vary between participants, practitioners, or study sites	✓
			Describe the comparator in similar detail to the intervention	✓
Objectives	5	Specific objectives and hypotheses		✓

Section	Item	Standard CONSORT description	Extension for pragmatic trials	Checklist
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors)	Explain why the chosen outcomes and, when relevant, the length of follow-up are considered important to those who will use the results of the trial	✓
Sample size	7	How sample size was determined; explanation of any interim analyses and stopping rules when applicable	If calculated using the smallest difference considered important by the target decision maker audience (the minimally important difference) then report where this difference was obtained	✓
Randomisation—sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification)		✓
Randomisation—allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned		✓
Randomisation—implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups		✓
Blinding (masking)	11	Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment	If blinding was not done, or was not possible, explain why	✓
Statistical methods	12	Statistical methods used to compare groups for primary outcomes; methods for additional analyses, such as subgroup analyses and adjusted analyses		✓
Results				
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended)—specifically, for each group, report the	The number of participants or units approached to take part in the trial, the number which were	✓

Section	Item	Standard CONSORT description	Extension for pragmatic trials	Checklist
		numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome; describe deviations from planned study protocol, together with reasons	eligible, and reasons for non-participation should be reported	
Recruitment	14	Dates defining the periods of recruitment and follow-up		✓
Baseline data	15	Baseline demographic and clinical characteristics of each group		TBD
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether analysis was by “intention-to-treat”; state the results in absolute numbers when feasible (eg, 10/20, not 50%)		TBD
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% CI)		TBD
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating which are prespecified and which are exploratory		TBD
Adverse events	19	All important adverse events or side effects in each intervention group		TBD
Discussion				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes		TBD
Generalisability	21	Generalisability (external validity) of the trial findings	Describe key aspects of the setting which determined the trial results. Discuss possible	TBD

Section	Item	Standard CONSORT description	Extension for pragmatic trials	Checklist
			differences in other settings where clinical traditions, health service organisation, staffing, or resources may vary from those of the trial	
Overall evidence	22	General interpretation of the results in the context of current evidence		TBD

Supplementary Table 5.3: Sample report for standard lifestyle intervention (GLB group)

Lifestyle Component	Population-Based Recommendations
Calories	Aim for a 500 calorie deficit per day for weight loss.
Protein	Consume 10-35% of calories from protein.
Total Fat	Consume 20-35% of calories from fat.
Saturated Fat	Limit your saturated fat intake to less than 10% of total calories.
Unsaturated Fat	Consume a balance of monounsaturated and polyunsaturated fat to meet your total fat needs.
Monounsaturated Fat	Consume a balance of monounsaturated and polyunsaturated fat to meet your total fat needs.
Polyunsaturated Fat	
Sodium	Consume less than 2300 mg sodium daily.
Eating Between Meals	Do not go longer than six hours without eating throughout the day. Ensure snacks and meals are calorie-controlled.
Physical Activity	Aim for 150 minutes/week of physical activity with muscle strengthening activities at least 2 days/week.
Endurance	Find an endurance-based activity that you enjoy – meet the physical activity guidelines stated above.
Strength and Power	Find a strength/power based activity that you enjoy – meet the physical activity guidelines stated above.

Supplementary Table 5.4: Sample report for personalized lifestyle intervention (GLB+NGx)

Lifestyle Component	Gene(s), rs number(s)	Your Genetic Variant	Your Risk/ Response	DNA-Based Recommendations and Implication
Calories	UCP1, rs1800592	AA	Typical	Your resting metabolism is typical. Aim for a 500 calorie deficit per day for weight loss.
Protein	FTO, rs9939609	AA	Enhanced	You can enhance your weight loss if you consume 25-35% of calories from protein.
Total Fat	TCF7L2, rs7903146	TC	Typical	Consume 20-35% of calories from fat.
Saturated Fat	APOA2, rs5082	CC	Enhanced	You can enhance your weight loss if you consume less than 10% of calories from saturated fat.
Unsaturated Fat	FTO, rs9939609	AA	Enhanced	You can enhance your weight loss if you limit your intake of saturated fat to less than 10% of calories and consume at least 5% of calories from polyunsaturated fat.
Monounsaturated Fat	PPARG2, rs1801282	CC	Typical	Consume a balance of monounsaturated and polyunsaturated fat to meet your total dietary fat intake goal.
Sodium	ACE, rs4343	GG	Typical	Limit your sodium intake to less than 2300 mg per day for heart health.
Eating Between Meals	MC4R, rs17782313	TT	Typical	You have a typical likelihood of eating between meals. Do not go longer than six hours without eating.
Physical Activity	FTO, rs9939609	AA	Enhanced	You can enhance your weight loss if you complete at least 30-60 minutes/day of cardio activity, 6 days/week and muscle-strengthening activities at least 2 days/week.
Endurance	ADRB, rs4994	TT	Typical	You have a typical genetic predisposition to excel in endurance-based physical activity.
	NRF2, rs12594956	CA		
	GSTP1, rs1695	AA		
	NFIA-AS2, rs1572312	CC		
Strength and Power	ACTN3, rs1815739	TC	Enhanced	You have an enhanced genetic predisposition to excel in strength and power based physical activity.
Participant Number	X			

Supplementary Table 5.5: GLB program/NOW trial curriculum and modifications for genetic testing intervention groups

Class Number	Class Topic	Modifications for Genetic Testing Intervention Groups¹
1	General Overview of Nutrition and Physical Activity Targets ²	<ul style="list-style-type: none"> Genetic information and recommendations provided to participants
2	Welcome to the Group Lifestyle Balance™ Program ³	<ul style="list-style-type: none"> The physical activity goal was verbally modified whereby participants were asked to refer to their personalized physical activity goals from their genetic report.
3	Be a Calorie Detective	<ul style="list-style-type: none"> Any reference made to counting fat grams was verbally modified. Participants were reminded about how response to different diets for weight loss differ from person to person. Based on their personalized genetic report, participants were advised and taught how to count a nutrient that would benefit their personal weight loss (i.e. some counted protein, others counted saturated fat, and/or total fat, etc). The calorie goals remained the same, but participants with the “diminished” result in their genetic report for calories were advised to be especially mindful of meeting their calorie goal, and were advised to aim for a 650 kcal deficit to lose 1 lb per week.
4	Healthy Eating	<ul style="list-style-type: none"> When reference was made to a nutrient included in the genetic report, participants were instructed to refer back to their genetic report to recall how this nutrient might be particularly important to them. The information in the genetic reports was then reviewed.
5	Move Those Muscles	<ul style="list-style-type: none"> The physical activity goal was verbally modified whereby participants were asked to refer to their personalized physical activity goals from their genetic report. Genetic predisposition to excel in endurance and/or strengthening activities (outlined in the genetic report) was reviewed.
6	Tip the Calorie Balance	<ul style="list-style-type: none"> For the daily calorie deficit for weight loss, participants were advised to refer to their genetic report to determine

		<p>if they should aim for a 500 kcal deficit/day or a 650 kcal deficit/day.</p> <ul style="list-style-type: none"> When reference was made to a nutrient included in the genetic report, participants were instructed to refer back to their genetic report to recall how this nutrient might be particularly important to them. The information in the genetic reports was then reviewed.
7	Take Charge of What's Around You	<ul style="list-style-type: none"> No¹ modifications were made. Some participants discussed components of their genetic report.
8	Problem Solving	<ul style="list-style-type: none"> No¹ modifications were made. Some participants discussed components of their genetic report.
9	Step Up Your Physical Activity Plan	<ul style="list-style-type: none"> The physical activity goal was verbally modified whereby participants were asked to refer to their personalized physical activity goals from their genetic report. Genetic predisposition to excel in endurance and/or strengthening activities (outlined in the genetic report) was reviewed. Participants with the “enhanced” weight loss response to physical activity (from the genetic report), were advised to continue working up to 30-60 mins/day, 6 days/week of moderate intensity physical activity.
10	Manage Slips & Self-Defeating Thoughts	<ul style="list-style-type: none"> The step goal was verbally modified for individuals with the “enhanced” weight loss response to physical activity; these individuals were advised to aim for 10,000 steps/day. When reference was made to a nutrient included in the genetic report, participants were instructed to refer back to their genetic report to recall how this nutrient might be particularly important to them. The information in the genetic reports was then reviewed.
11	Four Keys to Healthy Eating Out	<ul style="list-style-type: none"> No¹ modifications were made. Some participants discussed components of their genetic report.
12	Make Social Cues Work for You	<ul style="list-style-type: none"> No¹ modifications were made. Some participants discussed components of their genetic report.
13	Ways to Stay Motivated	<ul style="list-style-type: none"> The physical activity goal was verbally modified whereby participants were asked to refer to their

		<p>personalized physical activity goals from their genetic report.</p> <ul style="list-style-type: none"> • The step goal was verbally modified for individuals with the “enhanced” weight loss response to physical activity; these individuals were advised to aim for 10,000 steps/day.
14	Strengthen Your Physical Activity Plan	<ul style="list-style-type: none"> • The physical activity goal was verbally modified whereby participants were asked to refer to their personalized physical activity goals from their genetic report. • The step goal was verbally modified for individuals with the “enhanced” weight loss response to physical activity; these individuals were advised to aim for 10,000 steps/day. Genetic predisposition to excel in endurance and/or strengthening activities (outlined in the genetic report) was reviewed.
15	Take Charge of Your Lifestyle	<ul style="list-style-type: none"> • Reference made to fat grams was verbally modified. Participants were reminded about how response to different diets for weight loss differ from person to person. Based on their personalized genetic report, participants were advised to count a nutrient that would benefit their personal weight loss (i.e. some counted protein, others counted saturated fat, and/or total fat, etc).
16	Mindful Eating, Mindful Movement	<ul style="list-style-type: none"> • No¹ modifications were made. Some participants discussed components of their genetic report.
17	Manage Your Stress	<ul style="list-style-type: none"> • No¹ modifications were made. Some participants discussed components of their genetic report.
18	Sit Less for Your Health	<ul style="list-style-type: none"> • No¹ modifications were made. Some participants discussed components of their genetic report.
19	More Volume, Fewer Calories	<ul style="list-style-type: none"> • When reference was made to a nutrient included in the genetic report, participants were instructed to refer back to their genetic report to recall how this nutrient might be particularly important to them. The information in the genetic reports was then reviewed.
20	Stay Active	<ul style="list-style-type: none"> • No¹ modifications were made. Some participants discussed components of their genetic report.

21	Balance Your Thoughts	<ul style="list-style-type: none"> No¹ modifications were made. Some participants discussed components of their genetic report.
22	Heart Health	<ul style="list-style-type: none"> When reference was made to a nutrient included in the genetic report, participants were instructed to refer back to their genetic report to recall how this nutrient might be particularly important to them. The information in the genetic reports was then reviewed. The physical activity goal was verbally modified whereby participants were asked to refer to their personalized physical activity goals from their genetic report. The step goal was verbally modified for individuals with the “enhanced” weight loss response to physical activity; these individuals were advised to aim for 10,000 steps/day. Genetic predisposition to excel in endurance and/or strengthening activities (outlined in the genetic report) was reviewed.
23	Look Back & Look Forward	<ul style="list-style-type: none"> The physical activity goal was verbally modified whereby participants were asked to refer to their personalized physical activity goals from their genetic report. The step goal was verbally modified for individuals with the “enhanced” weight loss response to physical activity; these individuals were advised to aim for 10,000 steps/day. Genetic predisposition to excel in endurance and/or strengthening activities (outlined in the genetic report) was reviewed.

1. The physical activity goal and references to fat grams were verbally modified in the “To Do” lists at the end of sessions. Participants were reminded about how response to different diets and physical activity for weight loss differ from person to person. Based on their personalized genetic report, participants were advised and taught how to reach their personal nutrition and physical activity goals. This modification occurred throughout the GLB Program’s “To Do” lists and is not included in this table.

2. The GLB curriculum begins in class 2. Class 1 allows for an overview of nutrition and physical activity guidelines either based on 1) the Acceptable Macronutrient Distribution Ranges and population-based health information and recommendations or 2) genetic-based information and recommendations. Refer to Supplementary Tables 5.3 and 5.4 for sample reports provided in class 1.

3. Participants were informed about how the program is typically used for individuals with pre-diabetes, since our population consisted of overweight/obese adults who may or may not have pre-diabetes or type 2 diabetes.

Supplementary Table 5.6: Quality assessment tool for genetic interventions

Criteria	Yes	No	Other (CD, NR, NA)*
1. Were the results of the genetic test interpreted and explained by a trained healthcare professional?	✓		
2. Was a copy of the genetic testing report provided to the participants?	✓		
3. Were the results of the genetic test communicated to participants on more than one occasion (i.e. was there follow-up provided after the initial communication of the results)?	✓		
4. Were the results provided in the report, or discussed in the genetic counselling session actionable (i.e. did the report contain specific recommendations or did the genetic counsellor communicate specific recommendations)?	✓		
5. Were the participants provided with an opportunity to ask questions about their results?	✓		

Other Comments: N/A _____

Overall Rating (Good, Fair, Poor; if Poor state reasons): **Good**

*CD: cannot determine, NR: not reported, NA: not applicable

**CHAPTER 6: DIETARY ADHERENCE AND CHANGE IN
DIETARY INTAKE**

6.1 Title: Enhanced long-term dietary change and adherence in a nutrigenomics-guided lifestyle intervention program compared to a population-based (GLB/DPP) lifestyle intervention for weight management: Results from the NOW randomized controlled trial

6.1.1 Abstract

Background: Adherence to nutritional guidelines for chronic disease prevention and management remains a challenge in clinical practice. Innovative strategies are needed to help optimize dietary behaviour change.

Objective: The objective of this study was to determine if a nutrigenomics-guided lifestyle intervention program could be used to motivate greater dietary adherence and change in dietary intake short-term, moderate-term, and long-term compared to the gold-standard population-based weight management intervention [Group Lifestyle Balance™ (GLB)/Diabetes Prevention Program (DPP)].

Design: The nutrigenomics, overweight/obesity, and weight management randomized controlled trial is a pragmatic, parallel-group, superiority clinical trial ($N=140$), which was conducted at the East Elgin Family Health Team (EEFHT). GLB weight management groups were pre-randomized 1:1 to receive either the standard GLB program, or a modified GLB + nutrigenomics (GLB+NGx) program. Three-day food records were collected at baseline, 3, 6 and 12 months using the validated multiple pass method. Researcher assistants collecting 3-day food records were blinded to the participants' group assignments. Statistical analyses included: split plot analyses of variance (ANOVAs), two-way ANOVAs, binary logistic regression, chi-square and Fisher's exact tests. Using the Theory of Planned Behaviour as guidance, important confounding factors of behaviour change were considered in the analyses.

Results: Only the GLB+NGx group significantly reduced their total fat intake from baseline to 12-month follow-up ($36.0\pm 4.8\%$ kcal to $30.2\pm 8.7\%$ kcal, $p=0.02$). Long-term dietary adherence to total fat and saturated fat guidelines were also significantly ($p<0.05$) greater in the GLB+NGx group compared to the standard GLB group.

Conclusions: Nutrigenomics weight management interventions can motivate long-term improvements in dietary fat intake above and beyond standard guidelines.

6.1.2 Introduction

The science of nutrigenomics, which explores interactions between individual genetic variation, dietary intake and changes in gene expression, structure and function (Subbiah 2008), has garnered significant attention in recent years with consumers and healthcare professionals alike expressing overall positive attitudes towards genetic testing for personalized nutrition (Valée Marcotte et al. 2019; Nielsen and El-Sohehy 2014; Cormier et al. 2014). As such, a number of companies are offering nutrigenetic testing for weight management (Saukko 2013; Drabsch and Holzapfel 2019).

A recent review reported that personalized nutrition recommendations are of great potential for optimizing outcomes of weight management interventions, while also noting that research in this area is lacking and human intervention studies are needed (Drabsch and Holzapfel 2019). The potential value of personalized nutrition for weight management stems from studies indicating positive consumer attitudes towards genetic-based dietary advice (Nielsen and El-Sohehy 2014; Morin 2009), several indications that a one-size-fits all approach to weight management is not optimal (Drabsch and Holzapfel 2019), and the potential for genetically-

guided, actionable nutrition recommendations to help motivate changes in dietary intake (Horne et al. 2018).

According to the most recent systematic review on genetic testing behaviour change research, nutrition was found to be the most promising lifestyle component that could be motivated as a result of undergoing genetic testing, especially when the genetic intervention provided actionable recommendations (Horne et al. 2018). Furthermore, this review found that genetic testing behaviour change research has yet to incorporate the Theory of Planned Behaviour (TPB), and incorporation of behaviour change theory in general is fundamentally lacking (Horne et al. 2018). This is concerning given that the TPB is one of the most widely accepted behaviour change theories. It suggests that attitudes, subjective norms and behavioural control are the three key factors affecting human behaviour (Ajzen 1991). Furthermore, researchers in the field of genetic testing behaviour change research have called to action academia to incorporate this theory into genetic testing behaviour change studies to account for potential confounding factors; this has been further detailed elsewhere (Horne et al. 2017). Behaviour change theories provide important guidance for the development of interventions that are more likely to facilitate changes in lifestyle habits. Thus, failing to consider established behaviour change theories can lead to findings that do not demonstrate changes in dietary behaviours. As such, it is not surprising that the current limited knowledge related to change in dietary intake and eating habits in genetic-based weight management interventions does not appear to be promising (Horne et al. 2018; Meisel et al. 2015). Overall, the field of nutrigenomics and behaviour change is highly complex and warrants further investigation.

The purpose of this study was to address the limitations of previous work by considering the TPB in the dietary intervention and statistical analyses, providing a high-quality, personalized,

genetic-based lifestyle intervention, and ultimately determining if the provision of a nutrigenetic-based weight management intervention motivates greater dietary changes and adherence compared to a population-based weight management intervention.

6.1.3 Subjects and Methods

The current study is a sub-study within the nutrigenomics, overweight/obesity and weight management trial (NOW trial), which is a parallel-group, superiority, randomized, controlled clinical intervention study (N=140) incorporated into the Group Lifestyle Balance™ (GLB) program (formerly referred to as the Diabetes Prevention Program). The GLB program is one of the most effective public health weight management programs (Xiao et al. 2013; Diabetes Prevention Program Research Group 2002; McTigue et al. 2009; Piatt et al. 2012); it is offered in numerous clinics in the United States and Canada (University of Pittsburgh c2019) and has been extensively researched for long-term weight management and diabetes prevention (Xiao et al. 2013; Diabetes Prevention Program Research Group 2002; McTigue et al. 2009; Piatt et al. 2012). Detailed study methods for the NOW trial have been published elsewhere (Horne et al. 2019). One author (JH) conducted 1:1 computer-generated cohort randomization (Dallal 2017) of 12 GLB groups as this was the anticipated number of groups required to achieve the target sample size. A cohort randomization model was used rather than subject randomization to ensure that all participants in each GLB group received the same intervention [standard GLB or GLB + nutrigenomics (GLB + NGx)]. This study was approved by the Western University Research Ethics Board and registered with clinicaltrials.gov (NCT03015012).

Participants

Patients were recruited into the GLB program at the East Elgin Family Health Team (EEFHT) in Aylmer, Ontario, Canada through healthcare professional referrals and word-of-mouth referrals from members of the community from April 2017 – September 2018. Patients expressing interest in the GLB program were then invited to participate in the study if they met the following inclusion criteria: BMI ≥ 25.0 kg/m², ≥ 18 years of age, English-speaking, willing to undergo genetic testing, having access to the internet, and not seeing another healthcare provider for weight loss advice outside of the study. Pregnancy and lactation were exclusion criteria. The target total sample size was 74 participants (after dropout) in order to detect a 4% change in body fat percentage (primary outcome), using a standard deviation of 6.1%, with 80% power and an alpha of 5%. Since recruitment was quicker than anticipated, recruitment ended after 10 cohorts since there was an even 1:1 split of a GLB and GLB+NGx group in the last two pre-randomized cohorts as further detailed previously (Horne et al. 2019). Four of the five researchers (JG, JS, CO, JM) and all research assistants collecting 3-day food records (3DFRs) were blinded to participant group allocation. It was not possible to blind the researcher responsible for organizing and facilitating all intervention sessions (JH) and given the nature of the intervention, it was inappropriate to blind participants to their allocated intervention. The participants, setting and healthcare provider facilitating the interventions (JH) were all highly representative of typical/standard care. All interventions were delivered by one healthcare provider (JH) in order to standardise their delivery and enhance reliability and no additional resources were required to implement the interventions; the healthcare provider is a registered dietitian (RD) who has previous training in nutritional genomics.

Interventions

Staggered cohorts participated in the 12-month intervention and data collection occurred from May 2017 – September 2019. Participants received specific targets for eight nutrients: calories, protein, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), total unsaturated fat, total fat, and sodium. These targets were derived from genetics for half of the participants, and were derived from population-based guidelines (Health Canada 2010) for the other half of participants; the nutrition reports provided to participants have been previously published (Horne et al. 2019). For the standard GLB intervention, participants were advised primarily to follow a calorie-controlled, moderately-low fat (25% kcal) nutrition plan (University of Pittsburgh c2017). Both intervention groups followed the standard GLB program overall calorie intake targets (University of Pittsburgh c2017). For the personalized GLB+NGx group, individuals received information related to resting metabolism and subsequent personalized calorie deficits recommended for weight loss (Horne et al. 2019). Participants in the GLB+NGx group were advised to focus on the macronutrient recommendation(s) that was/were highlighted in their genetic report to enhance weight loss response. For example, an individual with the AA variant of FTO (rs9939609) was advised to focus on following a higher-protein nutrition plan to optimize weight loss, whereas an individual with the CC variant of APOA2 (rs5082) was advised to focus on following a low saturated fat (<10% kcal) nutrition plan to optimize weight loss (rather than all participants following the standard moderately-low total fat GLB nutrition intervention). Participants randomized to the GLB+NGx group were also informed of their genetic predisposition to eat more frequently during the day based on MC4R (rs17782313) genetic variation. If an individual had multiple genetic variants and genetic-based nutrition recommendations highlighted in their genetic report,

they were advised to focus on achieving one of the nutrition targets (of their choosing), and then work on another when they perceived that they were ready to engage in further dietary changes. A sample NOW trial genetic report has been previously published elsewhere; this report was selected for the present study based off commercially available nutrigenetic testing accessible by the general public through healthcare professionals (Horne et al. 2019).

All participants were advised to track their food and beverage intake closely (by completing food records/journals) for the first two to three months of the intervention while working towards their nutrition targets. They were further advised to measure their food and beverage intake for at least the first week of the intervention in order to increase awareness and accuracy of the portion sizes indicated in their dietary tracking. In the second week of the intervention, participants were educated on counting and tracking calories and nutrients (total fat for the standard GLB group; individualized nutrients for the GLB+NGx group). With weekly meetings for the first three months and meetings approximately once per month for the remainder of the 12-month intervention, participants had several opportunities to ask questions about their nutrition recommendations to ensure comprehension. These recommendations were also reviewed at a 3-month, 6-month and 12-month one-on-one follow-up appointment with an RD.

Incorporation of the TPB

This is the first study to intentionally incorporate the TPB into a genetic testing behaviour change study. Both interventions aimed to positively impact key components of the TPB (attitudes, subjective norms, and behavioural control). The interventions aimed to impact attitudes by informing individuals of the health benefits associated with engaging in a healthy lifestyle and providing education on positive mindsets and mindfulness (University of Pittsburgh c2017). The group-based nature of the intervention aimed to affect subjective norms. A stepwise,

goal-setting approach was used to help positively impact behavioural control. In the GLB+NGx group, the intervention aimed to further impact attitudes through the provision of more personalized dietary guidance. All participants completed a baseline TPB questionnaire. The TPB was used to guide the analyses of possible attrition bias and subsequently control for possible confounding factors of behaviour change as further indicated below.

Genotyping

Oragene ON-500 saliva collection kits (DNA Genotek, Ottawa, Ontario, Canada) were used to collect DNA saliva samples of participants at the EEFHT. The saliva samples were shipped and stored at -80°C at the University of Toronto until they were analysed. The iPLEX Gold assay with mass-spectrometry-based detection on the Sequenom MassARRAY® platform was used for all genotyping. This genotyping method has been utilized in previous research (Jenkins et al. 2018; Josse et al. 2012; Banks et al. 2019). The following single nucleotide polymorphisms (SNPs) of interest to the current study were analyzed: UCP1 (rs1800592), FTO (rs9939609), TCF7L2 (rs7903146), APOA2 (rs5082), PPAR γ 2 (rs1801282), MC4R (rs17782313).

Dietary Intake and Adherence

Dietary intake and adherence are important outcomes to address in a pragmatic randomized controlled trial given that altering nutrition-related behaviour change is a challenge in clinical practice. As such, dietary intake was a predetermined secondary outcome of the NOW trial (Madill 2016) and was measured using the validated multiple pass method (Conway et al. 2003) to collect three 24-hour recalls [i.e. three-day food records (3DFRs)] consisting of one weekend day and two week days. Data collection occurred at baseline (during a 14-day run-in

period), 3-month, 6-month and 12-month follow-up in order to assess short-term, moderate-term, and long-term changes. Trained research assistants who were blinded to participants' group allocations collected 3DFRs over the phone. In some rare cases where a participant could not be reached over the phone, 3DFRs were collected in-person at the EEFHT. Dietary adherence was measured by analyzing the quantity of participants adhering to the calorie, saturated fat, total fat and protein recommendations. ESHA Food Processor version 11.3.285 (ESHA Research, Salem, OR, United States) was used to analyze all 3DFRs.

Statistical Analyses

The mean and standard deviation (SD) were used to report continuous variables and percentages were used for categorical variables. Estimates of the different sources of attrition bias were conducted using two-way analysis of variance (ANOVA) models. The TPB (Ajzen 1991) was used to guide this analysis with data collected from a baseline TPB survey. The following possible confounding factors were analyzed to determine if there were significant differences between drop-outs in each group: attitudes towards changing their intake of calories, fat, and protein (attitudes); friends eating a healthy diet, family eating a healthy diet (subjective norms); stage of change/transtheoretical model; perceived difficulty altering calorie, fat, and protein intake (perceived behavioural control); income and education (actual behavioural control/social determinants of health).

Chi-square tests were used to analyze categorical variables (dietary adherence). In cases where there were fewer than five expected counts, Fisher's exact tests were used. To assess dietary adherence at 3 months while controlling for income, binary logistic regression was conducted. Split-plot ANOVAs were used to compare differences between groups (GLB vs. GLB+NGx) for change in dietary intake from baseline to 3-, 6-, and 12-month follow-up

(prespecified outcome). Repeated measures ANOVAs were used to assess within-group changes in dietary intake from baseline to 3-, 6-, and 12-month follow-up (prespecified outcome). SPSS Version 26.0 (IBM Corporation, Armonk, NY, United States) was used for all statistical analyses, which took place in October – November 2019. The analyses were by originally assigned groups.

Hypotheses

It was hypothesized that the GLB+NGx group would engage in greater dietary changes and better adhere to the dietary advice compared to the standard GLB group.

6.1.4 Results

Overall, mean values from demographic and TPB characteristics (Tables 6.1 and 6.2) indicated that the study population consisted of highly motivated, college-educated, middle-aged female subjects with obesity, who had positive attitudes towards changing their dietary intake, with neutral subjective norms related to friends/family consuming a healthy diet, and neutral perceived behavioural control for changing their dietary intake. The genetic results of participants in the GLB+NGx group are summarized in Table 6.3. There was significant attrition bias for one TPB component, income ($p=0.02$), at the 3-month follow-up only (Table 6.2) and therefore this was controlled for as a confounding factor in the 3-month analyses. There were no differential attrition rates between groups. At baseline, 112 participants completed the 3DFRs, with 86 completing the 3-month follow-up data collection (77% retention), 74 completing 6-month food records (66% retention) and 59 completing the 12-month food records (53% retention). No adverse events were reported.

Table 6.1: Baseline demographic and clinical characteristics of participants

	GLB Group Mean ± SD	GLB+NGx Group Mean ± SD
Age (years)	56.4 ± 12.1	53.5 ± 13.6
Gender	84.3% female	89.9% female
Ethnicity	98.6% Caucasian	97.1% Caucasian
Annual household income (CDN \$)	73,943 ± 41,403	71,389 ± 44,301
Weight (lbs)	217.3 ± 49.0	215.4 ± 51.8
BMI (kg/m²)	36.7 ± 7.3	37.3 ± 9.7
Body fat (%)	46.7 ± 7.0	45.7 ± 7.9

N=140 (n=70 participants per group)

Table 6.2: Baseline scores and values for components of the Theory of Planned Behaviour for dropouts and stayers

TIME POINT AND PARTICIPANT TYPE	TYPE OF GROUP	ATTITUDES			SUBJECTIVE NORMS		PERCEIVED BEHAVIOURAL CONTROL (PBC)				ACTUAL BEHAVIOURAL CONTROL	
		Attitudes (Calories)	Attitudes (Fat)	Attitudes (Protein)	Friends Eat a Healthy Diet	Family Eats a Healthy Diet	PBC (Calories)	PBC (Fat)	PBC (Protein)	Stage of Change	Income (CDN\$)	Level of Education
3-MONTH STAYERS	GLB	6.39 ± 0.75	6.27 ± 0.94	6.30 ± 0.73	4.06 ± 1.69	5.06 ± 1.64	4.45 ± 1.28	4.73 ± 1.38	4.76 ± 1.39	3.70 ± 1.05	70,619 ± 37,561 ^a	3.97 ± 0.73
	GLB+NGx	6.49 ± 0.98	6.23 ± 1.03	6.31 ± 1.05	4.57 ± 1.31	5.06 ± 1.32	4.31 ± 1.60	4.37 ± 1.65	4.80 ± 1.57	4.00 ± 1.06	85,059 ± 44,460 ^a	4.06 ± 0.79
3-MONTH DROP-OUTS	GLB	6.16 ± 0.99	5.89 ± 1.50	5.76 ± 1.28	4.19 ± 1.65	4.65 ± 1.58	4.25 ± 1.46	4.31 ± 1.60	4.56 ± 1.48	3.42 ± 1.00	76,806 ± 44,778 ^a	3.75 ± 0.84
	GLB+NGx	6.24 ± 1.10	6.26 ± 0.93	6.29 ± 0.91	4.18 ± 1.31	5.00 ± 1.30	4.50 ± 1.64	4.71 ± 1.51	5.35 ± 1.59	3.67 ± 0.88	56,865 ± 39,852 ^a	3.97 ± 0.76
6-MONTH STAYERS	GLB	6.50 ± 0.67	6.22 ± 0.97	6.31 ± 0.78	4.31 ± 1.60	5.06 ± 1.61	4.28 ± 1.28	4.63 ± 1.43	4.78 ± 1.39	3.59 ± 1.04	68,006 ± 33,432	3.97 ± 0.65
	GLB+NGx	6.51 ± 0.95	6.31 ± 1.00	6.41 ± 0.98	4.48 ± 1.30	5.00 ± 1.39	4.38 ± 1.68	4.41 ± 1.57	4.54 ± 1.48	3.93 ± 1.10	74,893 ± 45,009	4.04 ± 0.96
6-MONTH DROP-OUTS	GLB	6.01 ± 1.00	5.95 ± 1.49	5.76 ± 1.24	3.97 ± 1.72	4.66 ± 1.62	4.41 ± 1.46	4.52 ± 1.70	5.21 ± 1.66	3.51 ± 1.02	79,056 ± 47,079	3.76 ± 0.89
	GLB+NGx	6.36 ± 1.04	6.24 ± 0.98	6.23 ± 0.97	4.30 ± 1.34	5.05 ± 1.26	4.43 ± 1.58	4.55 ± 1.50	4.98 ± 1.56	3.78 ± 0.89	68,808 ± 44,197	4.00 ± 0.82
12-MONTH STAYERS	GLB	6.57 ± 0.60	6.43 ± 0.87	6.29 ± 0.85	4.43 ± 1.66	5.24 ± 1.44	4.38 ± 1.36	4.57 ± 1.60	4.81 ± 1.50	3.67 ± 1.11	68,760 ± 31,195	4.05 ± 0.67
	GLB+NGx	6.39 ± 1.10	6.21 ± 1.07	6.18 ± 1.12	4.53 ± 1.35	5.07 ± 1.39	4.57 ± 1.73	4.68 ± 1.76	5.18 ± 1.70	4.04 ± 1.10	81,574 ± 42,411	4.00 ± 0.92
12-MONTH DROP-OUTS	GLB	6.14 ± 0.96	5.92 ± 1.40	5.90 ± 1.16	4.00 ± 1.66	4.67 ± 1.66	4.33 ± 1.39	4.48 ± 1.47	4.58 ± 1.41	3.50 ± 0.99	76,149 ± 45,177	3.77 ± 0.83
	GLB+NGx	6.34 ± 1.02	6.27 ± 0.92	6.39 ± 0.86	4.27 ± 1.30	5.00 ± 1.26	4.29 ± 1.54	4.44 ± 1.45	5.00 ± 1.53	3.71 ± 0.87	64,338 ± 44,740	4.02 ± 0.85

Mean scores for attitudes, subjective norms, and PBC (calories, fat, protein) on a Likert scale of 1 (negative attitude/subjective norms/PBC) to 7 (positive attitude/subjective norms/PBC); Mean scores for stage of change on Likert scale of 1 to 6 (pre-contemplation, contemplation, motivation, action of <3 months, action of 3-6 months, maintenance of >6 months); Mean scores for highest level of education on a Likert scale of 1 to 5 (elementary school, middle school, high school, college, university); ‘Stayers’ were defined as individuals completing baseline and 3/6/12 month food records; a. *p*-interaction < 0.05.

Table 6.3: Nutrition-related genetic variation among participants in the GLB+NGx group

Nutrient, Gene (rs number)	Genotype Distribution (n, %)	Participants with Elevated Risk/Enhanced Response Genotype (n, %)	Associated Risk/Response
Calories, UCP1 (rs1800592)	AA (44, 62.9) AG (19, 27.1) GG (7, 10.0)	Elevated Risk (26, 37.1)	Lower resting metabolic rate
Protein, FTO (rs9939609)	AA (21, 30.0) TA (27, 38.6) TT (22, 31.4)	Enhanced Response (21, 30.0)	Weight loss
Total Fat, TCF7L2 (rs7903146)	TT (6, 8.6) CT (28, 40.0) CC (36, 51.4)	Enhanced Response (6, 8.6)	Weight loss
SFA, APOA2 (rs5082)	TT (21, 30.0) TC (44, 62.9) CC (5, 7.1)	Enhanced Response (5, 7.1)	Weight loss
PUFA:SFA, FTO (rs9939609)	AA (21, 30.0) TA (27, 38.6) TT (22, 31.4)	Enhanced Response (48, 68.6)	Weight loss
MUFA, PPARg2 (rs1801282)	CC (53, 75.7) CG (17, 24.3) GG (0, 0.0)	Enhanced Response (17, 24.3)	Weight loss
Snacking/Appetite, MC4R (rs17782313)	TT (30, 42.9) TC (35, 50.0) CC (5, 7.1)	Elevated Risk (40, 57.1)	Greater snacking/eating frequency

n=70

Change in Dietary Intake

Change in dietary intake from baseline to 3-, 6-, and 12-month follow-up is detailed in Table 6.4. For the analysis of overall change in dietary intake throughout the entire duration of the study, a total of 32 participants completed the food records at all four time points. As further depicted in Figures 6.1 and 6.2, only the GLB+NGx group significantly reduced total dietary fat intake from baseline to 12-month follow-up ($36.0 \pm 4.8\%$ kcal to $30.2 \pm 8.7\%$ kcal, $p=0.02$).

Furthermore, as depicted in Figure 6.3, the GLB+NGx group experienced a clinically meaningful reduction in SFA intake ($11.9 \pm 3.3\%$ kcal to $9.3 \pm 3.3\%$ kcal, $p=0.13$) and statistically significant reduction in grams, but not percent of calories (%kcal), of unsaturated fat. Overall, there were long-term (12-month) changes in dietary fat intake when participants in the GLB program received the addition of nutrigenetic information and advice compared to receiving only population-based dietary information and advice.

Dietary Adherence

As further detailed in Table 6.5, with more broad %kcal ranges, participants in the standard GLB group had significantly ($p<0.01$) greater adherence to the group-specific target for protein intake at all four time points (baseline, 3, 6 and 12 months) indicating that the group-specific targets in the GLB+NGx group were more difficult to achieve from the beginning. Similarly, with more broad %kcal ranges for total fat intake in the GLB+NGx ‘typical response’ group, participants in the GLB+NGx group had significantly ($p<0.01$) greater adherence to the group-based targets for total fat at all four time points, indicating that the target for total fat intake in the standard GLB group was more difficult to achieve. Interestingly, the GLB+NGx group had significantly greater long-term (12-month) adherence to the targets of $<25\%$ kcal from total fat ($p<0.01$) and $<10\%$ kcal from saturated fat ($p=0.02$), compared to the standard GLB group.

Table 6.4: Overall change in dietary intake from baseline to 3-, 6- and 12-month follow-up

NUTRIENT	Baseline		3-Months		6-Months		12-Months		RM-ANOVA	RM-ANOVA	Split-Plot ANOVA
	GLB	GLB+NGx	GLB	GLB+NGx	GLB	GLB+NGx	GLB	GLB+NGx	p-value GLB	p-value GLB+NGx	p-interaction
Calories (kcal ± SD)	1709.2±502.9	1873.9±528.2	1473.2±358.5	1662.9±543.4	1566.2±394.1	1713.2±602.6	1473.5±339.6	1639.1±680.8	0.17	0.30	0.99
Calories (% change ± SD)	0.0 ± 0.0	0.0 ± 0.0	-9.9±2.3	-7.7±3.2	-1.8±4.3	-6.7±2.6	-8.5±2.7	-12.9±3.1	0.49	0.39	0.22
Protein (g ± SD)	70.7±23.3	86.6±23.5	73.6±26.7	77.1±25.8	75.1±28.4	80.6±29.3	68.6±29.0	72.3±24.2	0.63	0.20	0.44
Protein (%kcal ± SD)	16.7±2.8	19.1±5.3	20.3±6.1	19.1±4.8	19.2±5.0	19.7±7.1	18.6±5.8	18.6±5.8	0.11	0.91	0.35
Total Fat (g ± SD)	74.1±33.6	75.0±22.6	53.3±20.8	61.2±28.3	62.8±27.9	60.6±28.3	59.7±19.1	55.4±29.4	0.14	0.01^a	0.63
Total Fat (%kcal ± SD)	37.7±8.2	36.0±4.8	31.2±8.3	31.9±7.4	35.5±10.1	31.4±9.2	36.2±7.2	30.2±8.7	0.12	0.02^b	0.24
SFA (g ± SD)	24.6±12.3	24.4±8.1	18.6±9.7	19.7±11.1	21.1±8.8	21.3±12.8	19.7±6.5	17.6±10.8	0.22	0.08	0.85
SFA (%kcal ± SD)	12.2±3.1	11.9±3.3	10.8±4.4	10.2±3.7	11.7±3.9	10.8±4.6	11.9±3.1	9.3±3.3	0.64	0.13	0.45
Total UnSFA (g ± SD)	48.7±22.4	49.6±17.2	33.7±13.0	40.5±18.7	41.1±23.1	38.2±16.4	38.6±14.7	36.8±19.2	0.17	0.02^c	0.56
Total UnSFA (%kcal ± SD)	24.5±6.1	23.3±3.8	20.2±5.7	20.8±5.6	22.7±8.4	19.7±5.4	22.8±5.2	19.7±6.0	0.23	0.05	0.35

GLB Group: n=16, GLB+NGx Group: n=18 (total n=32). Bold values are significant at p<0.05. Effect sizes: a. 0.190; b. 0.187; c. 0.191

Table 6.5: Differences between groups for dietary adherence at baseline, 3, 6 and 12 months

NUTRIENT	Baseline (n, % achieving target)		Significance	3-Months (n, % achieving target)		Significance	6-Months (n, % achieving target)		Significance	12-Months (n, % achieving target)		Significance
	GLB	GLB+NGx	p-value	GLB	GLB+NGx	p-value*	GLB	GLB+NGx	p-value	GLB	GLB+NGx	p-value
Individualized Calorie Target¹	20, 37.7%	26, 44.8%	0.45	22, 50.0%	22, 52.4%	0.86	23, 57.5%	15, 44.1%	0.25	16, 57.1%	17, 56.7%	0.97
<25% kcal from total fat	6, 11.3%	5, 8.4%	0.61	6, 13.6%	7, 16.7%	0.87	6, 15.0%	6, 17.6%	0.76	0, 0.0%	8, 25.8%	<0.01^a
Group-based total fat target²	6, 11.3%	23, 39.0%	<0.01^b	6, 13.6%	27, 64.3%	<0.01^c	6, 15.0%	19, 55.9%	<0.01^d	0, 0.0%	18, 58.1%	<0.01^e
10-35% kcal from protein	52, 98.1%	59, 100.0%	0.47	43, 97.7%	42, 100.0%	0.99	40, 100.0%	34, 100.0%	1.00	25, 89.3%	31, 100.0%	0.10
Group-based protein target³	52, 98.1%	44, 74.6%	<0.01^f	43, 97.7%	31, 70.5%	0.01^g	40, 100.0%	25, 73.5%	<0.01^h	27, 96.4%	22, 71.0%	0.01ⁱ
<10% kcal from saturated fat	14, 26.4%	14, 23.7%	0.74	21, 47.7%	22, 52.4%	0.57	15, 37.5%	15, 44.1%	0.56	8, 28.6%	18, 58.1%	0.02^j

1. Calorie targets were individualized based on baseline weight as outlined in the GLB Program curriculum (University of Pittsburgh, c2017)

2. Group-based total fat targets were: ≤25% of calories from total fat in the standard GLB group, 20-35% of calories from total fat in the GLB+NGx ‘typical response’ group and 20-25% of calories in the GLB+NGx ‘enhanced response’ group

3. Group-based protein targets were: 10-35% if calories in the standard GLB group and in the GLB+NGx ‘typical response’ group and 25-35% of calories in the GLB+NGx ‘enhanced response’ group

Odds ratios: a. NA; b. 5.00; c. 11.40; d. 7.18; e. NA; f. 17.727; g. 15.258; h. NA; i. 11.045; j. 3.46

*binary logistic regression, controlling for income

Baseline: GLB Group: n=53, GLB+NGx Group: n=59 (total n=112; n=111 for calories analysis as baseline weight data missing for n=1)

3-Months: GLB Group: n=44, GLB+NGx Group: n=42 (total n=86)

6-Months: GLB Group: n=40, GLB+NGx Group: n=34 (total n=74)

12-Months: GLB Group: n=28, GLB+NGx Group: n=31 (total n=59; n=58 for calories analysis as baseline weight data missing for n=1)

Fisher’s exact test used when expected counts were less than 5

Figure 6.1: Flow diagram of participants from baseline to 3-, 6- and 12-month follow-up

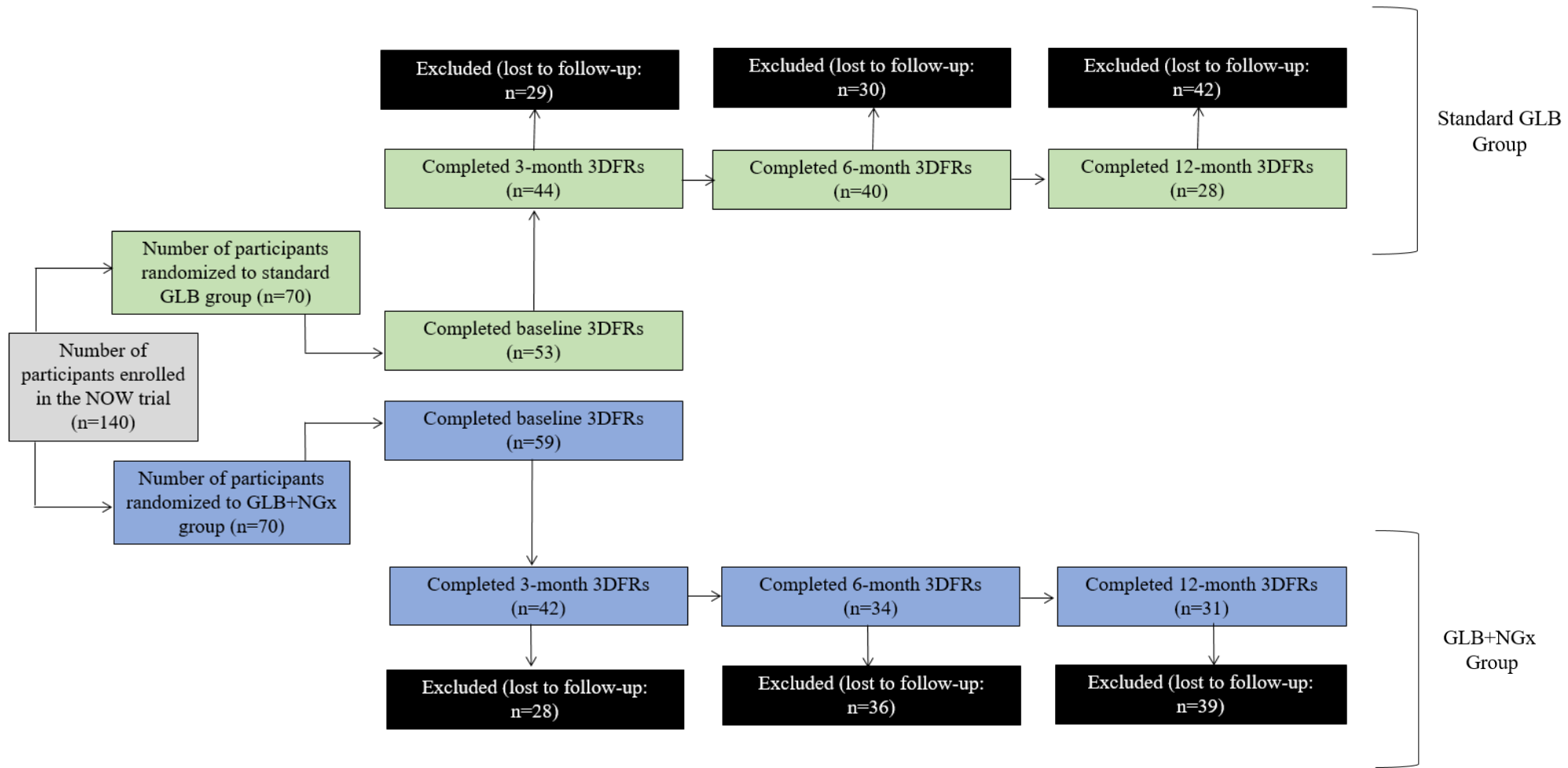


Figure 6.2: Change in percent of calories from total fat

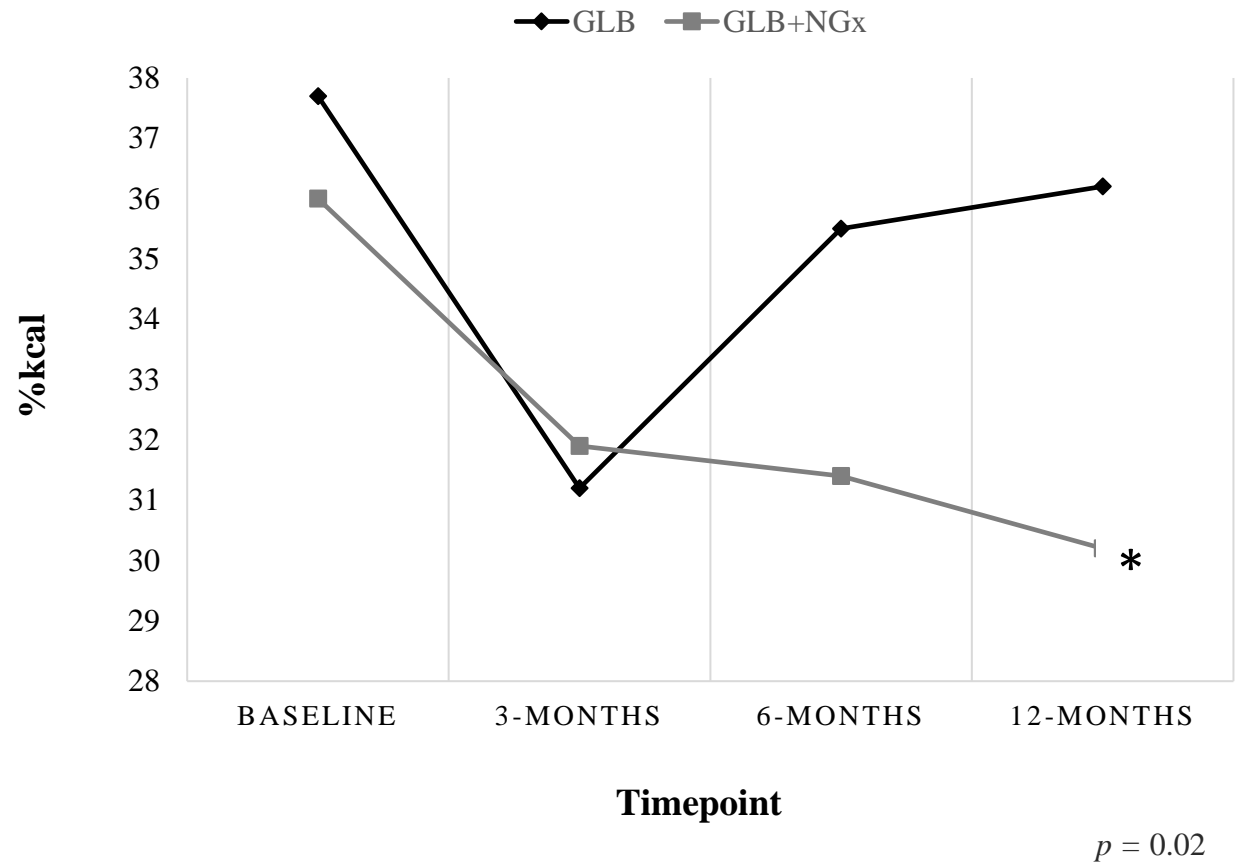
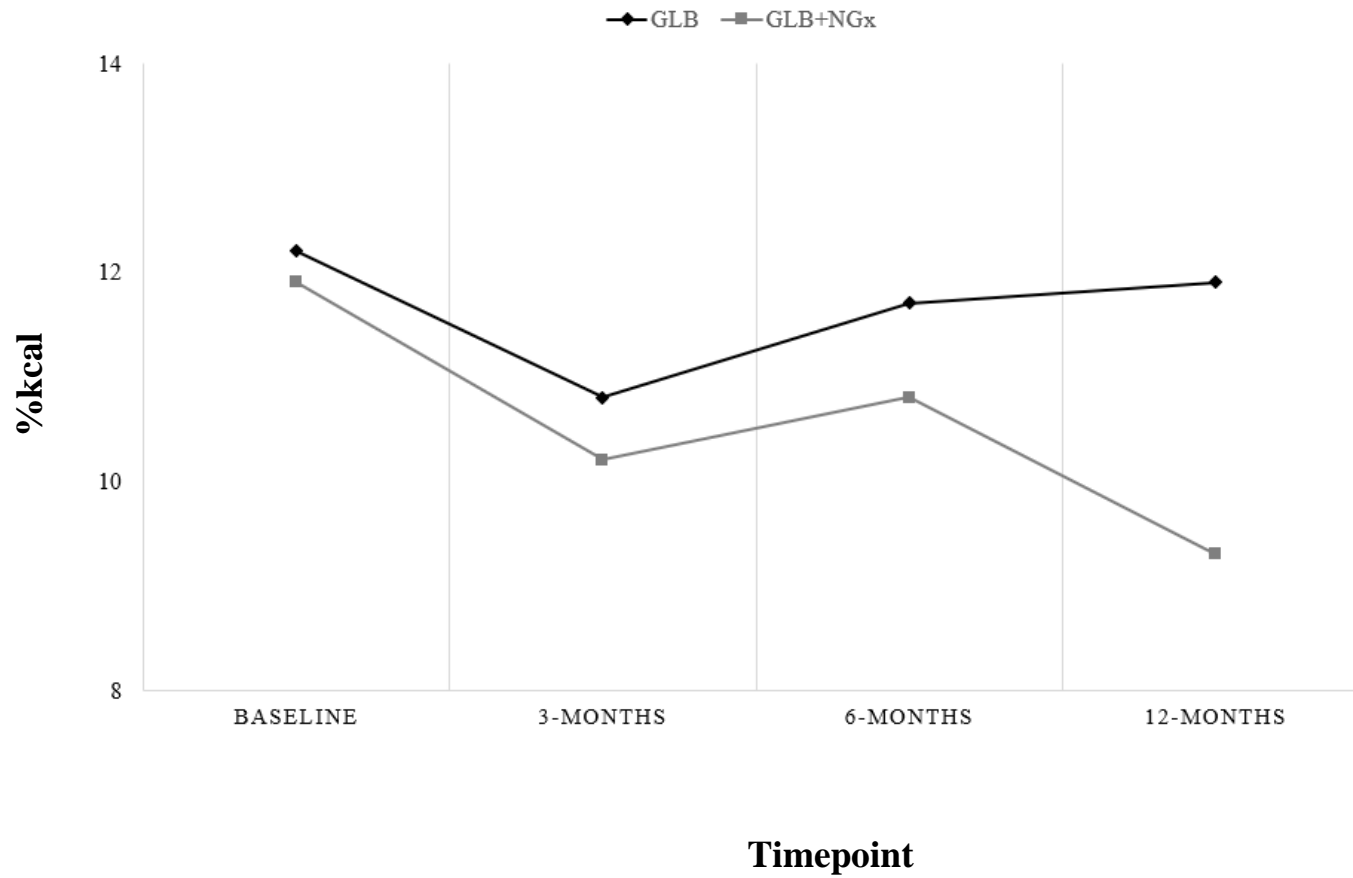


Figure 6.3: Change in percent of calories from saturated fat



$p > 0.05$

6.1.5 Discussion

This study demonstrates that a nutrigenomics weight management intervention can motivate greater long-term dietary change compared to population-based recommendations in one of the most effective public health weight management and diabetes prevention programs. Notably, this is the first genetic testing behaviour change study to incorporate the TPB and thus control for important confounding factors of behaviour change and is the first study to assess changes in calorie and macronutrient intake resulting from a genetic-based weight management intervention. It is also the first study to assess change in dietary intake when the GLB/DPP program is extended to patients with overweight/obesity, regardless of having a prediabetes diagnosis - a recommended program expansion by public health officials (Ontario Ministry of Health and Long-Term Care 2018).

Previous research has assessed change in dietary intake in participants diagnosed with prediabetes enrolled in the GLB/DPP program. Over the course of 12 months, it appears that the participants with prediabetes made greater overall dietary changes (-452 calories and -6.6% total fat) compared to the population of adults with overweight/obesity in the NOW trial who received the standard GLB program (-236 calories and -1.5% total fat), although different tools were used to measure dietary intake, therefore the results cannot be compared with complete accuracy (Mayer-Davis et al. 2004). Theoretical concepts of behaviour change support this finding; the extended parallel process model suggests that if individuals' perceptions about susceptibility to a threat (e.g., developing type 2 diabetes) and the magnitude of the threat are high, they are more likely to take action to control the threat (e.g., improve their nutrition) (Popova 2012). Interestingly, the NOW trial GLB+NGx group (with overweight/obesity but not necessarily a prediabetes diagnosis) changed their dietary intake to a similar extent as those in the original

GLB/DPP cohort, all of whom had a diagnosis of prediabetes, whereas the NOW trial standard GLB group made fewer changes to their diet (Mayer-Davis et al. 2004). In comparing these findings to the extended parallel process model, it is possible that the addition of genetic-based nutrition information and advice positively impacted *response efficacy* (beliefs about the effectiveness of the advice to improve weight management), and elicited greater *danger control responses* (beliefs, attitudes, intentions, and behaviours to manage weight) (Popova 2012). Future research should explore this concept further. Future research should also assess change in dietary intake in the GLB program (with and without the addition of nutrigenomics information/advice) in various locations across North America, and with a more ethnically diverse study sample in order to improve generalizability. The current study is primarily generalizable to Caucasian females with overweight and obesity enrolled in a weight management program. Notably, given the highly pragmatic nature of the NOW trial (Table 6.6), overall, this study has strong external validity.

In terms of the dietary analyses, while both grams and %kcal are reported in the present study, %kcal is a more accurate comparison between groups given that calorie intakes between groups were not identical. As such, differences in %kcal from macronutrients should be weighted more highly in the interpretation of the overall results compared to grams of nutrients. Given that the %kcal from protein recommendations for the GLB+NGx ‘enhanced response’ group proved to be challenging to achieve, and that a large proportion of the GLB+NGx group were advised to limit their SFA intake to <10%kcal to enhance weight loss (Table 6.3), it is not surprising that there was significantly greater dietary adherence to the SFA recommendations in the GLB+NGx group as many participants were focusing on reducing their SFA intake. This would also contribute to the significant reduction in total fat intake in the GLB+NGx group only

(in addition to a reduction in unsaturated fat). It was, however, surprising to see minimal change in total fat intake and poor dietary adherence to the total fat recommendations in the standard GLB group at 12-month follow-up since this was the focus of the standard program. While clinically meaningful (though not statistically significant) reductions in total fat intake occurred from baseline to 3-, and 6-month follow-up, these were not sustained after 12-months. As further explained above, it appears individuals with overweight/obesity, but not necessarily having a prediabetes diagnosis, have a more difficult time maintaining long-term dietary changes in the standard GLB program compared to those diagnosed with prediabetes (Mayer-Davis et al. 2004). According to the NOW trial findings, the addition of genetic-based dietary advice could help to mitigate this. Indeed, previous research has indicated that weight control is a motivator for the intention to adopt personalized nutrition strategies (Rankin et al. 2018).

Our finding that GLB+NGx group participants who dropped out at 3 months had a significantly lower income, on average, compared to 3-months dropouts from the standard GLB group was interesting. It is possible that purchasing food in order to adhere to the nutrigenomics intervention was perceived as, or in reality was, more expensive (e.g. 30% of participants were advised to follow a higher protein nutrition plan) and cost may have been prohibitive to following the dietary advice. Studies have reported cost is a barrier to consumption of higher protein foods (Appleton 2016; Best and Appleton 2013). However, the finding that dropouts from the GLB+NGx group tended to have lower incomes was not consistent after 6 and 12 months, and therefore, future research should explore this phenomenon further.

Table 6.6: PRECIS-2 Scoring Tool

PRECIS-2 Domain	Score [Likert scale 1 (very explanatory) - 5 (very pragmatic)]
<i>1. Eligibility: To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?</i>	5
<i>2. Recruitment: How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?</i>	5
<i>3. Setting: How different are the settings of the trial from the usual setting?</i>	5
<i>4. Organization: How different are the resources, provider expertise, and the organization of care delivery in the intervention arm of the trial from those available in usual care?</i>	4
<i>5. Flexibility (delivery): How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?</i>	4
<i>6. Flexibility (adherence): How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?</i>	4
<i>7. Follow-up: How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?</i>	3
<i>8. Primary outcome: To what extent is the trial's primary outcome directly relevant to participants?</i>	5
<i>9. Primary analysis: To what extent are all data included in the analysis of the primary outcome?</i>	<i>N/A (the present study provides an analysis of secondary outcome data)</i>
Mean score:	4.4

Strengths and Limitations

There are several specific strengths and limitations of the present work that should be noted. This was novel to the field, as it was one of only four randomized controlled trials (RCTs) to assess change in dietary intake resulting from a nutrigenetic intervention over a 12-month period. Previously, Hietaranta-Luoma et al. (2014) similarly found that a nutrigenetic cardiovascular disease intervention motivated greater long-term changes in dietary intake, and further motivated greater short-term and moderate-term changes compared to a control group. Nielsen and El-Soheemy's (2014) and Chao et al.'s (2008) 12-month RCTs also found that nutrigenomics interventions motivated greater long-term (12-month) changes in dietary intake. There have been no RCTs demonstrating that nutrigenomics is ineffective at motivating changes in dietary intake after 12-month follow-up (Horne et al. 2018). Thus, taken together, the body of evidence highly suggests that nutrigenomics is a useful tool for motivating positive nutritional intake over the long-term.

Consistent with the vast majority of nutrition research, there were limitations related to the methods used to collect dietary intake data such as possible recall bias and underreporting of intake (Shim, Oh, and Kim 2014). However, 3DFRs were collected using the multiple-pass method, which has been validated against direct observation in a similar population (Conway et al. 2003). Additionally, these food records provided highly detailed nutritional intake data, which is a strength of this dietary collection method (Shim, Oh, and Kim 2014). Nonetheless, 3DFRs are time consuming leading to respondent burden (Shim, Oh, and Kim 2014), which helps to explain why a smaller subset of the NOW trial sample participated in 3DFR collection throughout the entire duration of the study. In addition, 3DFRs were collected over the phone, whereas other NOW trial outcome data (e.g. weight and body composition) were collected in-

person (Horne et al. 2019; Madill 2016), leading to slightly different samples as some participants completed only the 3DFRs, while others completed only the in-person data collection, and others completed both.

Since the dietary analysis was a secondary outcome of the NOW trial, the sample size may not have been large enough to detect statistical significance in some cases. For example, while adherence to SFA was significantly greater ($p=0.02$) in the GLB+NGx group compared to the standard GLB group, a 12-month clinically meaningful reduction in SFA was observed in the GLB+NGx group only ($11.9\pm 3.3\%$ kcal to $9.3\pm 3.3\%$ kcal), but this change was not statistically significant ($p=0.13$). Nonetheless, this was a notable observation given that in addition to possible weight-related outcomes resulting from a decrease in SFA to $<10\%$ kcal from saturated fat (Corella et al. 2009), achieving $<10\%$ kcal from SFA can have further beneficial effects on LDL-cholesterol and other cardiovascular disease risk factors (Anderson et al. 2016). Future research should seek to replicate this study in a RCT adequately powered to detect significant differences in %kcal from SFA. Nonetheless, this long-term 22% reduction in SFA observed in the GLB+NGx group is notable, and relates to the statistically significant greater adherence to the SFA guidelines after 12 months in the GLB+NGx group compared to the standard GLB group.

Lastly, baseline portion sizes were likely underreported given that baseline data collection occurred during the run-in period and participants learned how to measure their food and beverage intake in the first week of the intervention. This may have affected results for calories and grams of nutrients (but not percent of intake from macronutrients). However, since participants were advised to measure all food and beverages for one week and track their intake

for two to three months, this likely improved the accuracy of the follow-up 3DFRs. Thus, the actual change in dietary intake may in fact have been greater than the data suggest.

6.1.6 Conclusion

Overall, the NOW trial provides important, novel insights into genetic testing behaviour change research, grounded in fundamental theoretical concepts. The results of this study provide convincing evidence that the addition of nutrigenomics to one of the most effective public health weight management and diabetes prevention programs can help motivate and optimize long-term, clinically meaningful differences in nutritional intake and adherence to dietary guidelines.

**CHAPTER 7: CHANGE IN WEIGHT, BMI AND BODY
COMPOSITION**

7.1 Title: Change in weight, BMI and body composition after 3, 6 and 12 months in a population-based intervention vs. genetic-based intervention: Results from the NOW randomized controlled trial

7.1.1 Abstract

Importance: Nutrigenomics testing for weight management is widely available to the general public through direct-to-consumer testing and via healthcare professionals, but limited research has assessed its effectiveness.

Objective: To compare changes in body fat percentage (BFP), weight and body mass index (BMI) between a standard intervention and a nutrigenomics intervention.

Design: The nutrigenomics, overweight/obesity and weight management (NOW) trial is a parallel group, pragmatic, randomized, controlled clinical trial incorporated into the Group Lifestyle Balance (GLB)/Diabetes Prevention Program. Participants were followed from baseline to 3, 6, and 12 months through staggered cohorts occurring between April 2017 and September 2019. Statistical analyses included two-way analyses of variance (ANOVAs) for analyses of potential attrition bias, and split plot ANOVAs to assess between-group differences from baseline to 3-, 6-, and 12-month follow-up.

Setting: This study took place at the East Elgin Family Health Team in Aylmer, Ontario, Canada.

Participants: Participants enrolled in the GLB/Diabetes Prevention Program were invited to participate if they had a BMI ≥ 25.0 kg/m², were ≥ 18 years of age, English-speaking, willing to undergo genetic testing, had internet access and were not seeing another healthcare provider for weight loss advice outside of the study. Pregnancy and lactation were exclusion criteria. Only one participant declined study participation, with a total of 140 enrolling.

Interventions: GLB groups were randomized 1:1 to receive either the standard 12-month GLB program or a modified 12-month program (GLB+NGx), which included the provision of nutrigenomics information and advice for weight management.

Main Outcome(s) and Measure(s): The primary study outcome was change in BFP. Change in weight and BMI were secondary outcomes.

Results: The sample consisted primarily of middle-aged Caucasian females with class II obesity (n=75). The GLB+NGx group experienced significantly ($p<0.05$) greater reductions in percent and absolute BFP at the 3-month follow-up (percent BFP change: $-4.95\pm 5.52\%$, 95% CI: -3.3 to -6.6; absolute BFP change: $-2.12\pm 1.96\%$, 95% CI: -1.5 to -2.8) and percent BFP at 6-month follow-up ($-7.76\pm 6.33\%$, 95% CI: -5.8 to -9.6) compared to the standard GLB group (3-month percent BFP change: $-2.24\pm 4.13\%$, 95% CI: -0.5 to -3.9; 3-month absolute BFP change: -1.02 ± 1.89 , 95% CI: -0.4 to -1.7; 6-month percent BFP change: $-4.80\pm 4.85\%$, 95% CI: -2.8 to -6.8, respectively).

Conclusions and Relevance: The nutrigenomics intervention used in the NOW trial is a valuable intervention for optimizing body composition, especially over the short- and moderate-term.

Trial Registration: This trial is registered with clinicaltrials.gov (NCT03015012).

7.1.2 Introduction

Weight management is an ongoing challenge for a substantial proportion of the population. It is estimated that two-fifths of the adult population worldwide are attempting to lose weight, with another quarter of the population attempting to maintain weight (Santos et al.

2017). Patients' motivations for weight control are broad and include desires to improve health, well-being, physical appearance, fitness, and self-esteem (Santos et al. 2017).

The most current American Heart Association/American College of Cardiology/Task Force on Practice Guidelines and the Obesity Society (AHA/ACC/TOS) clinical practice guidelines for overweight and obesity management state that there is “strong evidence” (NHLBI Grade A) for the effectiveness of several interventions in achieving sustained weight loss (Jensen et al. 2014). Despite this knowledge, successful long-term weight loss still proves to be challenging, with many interventions demonstrating weight regain after long-term follow-up (Aller et al. 2014; Miura et al. 1989; Brock et al. 2010; Wadden and Sarwer 1999). While there are numerous weight management programs available to the public, the Group Lifestyle Balance™ (GLB) program (formerly referred to as the Diabetes Prevention Program) can be considered the gold standard weight management intervention for long-term, sustainable weight loss and diabetes prevention (Diabetes Prevention Program Research Group 2002; McTigue et al. 2009; Piatt et al. 2012; Xiao et al. 2013). This program meets all of the criteria from the AHA/ACC/TOS clinical practice guidelines, while addressing various modifiable health and lifestyle behaviours (Jensen, Ryan, Apovian, et al. 2014).

Complex factors affect weight and body composition. Factors contributing to the development and management of overweight/obesity include stress, sleep, nutrition, physical activity (PA), social determinants of health, the built environment, medications, certain diseases/conditions and genetics (Moore et al. 2010; Eriksson et al. 2003; Finkelstein, Ruhm, and Kosa 2005; Seabrook and Avison 2010; Gilliland et al. 2012; Sarma et al. 2014). With increasing

knowledge of how individual genetic variation affects nutrient metabolism, absorption, and other physiological processes, genetics are an important factor to consider in weight management interventions. The science of nutrigenomics explores interactions between nutrition, genetics, and health outcomes (Subbiah 2008). The science of lifestyle genomics is broader, and explores interactions between various lifestyle components (such as smoking, PA, sleep, and nutrition), genetics, and health outcomes (Horne et al. 2018).

Consumers have demonstrated consistently positive attitudes towards nutrigenetic testing (Vallée Marcotte et al. 2019; Morin 2009; Stewart-Knox et al. 2009; Nielsen and El-Soheemy 2012). As such, many consumer nutrigenomics and lifestyle genomics tests are available to the general public, often including personalized weight management lifestyle advice. While primary research has demonstrated several relationships between genetic variation, weight/body composition and specific dietary and PA strategies (Zhang et al. 2012; Eller et al. 2008; Paniagua et al. 2007; Corella et al. 2010; Corella et al. 2011; De Luis, Aller, and Pacheco 2015; Phillips et al. 2012; Memisoglu et al. 2003; Garaulet et al. 2011; Sonestedt et al. 2011; J. Zhu et al. 2014; Xi et al. 2011; Rampersaud et al. 2008), the efficacy of the practical application of this science in a clinical setting has yet to be thoroughly explored. To date, only three studies have assessed the efficacy of using nutrigenomics and lifestyle genomics to optimize weight management (Arkadianos et al. 2007; Frankwich et al. 2015; Celis-Morales et al. 2017). These studies provided a solid starting point for enhancing our knowledge on this topic, but exhibit notable limitations related to statistical power, methodology and the quality of the interventions delivered to study participants. Nonetheless, findings have been variable (Arkadianos et al. 2007; Frankwich et al. 2015; Celis-Morales et al. 2017) with some promise for the use of

genetic-based advice to optimize weight management (Arkadianos et al. 2007). The present randomized controlled trial (RCT) aimed to address the limitations of the current body of knowledge in order to answer the important research question, *does the provision of personalized genetic-based lifestyle information and advice enhance weight loss and improve body composition to a greater extent than the gold-standard, population-based weight management program?*

7.1.3 Methods

The nutrigenomics, overweight/obesity and weight management (NOW) trial is a pragmatic, parallel-group, superiority randomized controlled trial. Complete details of the study methods for this clinical trial, including a SPIRIT flow diagram, have been published elsewhere (Horne et al. 2019). Briefly, a personalized genetic-based lifestyle intervention program was compared (1:1) to the gold standard, population-based lifestyle intervention program (GLB) for weight management. Inclusion criteria consisted of having a BMI ≥ 25.0 kg/m², being ≥ 18 years of age, English-speaking, willing to undergo genetic testing, having internet access, and not seeing another healthcare provider for weight loss advice outside of the study. Pregnancy and lactation were considered exclusion criteria. This study took place at the East Elgin Family Health Team (EEFHT) in Aylmer, Ontario, Canada and was registered with clinicaltrials.gov (NCT03015012) (Madill 2016).

Recruitment

Adults from Elgin and Middlesex Counties in Ontario, Canada were either referred to the GLB program by healthcare professionals in the area, or signed up for the program through word-of-mouth referrals from members of the community. Participants expressing interest in joining the GLB program were invited to the EEFHT for an in-person NOW trial information meeting, and provided written, informed consent if they decided to take part in the study.

Primary and Secondary Outcomes

The primary outcome of this RCT was percent change in body fat percentage (BFP). Changes in weight and body mass index (BMI) were secondary outcomes as indicated on clinicaltrials.gov (Madill 2016).

Sample Size

As indicated in the study protocol (Horne et al. 2019), in order to detect a 4% change in BFP, using a standard deviation of 6.1%, the sample size calculation indicated that a total of 74 participants (37 participants per group) were needed to test the primary outcome of this trial with 80% power and an alpha of 5%.

Randomization and Blinding

For the cohort randomization, randomly permuted blocks were generated by one author (JH) using the original generator on an internet-based randomization program (Dallal 2017). This allowed for pre-randomization of GLB groups in order to determine if the group intervention sessions would be population-based, or genetic-based as further detailed in ‘Interventions and Data Collection,’ below. Participants selected a GLB group that best suited their schedule and were blinded to the group assignment at this time. Four authors were blinded throughout the duration of the study, with one author unblinded (JH) for logistical reasons as this investigator was responsible for scheduling participants, arranging the genetic testing, facilitating all group and one-on-one sessions and completing data collection.

Run-In

Baseline data collection occurred within approximately 14 days (mean \pm SD = 9.3 \pm 5.7) prior to the intervention start date. No lifestyle advice was provided to participants during this run-in period.

Interventions and Data Collection

Participant recruitment took place between April 2017 and September 2018. Recruitment ended in September 2018 given the allocated timeline for this project and given that the target recruitment sample number had been achieved. One author (JH) was responsible for enrolling participants and assigning them to interventions (based on their availability and the GLB group times/dates selected by the blinded participants). Data collection and lifestyle interventions

occurred between May 2017 and September 2019, with staggered cohorts throughout this period. Group allocation was concealed for the participants until the first group intervention session (after baseline data collection). Those randomized to the population-based lifestyle intervention (GLB) group participated in the standard 22-session, 12-month GLB program (University of Pittsburgh, c2017). They also received an additional information session detailing population-based guidelines for 11 nutrition and PA-related items: calories, protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, sodium, snacking, overall PA, endurance and strength/power as previously published (Horne et al. 2019). Individuals randomized to the standard GLB program received their nutrigenomics/lifestyle genomics report after the 12-month study was complete.

Individuals randomized to the personalized, genetic-based nutrition and PA-intervention (GLB+NGx) received information/advice on the 11 nutrition and PA-related items listed above, with their advice based on individual genetic variation in 12 unique genetic variants: FTO (rs9939609), UCP1 (rs1800592), TCF7L2 (rs7903146), APOA2 (rs5082), PPARg2 (rs1801282), ACE (rs4343), MC4R (rs17782313), ADRB (rs4994), NRF2 (rs12594956), GSTP (rs1695), NFIA-AS2 (rs1572312), and ACTN3 (rs1815739). These genetic variants were chosen as they are reflective of currently available consumer nutrigenetic testing. Participants were also involved in the 12-month GLB program, which was modified by the program facilitator (JH) throughout its duration to highlight nutrition and PA guidelines that may differ according to genetic variation (Horne et al. 2019). In addition to the 22 GLB program group sessions, a supplementary group session occurred at the beginning of the program, which consisted of an overview of the nutrition and PA advice, based on genetics. Furthermore, all participants'

nutrition and PA guidelines (for both the GLB and GLB+NGx groups) were reviewed during their three follow-up data collection appointments (occurring at months 3, 6, and 12) with a registered dietitian (RD).

Baseline and follow-up anthropometric data included weight and height (used to calculate BMI) and body composition conducted using the Bodystat 1500MDD (Bodystat, Douglas, Isle of Man, United Kingdom) bioelectrical impedance analysis (BIA) device.

Genotyping

Oragene ON-500 saliva collection kits (DNA Genotek, Ottawa, Ontario, Canada) were used to collect DNA saliva samples of participants at the EEFHT. The saliva samples were shipped to the University of Toronto and stored at -80°C. The iPLEX Gold assay with mass-spectrometry-based detection on the Sequenom MassARRAY® platform was used for genotyping of the 12 single nucleotide polymorphisms (SNPs) listed above. This method of genotype analysis has been used in previous research (Jenkins et al. 2018; Josse et al. 2012; Banks et al. 2019).

Statistical Analysis

All statistical analyses were completed using IBM SPSS Statistics version 26.0 (Armonk, NY: IBM Corp.). Two-way analyses of variance (ANOVAs) facilitated the analysis of potential attrition bias for the following participant characteristics: level of education, annual household

income (CDN dollars), age (years), baseline stage of change (transtheoretical model), and perceived difficulty managing weight (behavioural control construct of the theory of planned behaviour [TPB]) (Ajzen 2011). To account for potential BIA equipment error, descriptive statistics were used to identify far-out outliers, which were then removed from the final analyses (Figure 7.1). Split plot ANOVAs were used to assess between-group changes in anthropometric data from baseline to 3-, 6-, and 12-month follow-up. Hypothesis tests were 2-sided and a p-value < 0.05 was considered statistically significant.

7.1.4 Results

Baseline participant demographic and clinical characteristics were outlined in Chapter 6, Table 6.1. A total of 140 participants enrolled in the study with 75 participants completing anthropometric data collection for all four time points (Figure 7.1). No statistically significant sources of attrition bias were revealed for level of education, annual household income (CDN dollars), age (years), baseline stage of change (transtheoretical model), and perceived difficulty managing weight (TPB). There were no reported harms or unintended consequences reported in either group.

Far-out (extreme) outliers (n=2) were removed from the body composition data (one in the standard GLB group and one in the personalized GLB+NGx group). Results from the analyses of changes in anthropometric characteristics are outlined in Tables 7.1 and 7.2, as well as Figure 7.2. After 3- and 6-month follow-up, the GLB+NGx group had significantly (p<0.05) greater reductions in percent BFP change compared to the standard GLB group. The GLB+NGx

group additionally had significantly ($p < 0.05$) greater reductions in absolute BFP change after 3 months. There were no significant interactions between group and BFP (percent and absolute) after 12-month follow-up ($p > 0.05$). Furthermore, while the GLB+NGx group had clinically meaningful, greater reductions in weight and BMI after 3 and 6 months (percent and absolute) compared to the standard GLB group, there were no significant interactions between group and weight or BMI at 3-, 6-, and 12-month follow-up ($p > 0.05$).

Table 7.1: Anthropometric measurements at baseline, 3, 6, and 12 months

Anthropometric Measures	Baseline (Mean ± SD, 95% CI)	3 Months (Mean ± SD, 95% CI)	6 Months (Mean ± SD, 95% CI)	12 Months (Mean ± SD, 95% CI)
GLB Group:				
Body Fat (%)	48.18 ± 6.60, 45.6 to 50.7	47.16 ± 7.18,^a 44.5 to 49.9	45.91 ± 6.97,^b 43.3 to 48.9	44.70 ± 7.02, 42.1 to 47.4
Weight (lbs)	219.83±49.71, 206.1 to 233.5	212.97±49.36, 199.4 to 226.6	211.72±51.41, 197.7 to 225.8	213.51±51.64, 199.2 to 227.8
BMI (kg/m ²)	37.82 ± 7.70, 35.6 to 40.1	36.65 ± 7.91, 34.3 to 39.0	36.38 ± 8.12, 34.0 to 38.7	36.68 ± 8.07, 34.2 to 39.1
GLB+NGx Group:				
Body Fat (%)	44.93 ± 7.95, 42.5 to 47.4	42.77 ± 8.29,^a 40.2 to 45.4	41.55 ± 8.24,^b 39.0 to 44.1	42.32 ± 8.15, 39.7 to 44.9
Weight (lbs)	203.34±32.29, 189.8 to 216.9	194.56±32.10, 181.1 to 208.0	192.48 ± 32.60, 178.6 to 206.4	196.85±34.16, 182.7 to 211.0
BMI (kg/m ²)	35.22 ± 6.06, 33.0 to 37.5	33.72 ± 6.13, 31.4 to 36.0	33.36 ± 6.20, 31.0 to 35.7	34.11 ± 6.46, 31.8 to 36.5

p-interaction for body fat (%) = 0.002, effect size = 0.087; a. p = 0.023; b. p = 0.022

Standard GLB Group: Weight and BMI, n=37; Body Fat, n=33

GLB+NGx Group: Weight and BMI, n=38; Body Fat, n=35

Analyses were all by originally assigned groups.

Table 7.2: Change in anthropometric measurements at 3, 6, and 12 months

Anthropometric Measure	3-Month (Absolute $\Delta \pm$ SD, 95% CI)	3-Month (Percent $\Delta \pm$ SD, 95% CI)	6-Month (Absolute $\Delta \pm$ SD, 95% CI)	6-Month (Percent $\Delta \pm$ SD, 95% CI)	12-Month (Absolute $\Delta \pm$ SD, 95% CI)	12-Month (Percent $\Delta \pm$ SD, 95% CI)
GLB Group:						
Body Fat (%)	-1.02 \pm 1.89,^a -0.4 to -1.7	-2.24 \pm 4.13,^b -0.5 to -3.9	-2.27 \pm 2.26, -1.4 to -3.2	-4.80 \pm 4.85,^c -2.8 to -6.8	-3.48 \pm 2.55, -2.6 to -4.4	-7.31 \pm 5.35, -5.4 to -9.2
Weight (lbs)	-6.86 \pm 7.36, -4.5 to -9.2	-3.23 \pm 3.57, -2.1 to -4.4	-8.11 \pm 9.11, -4.7 to -11.5	-3.96 \pm 4.70, -2.3 to -5.7	-6.32 \pm 9.25, -2.6 to -10.0	-3.13 \pm 4.81, -1.3 to -4.9
BMI (kg/m ²)	-1.12 \pm 1.28, -0.8 to -1.6	-3.27 \pm 3.60, -2.1 to -4.4	-1.44 \pm 1.64, -0.9 to -2.0	-4.06 \pm 4.70, -2.4 to -5.8	-1.14 \pm 1.67, -0.5 to -1.8	-3.22 \pm 4.79, -1.4 to -5.0
GLB+NGx Group:						
Body Fat (%)	-2.12 \pm 1.96,^a -1.5 to -2.8	-4.95 \pm 5.52,^b -3.3 to -6.6	-3.38 \pm 2.83, -2.5 to -4.2	-7.74 \pm 6.33,^c -5.8 to -9.6	-2.61 \pm 2.66, -1.7 to -3.5	-6.00 \pm 5.76, -4.1 to -7.9
Weight (lbs)	-8.77 \pm 7.04, -6.4 to -11.1	-4.37 \pm 3.44, -3.2 to -5.5	-10.86 \pm 11.48, -7.5 to -14.2	-5.38 \pm 5.57, -3.7 to -7.0	-6.48 \pm 12.91, -2.8 to -10.1	-3.26 \pm 6.03, -1.5 to -5.0
BMI (kg/m ²)	-1.50 \pm 1.19, -1.1 to -1.9	-4.35 \pm 3.45, -3.2 to -5.5	-1.86 \pm 1.97, -1.3 to -2.4	-5.35 \pm 5.62, -3.7 to -7.0	-1.11 \pm 2.24, -0.5 to -1.7	-3.24 \pm 6.06, -1.5 to -5.0

Δ : change

p-interaction for absolute BFP Δ = 0.002, effect size = 0.087; a. p = 0.018

p-interaction for percent BFP Δ = 0.003; effect size = 0.076; b. p = 0.026; c. 0.036

Standard GLB Group: Weight and BMI, n=37; Body Fat, n=33

GLB+NGx Group: Weight and BMI, n=38; Body Fat, n=35

Note: Differences in percent weight and BMI change are due to rounding.

Analyses were all by originally assigned groups.



CONSORT

TRANSPARENT REPORTING of TRIALS

Figure 7. 1: CONSORT 2010 Flow Diagram

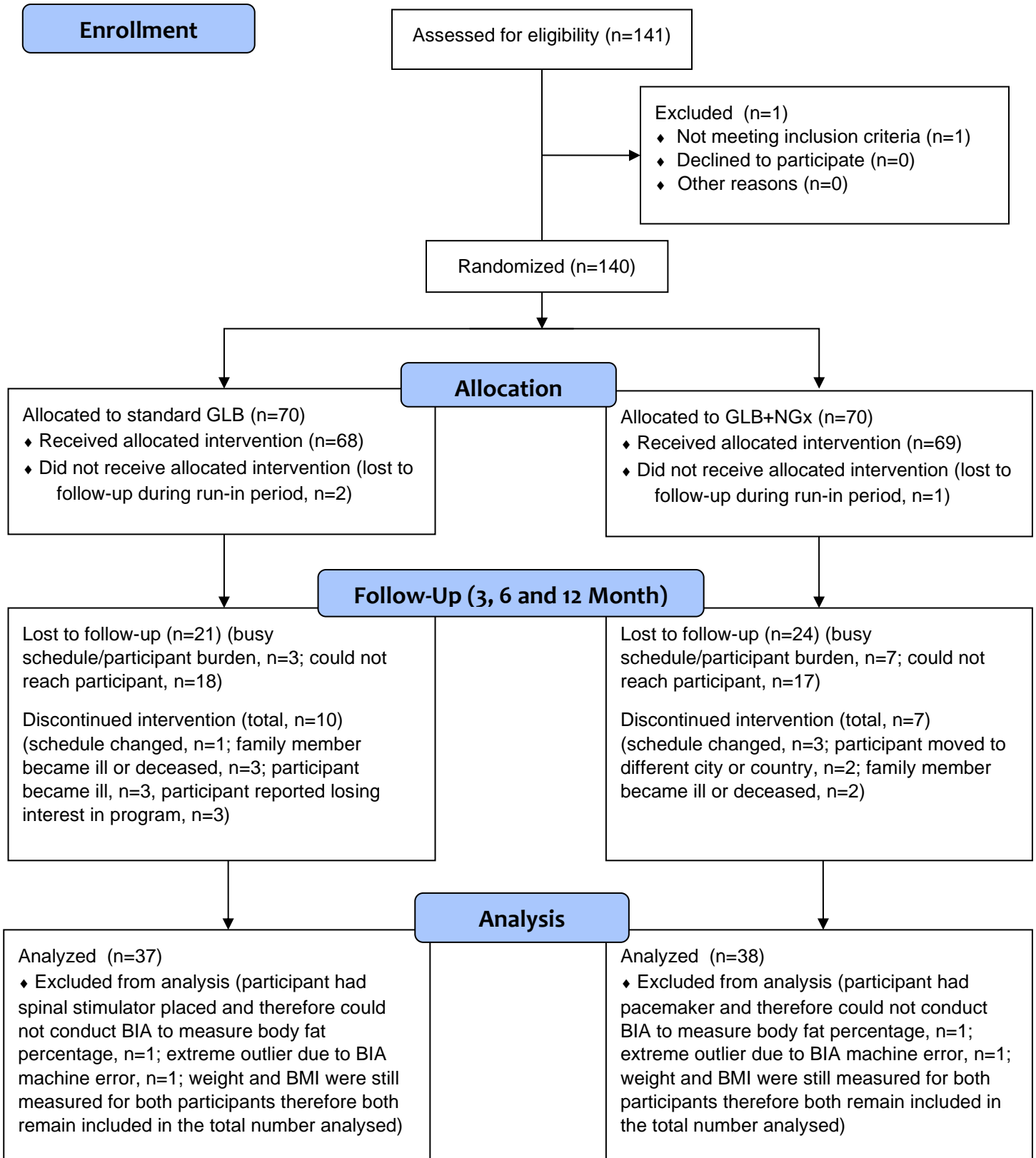
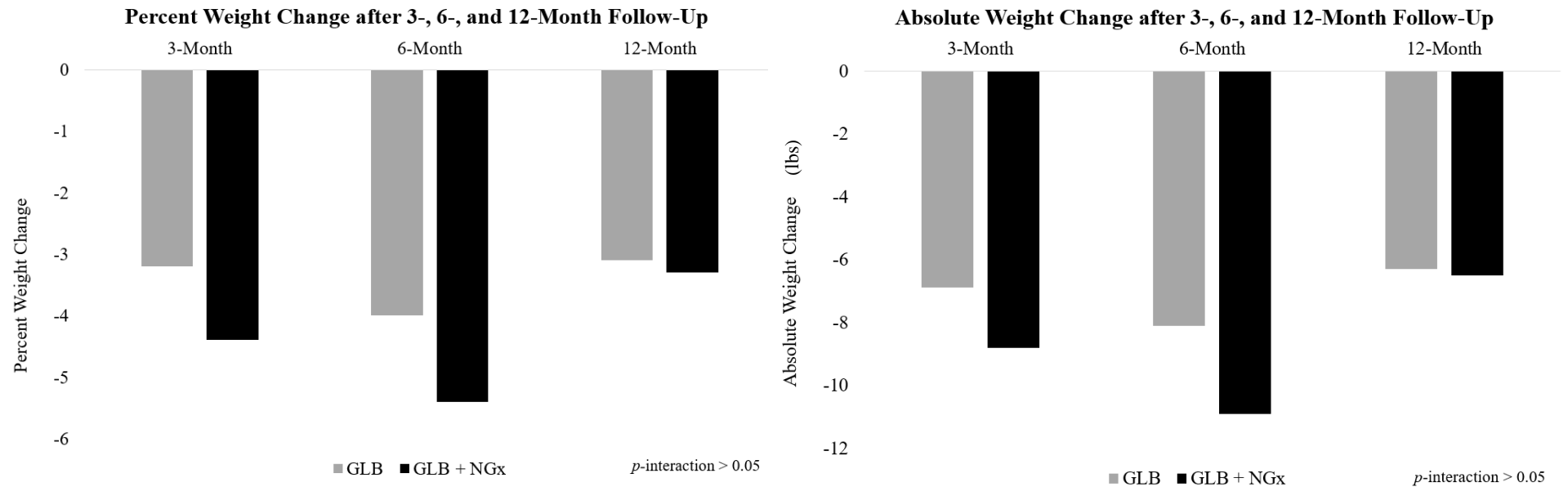
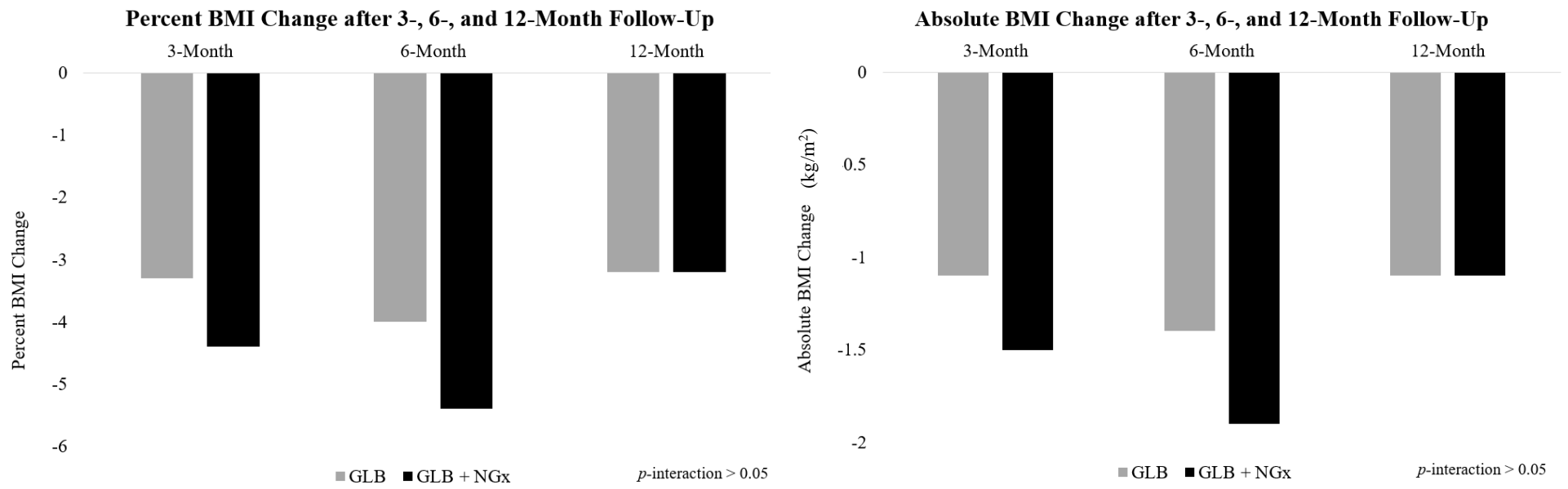


Figure 7.2: Change in anthropometric measures after 3-, 6-, and 12-month follow-up

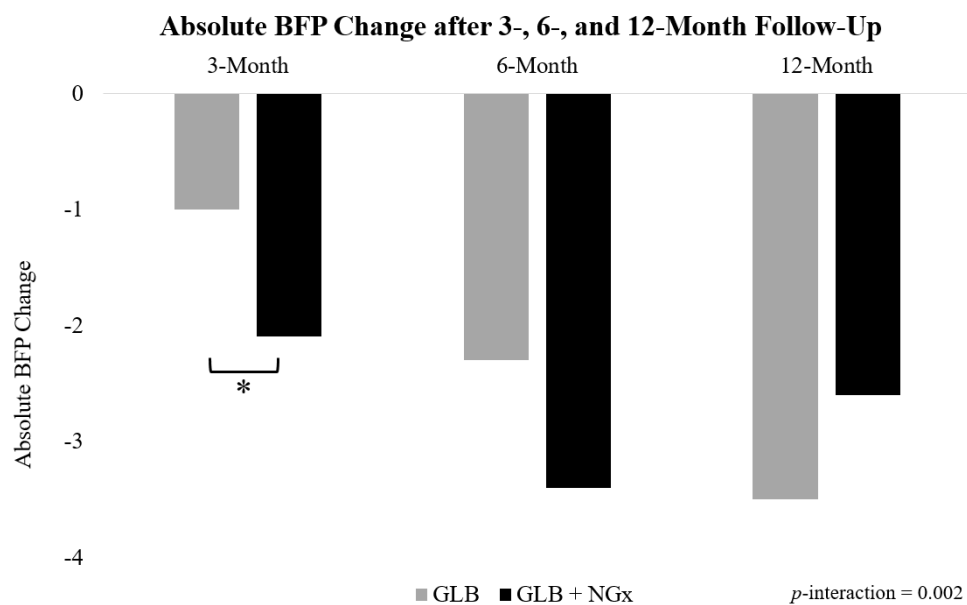
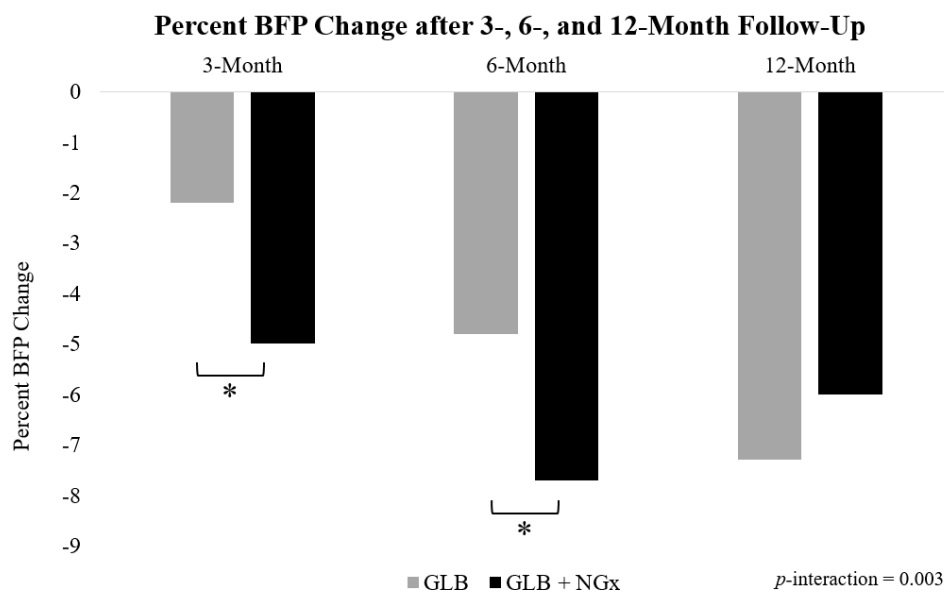
A.



B.



C.



7.1.5 Discussion

This study provides several notable, novel contributions to the literature. From a public health perspective, it is the first study to explore short-, moderate- and long-term anthropometric changes resulting from the standard GLB program in a population of adults with a baseline BMI ≥ 25.0 kg/m² regardless of having a prediabetes diagnosis. While originally piloted and intended for diabetes prevention in individuals diagnosed with prediabetes (Diabetes Prevention Program Research Group 2002), public health officials have since encouraged the GLB program expansion to more broad patient populations such as those with a BMI ≥ 25.0 kg/m² (Ontario Ministry of Health and Long-Term Care 2018). This study demonstrates that a clinically meaningful 3-5% sustained weight loss (Jensen et al. 2014) can be achieved with program expansion to this broader population, thus supporting public health authority recommendations. However, it should be noted that weight-related outcomes in patients with prediabetes appear to be even greater (Diabetes Prevention Program Research Group 2002). Additionally, to our knowledge this is the first study to explore body composition changes within the GLB program. Measures of body composition are superior to weight and BMI given that body composition accounts for changes in fat, water and muscle mass as opposed to overall weight changes (Nuttall 2015).

Gold-standard clinical practice guidelines for weight management interventions indicate that such interventions should include: calorie restriction; participation in a comprehensive lifestyle program for ≥ 6 months with at least 14 sessions in 6 months; counselling on the cardiovascular benefits associated with ≥ 3 -5% weight loss; participation in long-term (≥ 12 -month) weight loss maintenance programs; and regular contact with an ‘interventionist’ who

assists with engagement in PA and monitoring body weight regularly (Jensen et al. 2014). Both the standard GLB and GLB+NGx interventions adhered to these guidelines. A minimum of 3-5% sustained weight loss is clinically meaningful in order to produce several health benefits including reduced triglycerides, reduced blood glucose and hemoglobin-A1C, as well as a reduced risk of developing type 2 diabetes; higher weight loss is associated with greater benefits (Jensen et al. 2014). Both the standard GLB and GLB+NGx groups achieved such sustained weight loss over a 12-month period demonstrating the success of both the standard and modified (personalized) versions of the GLB program. Clinically meaningful changes in BFP are not as well-established as changes in weight, but population reference standard charts of BFP have been published (Imboden et al. 2017). Women tend to experience an approximate 2% absolute increase in BFP per decade from ages 20-29 until ages 50-59. From ages 60-69 to 70-79, less than a 1% absolute BFP increase is observed (Imboden et al. 2017). In comparing the percentiles for reference standards of women's BFP (given that the current study consisted primarily of female participants) to the current study, the NOW trial participants exhibited a 1-2 decile change in BFP throughout the GLB and GLB+NGx programs across various study time points (3, 6, and 12 months) and long-term reductions of approximately 3% absolute BFP. Given that overall, BFP tends to increase with time (Imboden et al. 2017), this 3% reduction represents a clinically meaningful change. Moreover, as there were clinically meaningful changes observed for weight at all time points, this further demonstrates that the overall change in BFP would also be considered clinically meaningful. Furthermore, with body fat mass specifically having major impacts on health outcomes (Nuttall 2015), a 3-5% change in BFP is likely of greater clinical benefit than a 3-5% change in overall weight, which may also include reductions in muscle and/or fat mass.

Notably, the GLB+NGx group experienced significantly greater reductions in BFP after 3 and 6 months compared to the standard GLB group. This speaks to the scientific validity and/or clinical utility of the nutrigenetic and lifestyle genomics information and advice provided to participants. The precise details of the genetic information provided, including a sample genetic report, have been previously detailed elsewhere (Horne et al. 2019). There are many clinical cases where short- and moderate-term weight loss and/or achieving a specific BMI cut-off have demonstrated positive impacts on major and critical patient outcomes. Examples include: pre-transplant weight loss to reduce the risk of organ rejection, reduce the risk of wound complications, reduce hospital length-of-stay and increase chances of survival (Clausen et al. 2018; Knoll et al. 2005); pre-surgery to reduce the risk of complications after hernia repair (Menzo et al. 2018); in kidney, heart, liver, and lung disease patients for transplant listing (Mehra et al. 2006; Knoll et al. 2005; Martin et al. 2014); to be eligible as a living organ donor at most transplant centres (UNOS Transplant Living c2019); improvement in pregnancy rates in patients with infertility (Best, Avenell, and Bhattacharya 2017); prior to total joint arthroplasty to increase chances of implant survivorship and postoperative functional scores (Bookman et al. 2018); and pre-surgery weight loss to reduce the risk of dislocation following total hip replacement (Annan et al. 2018). With this in mind, studying the effectiveness of nutrigenomics and lifestyle genomics interventions for these specific clinical cases, and others where short-to-moderate-term reductions in weight-related outcomes are beneficial, is an important recommended next step for the field of precision nutrition. Interestingly, a recent study found that only 6% of clinical dietitians working in the public health setting participated in nutrigenomics training, as opposed to 33% of industry dietitians and 14% of private practice

dietitians (Cormier et al. 2014). This suggests that there is likely minimal uptake of nutrigenomics in acute-care settings, such as hospitals, where the abovementioned cases are more prevalent; perhaps these are the clinical settings in which patients could benefit most from nutrigenomics and lifestyle genomics weight management interventions?

Our finding of significant differences in BFP between groups diminishing at the 12-month follow-up is intriguing, especially given that the GLB+NGx group made significantly greater dietary changes and better adhered to specific dietary advice compared to the standard GLB group at 12 months. There are multiple possible explanations for these findings. First, biological mechanisms promote weight regain after periods of weight loss. Over time, physiological mechanisms including adipose cellularity, endocrine function, energy metabolism, neural responsivity and addiction-like neural mechanisms promote weight regain after a period of weight loss (Ochner et al. 2013). Decades of research have demonstrated that increased energy (calorie) intake can lead to increased fat cell size and fat cell number (Martinsson 1969; Hirsch and Batchelor 1976; Tchoukalova et al. 2010), and while weight loss may reduce the size of fat cells, it may not reduce the number of fat cells (Martinsson 1969; Björntorp et al. 1975; Hirsch and Han 1969; Arner and Spalding 2010; Gurr et al. 1982; Löfgren et al. 2005). Furthermore, preliminary research has demonstrated that this could encourage weight regain following periods of weight loss due to a reduction in the rate of fat oxidation and increased retention of ingested energy (MacLean et al. 2006; Jackman et al. 2008; Knittle and Hirsch 1968; Kelley et al. 1999; Berggren et al. 2008). In addition, some research has demonstrated a decrease in thyroid function (and thus, a decrease in metabolic rate) after weight loss in individuals with obesity (Rosenbaum et al. 2000; Kozłowska and Rosołowska-Huszcz 2004; Moreno et al. 2008). Moreover, the

activity of the hypothalamic-pituitary-adrenal axis, which regulates cortisol levels, is heightened following weight loss and this can lead to increased appetite and fat accumulation (Björntorp 2001). In terms of changes in metabolic rate, a decrease in fat mass and lean mass will both lead to reductions in energy output/expenditure (Gallagher et al. 1996; Leibel, Rosenbaum, and Hirsch 1995). While a reduction in metabolic rate is normal and expected, studies have demonstrated that weight loss occurring from lifestyle interventions results in ‘metabolic adaptation.’ *Metabolic adaptation* refers to the concept that following weight loss, individuals experience a greater reduction in metabolic rate than would be expected based on an individual’s body composition (Leibel, Rosenbaum, and Hirsch 1995; Gallagher et al. 1996; Astrup et al. 1999; Rosenbaum and Leibel 2010; Johannsen et al. 2012; Camps, Verhoef, and Westerterp 2013; Tremblay and Chaput 2009). This decrease in resting metabolic rate following weight loss leads to biological challenges with weight loss maintenance. The classic Minnesota semi-starvation experiment was one of the first studies to demonstrate a reduced resting metabolic rate during a period of weight regain following weight loss (Keys 1950), with several later studies corroborating these findings (Leibel, Rosenbaum, and Hirsch 1995; Astrup et al. 1999; Rosenbaum and Leibel 2010; Johannsen et al. 2012; Camps, Verhoef, and Westerterp 2013; Tremblay and Chaput 2009). Ultimately, there are a number of biological mechanisms leading the body to resist weight loss, and drive weight regain. This could explain why results from the NOW trial demonstrated weight regain occurring from 6-month to 12-month follow-up in both the GLB and GLB+NGx groups. It is further interesting to notice the continued trend towards decreasing BFP (but not weight) in the standard GLB group only. Although differences were not significant between groups for BFP at 12-months, it is possible that the faster rate of BFP loss

experienced in the GLB+NGx group led to an earlier onset of the biological responses promoting weight regain. Indeed, research supports this idea (MacLean et al. 2011).

Second, while the abovementioned biological mechanisms promoting weight regain provide a plausible explanation for our findings, it is also possible that participants noticed some weight regain occurring between 6 and 12 months, and thus at 12 months became increasingly motivated to follow the genetically-guided advice. Given that weight and BFP losses take time, if participants were followed beyond 12 months, it is plausible that we would, again, observe significant differences between the standard GLB and GLB+NGx groups for BFP changes, as we observed at 3 and 6 months. Indeed, this is an important future research endeavour. Since data collection did not occur between 6- and 12-months, it is not possible to comprehend how well participants were following the dietary guidelines in between these two time points.

There are some limitations of the present work that should be noted. Difficulty with participant retention and thus reduced statistical power may have limited the ability to detect statistical significance for the secondary outcomes, weight and BMI. Additionally, while the target dropout rate for an RCT is <20% (National Institutes of Health n.d.), studies demonstrate that this is typically challenging for long-term weight loss studies (Hillmer et al. 2017; Truby et al. 2006; Jebb et al. 2011; Wadden et al. 2004; Gill et al. 2012; Foster et al. 2003). Thus, the dropout rate for the NOW trial was not remarkable. Reasons for reduced participant retention can include scheduling conflicts, dissatisfaction with treatment, and lack of time to meet the study requirements (Wadden et al. 2004). Having a lower education level (less than university level),

and higher level of obesity are also risk factors for dropping out of weight loss programs/studies (Michelini et al. 2014; Hadžiabdić et al. 2015). These factors contributed to participant dropout in the NOW trial as further indicated in Figure 7.1, Table 7.1 and Chapter 6, Table 6.2. Given the higher dropout rate, a modified intention-to-treat (ITT) analysis was performed. Dropouts were not treated as treatment failures and last observation carried forward methods of imputing missing data were not conducted. However, participants were not excluded based on adherence. ITT can be beneficial for increasing statistical power, improving generalizability and minimizing the risk of a type 1 error (Gupta 2011). However, when there is considerable variability in the endpoint data, it becomes difficult to predict outcomes (Gupta 2011). Furthermore, ITT can increase the susceptibility to type 2 errors, especially with higher dropout rates (Gupta 2011). In addition, the research question should be carefully considered prior to conducting an ITT analysis (Feinman 2009). In the NOW trial, we aimed to determine if individuals enrolled in a genetically tailored weight management program reduced their weight and body fat percentage and improved their dietary intake to a greater extent than those enrolled in population-based weight management program. Therefore, a modified ITT approach was more appropriate given that dropouts were no longer enrolled in the weight management programs.

Previous research has been conducted within the GLB program at the EEFHT and five other Ontario primary care locations. In this previous study, the GLB program was offered during a 9-month period, and dropout rates throughout the study were 26.8% at 3-months, 46.8% at 6-months, and 63.0% at 9-months (Hillmer et al. 2017). This is the most comparable study to the NOW trial given the direct similarities in the intervention (GLB program) and setting (EEFHT in Aylmer, Ontario). With a longer intervention and study duration of 12 months, the

NOW trial still had an overall retention rate approximately 17% higher than previous research in the GLB program, which ran for only 9 months (Hillmer et al. 2017). We suspect that the provision of genetic information (at baseline for the GLB+NGx group and after 12-months for the standard GLB group) enhanced overall interest in the intervention/study, therefore helping to improve retention. This participant interest is further highlighted in Figure 7.1, whereby 140 participants enrolled in the NOW trial out of the 141 patients who were invited to join the study. Nonetheless, although not statistically significant, there were notable clinically meaningful differences in percent weight change, whereby only the GLB+NGx group achieved >5% weight loss (at 6-months follow-up) and both the GLB and GLB+NGx group achieved 3-5% weight loss after 12-months (Jensen et al. 2014). Thus, both interventions were overall effective.

The results of this study are primarily generalizable to populations of middle-aged, middle socio-economic status, Caucasian women with obesity (class II) enrolled in a lifestyle change weight management program. Given that participants who were enrolled in the GLB program were invited to participate in the study, this appears to be a representative sample of individuals interested in this weight management program. Furthermore, the NOW trial study population is similar to other reported GLB study populations (Alva 2019; Alva, Romaine, and Acquah 2019; Jeffers et al. 2019; McTigue et al. 2009).

This study further demonstrated the feasibility of communicating genetic-based nutrition and PA information and advice in a group setting. The literature supports that group-based nutrition education can be more effective in motivating nutrition behaviour change and can be more meaningful for patients (Siero 2000; Abusabha, Peacock, and Achterberg 1999). However,

since this type of personalized nutrition advice is typically communicated in one-on-one patient settings, future research should seek to compare a nutrigenetic and/or lifestyle genomics intervention to standard of care, rather than gold-standard care as we have studied here. While the GLB program is the ‘gold-standard,’ it is only currently offered in nine primary care facilities in Canada (University of Pittsburgh, c2017). In the United States, this program is currently offered to the general public in over 50 facilities (University of Pittsburgh, c2017). As such, standard of care for weight management in dietetics typically consists of individual lifestyle counselling.

7.1.6 Conclusion

Nutrigenomics interventions can produce clinically meaningful health-related outcomes for patients over the short-term, moderate-term and long-term, with additional benefits observed above those achieved with gold-standard care over the short-term and moderate-term. Clinicians should consider implementing the GLB+NGx intervention for patients. As research continues to advance with the hopes of nutrigenetic tests becoming increasingly accurate, genetic-based lifestyle interventions hold considerable promise for improving health and wellbeing in a manner that is innovative and exciting for patients and healthcare professionals alike. It is certainly a science worth exploring further.

CHAPTER 8: DISCUSSION

This dissertation investigated the practical application of nutrigenomics in primary care for improving weight management, body composition, dietary intake, and adherence to specific dietary guidelines. The results indicated that the nutrigenetic-guided intervention was effective at improving body composition to a greater extent than standard advice after 3- and 6-month follow-up. Furthermore, the nutrigenetic-guided intervention motivated long-term changes in dietary fat intake and enhanced adherence to recommendations for total fat and saturated fat intake after 12-month follow-up. The results of this dissertation are generalizable primarily to college-educated, middle-aged women with overweight and obesity who are enrolled in a weight management program. Participants involved in the nutrigenomics, overweight/obesity and weight management (NOW) trial had positive attitudes towards improving their dietary intake and towards weight management, with neutral lifestyle-related subjective norms and perceived behavioural control, based on the TPB.

8.1 Novel Research Contributions

8.1.1 Overall

This randomized controlled trial (RCT) provided a number of novel research contributions, building on previous work in the field (Arkadianos et al. 2007; Frankwich et al. 2015; Celis-Morales et al. 2017). The NOW trial was the first adequately powered RCT to assess the pragmatic delivery of a nutrigenomics intervention with a weight-related primary outcome. Furthermore, the measurement of body fat percentage (BFP) provided a more informative health-related outcome compared to the measurement of weight and body mass index (BMI). With the study taking place within the East Elgin Family Health Team's (EEFHT's) Group Lifestyle

Balance™ (GLB) program, the research proved to be highly pragmatic. This is further detailed in the PRECIS-2 scoring tool (Chapter 6, Table 6.6). Overall, this trial provided a robust exploration of the impact of nutrigenomics testing on nutritional habits and weight-related (including body composition) outcomes.

8.1.2 Methodological Contributions

Cohort randomization was used in the NOW trial to allow all participants in each GLB group to receive the same intervention – either personalized based on genetics, or population-based. Thus, the feasibility of cohort randomization in personalized nutrition research has been demonstrated.

8.1.3 Theoretical Contributions

This was the first genetic testing behaviour change study to intentionally incorporate the TPB into the study methods, including the statistical analyses. Interestingly, we found that income (a sub-component of behavioural control) was an important confounding factor to consider in the 3-month analysis of dietary adherence. Furthermore, the interventions (standard GLB and GLB+NGx) aimed to positively affect the key components of the TPB, in order to promote optimal health behaviour change.

8.1.4 Clinical and Public Health Contributions

With nutrigenomics typically offered through direct-to-consumer (DTC) genetic testing or through a one-on-one session with a healthcare professional, the NOW trial demonstrated the feasibility of incorporating personalized nutrition into a group-based public health program. This is a more efficient method of delivering nutrition information given that nutrition education can

be communicated to multiple patients at one time. Furthermore, the NOW trial provided novel insights into the clinical utility of the only nutrigenetic test currently offered to Canadian consumers exclusively through healthcare providers. Specifically, this was the first study to assess changes in calories, dietary fat and protein as well as weight-related (including body composition) outcomes resulting from the provision of this nutrigenetic test.

8.2 Body Composition: An Overview

8.2.1 Adiposity and Health

Body fat percentage was selected as the primary outcome of this study given its association with health, and its importance to patients enrolled in weight management programs. Total adiposity is a more accurate measure of metabolic phenotypes when compared to measures of BMI (Goossens 2017). Body fat is positively correlated with insulin resistance and cardiometabolic disease (Goossens 2017). It has also been cross-sectionally associated with joint pain (Walsh et al. 2018), and linked to cancer and cognitive dysfunction (Guo et al. 1999; Lutz et al. 2008). In addition to total adiposity, body fat distribution is further important given that adipose accumulation in the abdominal region is associated with comorbidities and all-cause mortality, whereas adipose accumulation in the gluteofemoral region has been shown to have a protective effect on cardiometabolic diseases (Snijder et al. 2004; Yusuf et al. 2005).

8.2.2 Body Composition Tools and Techniques

Various tools and techniques are available to assess body composition. Skinfold measurements provide the least expensive method of measuring body composition, but this method is also the least accurate (Lee and Nieman 2013). Calipers are used to measure a double fold of skin and subcutaneous adipose tissue, without muscle tissue. A tape measure is needed to

measure the appropriate skinfold locations, which can include chest, triceps, subscapular, midaxillary, suprailiac, abdomen, thigh and calf (Lee and Nieman 2013).

Bioelectrical impedance analysis (BIA) is more accurate than skinfold measurements for assessing body composition. It involves the use of a low-frequency electrical current to measure impedance throughout the body. This is then used to estimate measures of body composition using regression equations (Nelms, Sucher and Lacey 2016).

Hydrostatic (underwater) weighing is known to be a highly accurate method of body composition measurement, though it is also the least readily available tool. This method is based on the Archimedes Principle, which states that the buoyancy of an object submerged in water equals the weight of the displaced fluid of that object. This Principle can be used in hydrostatic weighing given that lean tissue (bone and muscle) are denser than water, and water is denser than fat tissue (Lee and Gallagher 2008). While highly accurate, this method is often not well tolerated by participants as it requires the participant to be completely submerged in water (Fosbol and Zerahn 2015).

Dual energy X-ray absorptiometry (DXA) is another accurate method, and uses two different energy levels of X-rays, which pass through the body. The absorption of photons is measured and used to determine whole body bone mass and soft tissue composition (Shepherd et al. 2017). According to 2020 Clinical Practice Guidelines, DXA is considered a valid method of assessing fat mass in patients with various clinical conditions (Sheean et al. 2020). Notably, some newer DXA technologies can measure abdominal (visceral) fat mass in addition to total body fat.

Air displacement plethysmography is another body composition method that uses a measurement of the air displaced in a sealed chamber to estimate body composition. This method measures changes in pressure between two chambers: the test chamber and reference chamber. The equation used to measure body composition involves the measurement of volume and pressure prior to and while the subject enters the test chamber (Fields, Higgins and Hunter 2004). Air displacement plethysmography, DXA and hydrostatic weighing are generally considered to be comparably accurate for measuring body composition across the lifespan, including measures in infants, children and adults (Heds and Allison 2012; Bedogni et al. 2013; Edwards et al. 2011).

Lastly, computed tomography (CT) and magnetic resonance imaging (MRI) are generally considered the most accurate methods of measuring body composition, and can be used to measure total adipose tissue, visceral adipose tissue, subcutaneous adipose tissue, and interstitial adipose tissue (Ross and Janssen, 2005; Fosbol and Zerahn 2015). CT scans use an X-ray beam, which passes through tissues to construct images using mathematical techniques. One of the major downfalls of CT scans is the substantial radiation dosage needed to create the images. This is especially a concern in studies with multiple follow-ups (Fosbol and Zerahn 2015). MRIs do not expose participants to radiation, but rather determine body composition based on the interaction between hydrogen nuclei. Hydrogen nuclei align themselves with a magnetic field. In MRIs, a radio frequency signal is used to generate images based on energy released from the hydrogen nuclei (Edelman et al. 2006).

These more accurate tools were not available or feasible in our research setting, therefore we used BIA given that it is more accurate than skinfold thickness, which was another option available for use in the NOW trial. Furthermore, BIA is safe (except in patients with electrical

devices such as pacemakers), inexpensive, low-maintenance, portable, rapid, and requires only minimal operator training (Buchholz, Bartok and Schoeller, 2004; Fosbol and Zerahn 2015).

8.2.3 BIA Theory

The link between bioimpedance and blood flow was first discovered in the 1950's (Nyboer et al. 1959). Later, it was determined that bioimpedance could be used to predict body composition, based on the underlying theory that the impedance of a cylindrical conductor is related to its length, cross-sectional area, and the signal of the frequency that's applied (Mulasi et al. 2015). Impedance, a measure of current obstruction, is calculated using resistance and reactance. Resistance refers to the resistive effect exhibited on the current (or current flow opposition). Thus, water and ionic substances provide a low-resistance pathway. Since water is contained in fat-free (lean) mass, lower fat-free (lean) mass results in more resistance; higher lean mass leads to lower resistance. Reactance refers to the conduction delay, which occurs when the current passes through cell membranes, tissues and non-ionic substances (Mulasi et al. 2015). The tetrapolar electrode approach that is commonly used today was first validated several decades ago by Hoffer et al. (1969). This approach involves the administration of electrical currents via leads attached to electrodes, typically placed on the hand and foot of the subject, which then differentiates the conductive and nonconductive tissues and fluids of the body (Mulasi et al. 2015). Tissues containing water and electrolytes (e.g. blood and muscle) conduct current well. Tissues that resist current include fat, bone and air-filled spaces. Predictions are then used, based on these measures, to predict body composition (Buchholz, Bartok and Schoeller, 2004; Mulasi et al. 2015).

Overall, BIA uses a low amperage current, which passes through the body, to estimate the amount of water contained in various biological tissues such as skeletal muscle, adipose tissue and bone. Distal (current injection) electrodes pass an alternating current through the body, and this current is returned to the proximal (voltage detection) electrodes. The amount of electricity conducted is proportionate to the concentration of ions in the conductor; thus, when the concentration of ions decreases, resistance increases. Furthermore, when body fluid viscosity increases, height increases or the cross-sectional area of the body decreases, resistance subsequently increases. It is well-established that skeletal muscles are more highly conductive compared to adipose tissue, which contains less water (Scharfetter et al. 2001; Lukaski et al. 1985). In fact, body fat is considered a non-conducting material, thus providing resistance to electrical current flowing through the body. Skeletal muscle is more conductive than bone (Buchholz, Bartok and Schoeller, 2004).

8.2.4 BIA Device and Equation

Body impedance refers to a bodily conductor opposing the flow of an alternating current. It is made up of resistance and reactance, which are measured using the unit, ohms. Higher frequency electrical currents can be used to determine total body water, while lower frequencies can be used to determine extracellular fluid. Extracellular fluid is then calculated based off these two measures. From there, fat-free mass is derived using proprietary equations that are based on the assumption that this mass is 73.2% hydrated. Then, fat mass can be determined by subtracting fat-free mass from total weight. There are also other methods of calculating body composition using various regression equations (Mulasi et al. 2015). Segmental BIA tends to be more accurate than whole body BIA given that segmental BIA equations are derived from the

segmentation of the body into five cylindrical compartments (2 arms, 1 trunk, 2 legs) as opposed to a single cylindrical compartment (Mulasi et al. 2015).

The relationship between resistance and/or reactance and body fat is indirect. BIA devices use regression equations to estimate body composition, including BFP. These equations take into consideration age, gender, weight, height, resistance and reactance (National Institutes of Health, 1994).

The literature suggests that a midrange frequency current of 50 kHz, used to measure total body water, will incompletely penetrate intracellular water and therefore detects primarily extracellular fluid with some intracellular fluid. This can lead to inaccuracies in patients with altered body water compartmentalization for both intracellular water and extracellular water (Buchholz, Bartok and Schoeller, 2004; Mulasi et al. 2015). Thus, the addition of a low frequency, 5 kHz current, helps to more accurately predict extracellular water given that this low current negligibly penetrates the intracellular water (Gudivaka et al. 1999). The BodyStat MDD1500 device used in the NOW trial measures resistance and reactance using dual frequency currents of 5 and 50 kHz. This whole body BIA device measures resistance and reactance, and based on this impedance measurement, body fat percentage is indirectly derived using a proprietary equation (BodyStat, 2017).

8.2.5 Contraindications to BIA Use

BIA is more accurate for the measurement of changes in body composition over time, as opposed to a single, cross-sectional measurement of body composition that may be taken in a clinical setting (Buchholz, Bartok and Schoeller, 2004). Importantly, BIA should not be used in individuals who have a pacemaker as the electrical signal from the BIA could alter the function

of the pacemaker device. Additionally, the safety of BIA has not been assessed in patients with other implanted electrical devices (e.g. spinal stimulators), and therefore it is recommended that the device not be used with these patients (BodyStat, 2017).

8.2.6 BIA Limitations

It is normal for fluid shifts to occur throughout the day, which can impact the BIA results. Asking participants to void prior to conducting the BIA can help to standardize total body fluid. In addition, repeating the BIA test at the same time of day throughout the duration of a study is additionally important (Most et al. 2018). However, due to logistical considerations, we were unable to standardize the time of day that the BIA assessments were conducted in the NOW trial; this was a limitation of the study.

8.2.7 BIA Data Interpretation

While body mass index (BMI) can be used to classify individuals into categories of underweight, normal weight, overweight and obese, established categories do not exist for body composition. This complicates the interpretation of body composition results, but some research groups have attempted to provide preliminary methods for data interpretation. Ozenoglu and colleagues (2009) compared body composition measured using BIA to established BMI categories in 327 adult females residing in Istanbul and found the following mean values for BFP within each BMI category, with significant differences ($p=0.0001$) in BFP between categories:

- Normal Weight: $22.8\pm 4.6\%$
- Overweight: $29.7\pm 3.3\%$
- Obese: $35.0\pm 3.3\%$
- Morbid Obese: $40.2\pm 3.6\%$

More recently, Sladjana et al. (2019) profiled BFP stratified by age in a sample of adult females from the Republic of Serbia. The results are as follows:

- 18.0-19.9 years: 23.8±6.8%
- 20.0-29.9 years: 24.8±7.4%
- 30.0-39.9 years: 28.1±9.3%
- 40.0-49.9 years: 32.4±8.3%
- 50.0-59.9 years: 36.3±7.9%
- 60.0-69.9 years: 39.9±7.9%

To our knowledge, these are the only established interpretations of BIA for female adults. Reference standards, stratified using percentiles, for BIA-measured BFP in adults are not available. However, DXA-measured BFP reference standards for Caucasian adults have been recently published by Imboden and colleagues (2017), with decile cut-offs established for both male and female Caucasian adults in the United States. These are further detailed elsewhere (Imboden et al. 2017).

The lack of available reference standards for BIA-measured BFP in samples of Canadian women poses challenges for the interpretation of the NOW trial results. In comparing the NOW trial results to the abovementioned studies (Sladjana et al. 2019; Ozenoglu et al. 2009; Imboden et al. 2017), the GLB group (mean age 56 years, 84% female, 99% Caucasian) exhibited a mean BFP higher than the mean reported BFP for this age group in Sladjana et al.'s (2019) study. At baseline, they were between the 20th and 30th percentile for BFP and at 12-months, were

between the 40th and 50th percentiles (with BFP and percentile values being inversely related). The GLB+NGx group (mean age 54 years, 90% female, 97% Caucasian) also exhibited a mean BFP higher than the mean reported BFP for this age group in Sladjana et al.'s (2019) study. According to Imboden et al.'s (2017) reference standard charts, this group was between the 40th and 50th percentiles for BFP at baseline, and was between the 50th and 60th percentiles for BFP at 12 months. Both the GLB and GLB+NGx group fell within the 'Morbid Obese' category according to Ozenoglu et al.'s (2009) study. However, these interpretations should be cautioned given the differences in study samples (Sladjana et al. 2019; Ozenoglu et al. 2009) and body composition devices (Imboden et al. 2017). Future research should seek to develop reference standard charts for BIA using a variety of devices and populations. In addition, future research should aim to explore associations between health outcomes such as blood pressure, cholesterol, blood glucose and other measures, and these reference standards of BFP.

8.3 Challenges Associated with Long-Term Lifestyle Behaviour Change

Altering lifestyle habits established over the course of an individual's lifespan is a highly complex and challenging endeavour. This is referred to in the literature as "the adherence problem" and is a notable concern given that individuals who do not adhere to a lifestyle intervention experience fewer health benefits (Dimatteo et al. 2002). Adherence to weight management programs have demonstrated particularly low rates of long-term adherence (Middleton, Anton, and Perri 2013). Typically, lifestyle interventions (both weight-related and non-weight-related) experience short-term initial adherence, followed by reduced adherence over the long-term (Middleton, Anton, and Perri 2013). Consequently, it is of great interest to find

that a nutrigenetic-guided intervention was able to motivate long-term dietary adherence to a significantly greater extent than a population-based lifestyle intervention. The discussion below provides greater detail on the challenges of long-term behavioural adherence, while linking this previous knowledge to the results of the NOW trial.

A variety of factors contribute to challenges with long-term behavioural adherence. The obesogenic food environment makes high-calorie, high-fat foods easily accessible at a low cost (Brownell 2005). Technological innovation has led to highly sedentary lifestyles, with workers spending at least 6-8 hours daily sitting at a desk (Lakdawalla and Philipson 2009). In terms of fitting planned, moderate-intensity physical activity into one's day, lack of time as well as feelings of stress and fatigue after work are commonly reported as perceived barriers to completing physical activity (Schutzer and Graves 2004; Heesch, Brown, and Blanton 2000). Furthermore, individuals tend to struggle with long-term adherence to lifestyle changes without ongoing support from a healthcare provider. Following initial treatment, which should include regular healthcare provider contact, long-term adherence to lifestyle changes can be optimized through meetings once or twice monthly (Perri et al. 2008; Wing et al. 2006; Svetkey et al. 2008). The NOW trial was designed to provide ongoing support with a healthcare provider by including meetings approximately monthly between 3- and 12-month follow-up (with weekly meetings occurring in the first three months). Reported barriers to healthy eating include a lack of cooking skills, taste preferences, frequency of eating foods away from home, calorically-dense and large portion sizes served at family meals, perceived cost, the built environment, food availability, and behaviours of friends and family (social norms) (McMorrow et al. 2017; Scherme et al. 2014; Seguin et al. 2014). Therefore, individualized factors as well as the social and built environment can significantly impact dietary intake and adherence. While not

specifically assessed in the NOW trial, it is suspected that these challenges were similar between the GLB and the GLB+NGx groups, given that participant groups were randomized.

From a theoretical perspective, the TPB can be used to demonstrate the impact of attitudes, subjective norms and behavioural control on health behaviours. Given that the GLB+NGx group had greater behaviour change outcomes with respect to nutrition over the long-term, it is possible that the more personalized lifestyle intervention had a greater impact on attitudes and/or subjective norms than the standard, population-based lifestyle intervention. This is an important future research endeavour, which can be completed using the NOW trial data. Other theories can further our comprehension of human behaviour in the context of lifestyle changes. The social cognitive theory, for example, suggests that *personal factors* (i.e. cognitions and emotions), as well as *environmental factors* (both social and physical environments) contribute to one's behaviour, and that one's behaviour can also impact personal and environmental factors (Bandura 1991). The social cognitive theory can be further broken down into four key constructs: *health knowledge, self-efficacy beliefs and outcome expectations, self-regulatory skills, and barriers to change* (Bandura 1991). The standard GLB intervention promoted *health knowledge* through the 23 group-based and three one-on-one educational sessions about lifestyle guidelines and their importance for optimal health and weight management. This intervention encouraged positive *self-efficacy beliefs and outcome expectations* through weekly goal setting leading to successful experiences altering lifestyle habits. It promoted *self-regulatory skills* using goal setting, food and beverage tracking, and positive reinforcement from the facilitator and GLB group members alike. Lastly, the program educated participants on problem-solving and included participant-guided discussions related to problem-solving, thus positively impacting *barriers to change*. The GLB+NGx program also

affected the abovementioned components of the social cognitive theory, but may have further affected *health knowledge* and *outcome expectations* through the provision of personalized, genetic-based lifestyle information and advice. These theoretical perspectives demonstrate the complexities and multifactorial nature of behaviour change, while also helping to explain why the provision of genetic-based nutrition information resulted in greater nutrition-related behaviour change.

8.4 Comparison to Outcomes of Previous Research on Nutrigenomics and Change in Nutrition-Related Behaviours

With respect to behaviour change, the NOW trial adds promise to the body of literature by demonstrating that genetic-based nutrition information can better motivate individuals to change their nutritional habits. The NOW trial results also support literature demonstrating that the provision of actionable genetic-based recommendations is more likely to facilitate health behaviour change compared to the provision of non-actionable genetic-based information such as disease risk estimates (Horne et al. 2018). Examples of previous, related research are detailed below.

A RCT conducted by Hieteranta-Luoma et al. (2014) found that when individuals were given genetic-based information related cardiovascular disease, they improved the quality of their diet to a greater extent than the control group. Similarly, in Nielsen and El-Sohehy's RCT (2014), DNA-based nutrition advice motivated participants with high-risk genetic variants to reduce their sodium intake over the long-term (12-months), more so than the control group. These studies, and several others, were conducted in samples of participants who received the

genetic testing free of charge or at a reduced rate. Thus, it is interesting and important to also review the results of studies conducted in real-world genetic testing consumers. Kaufman et al. (2012) surveyed consumers of DTC genetic testing and found that one third of participants reported being more careful with their diet, 10% reported changing a nutritional supplement, and 14% reported exercising more. Egglestone et al. (2013) surveyed consumers who had purchased DTC genetic tests and compared them to consumers considering purchasing a test or waiting for their results (control group). Of the consumers who had purchased DTC genetic tests and received their results, 27% reported changing health behaviours. The most commonly reported changes were “healthier diet,” “more exercise” and “taking vitamins or supplements” (Egglestone, Morris, and O’Brien 2013). With DTC genetic testing, consumers typically receive a substantial amount of health-related information. Therefore, there may be one or two specific components of the genetic report that stand out to an individual, and this is likely where the individual will focus their efforts in improving health behaviours. By assessing health behaviour change through asking more broad, open-ended questions, Egglestone et al. (2013) and Kaufman et al. (2012) provided an important assessment of overall behaviour change. With differing health priorities for different people, the focus of health behaviour change in genetic testing consumers can be highly variable.

Many studies have, conversely, found a lack of health behaviour change resulting from genetic testing, as further detailed in Chapter 3. The first study to assess change in nutritional habits from genetic testing focused on changes in dietary fat intake as a result of receiving a routine clinical diagnosis of familial hypercholesterolemia, or receiving a routine clinical diagnosis in addition to genetic testing. This was a randomized trial and found no significant differences in nutritional intake over the 6-month follow-up (Marteau et al. 2004). Another of the

earlier studies randomized participants with obesity to receive a 1-session consult on how to manage obesity, which either included or excluded genetic information. They measured dietary restraint and found no significant differences between groups after 6-month follow-up (Rief et al. 2007). Roke and colleagues' (2017) RCT of young female adults found no significant differences in omega-3 intake after 12-week follow-up in a group receiving genetic-based information about FADS1 genotype and omega-3 compared to those receiving non-genetic-based information about omega-3. Another RCT of over 1200 young adults followed up after one month found no significant differences in nutrition and physical activity habits in a group receiving standard weight management advice, compared to a group receiving standard weight management advice in addition to information about FTO genotype (general information about the FTO gene, personal FTO genotype, mode of inheritance, and impact on weight) (Meisel et al. 2015). With respect to the weight-related interventional studies (Meisel et al. 2015; Rief et al. 2007), given the complexities of weight management discussed throughout the present dissertation, it is perhaps not surprising to find that the abovementioned weight management behaviour change research found no significant nutrition-related changes stemming from genetic-based interventions after 1-, 3-, or 6-month follow-up. It is also possible that participants were not followed up for long enough to exhibit substantial lifestyle behaviour changes, which can take time to develop and become habits. Following participants for at least 12-months appears to be a warranted endeavour. Notably, there are now four completed 12-month RCTs (including the NOW trial) assessing dietary change resulting from genetically-tailored advice, all of which demonstrated positive dietary changes after 12-month follow-up (Nielsen and El-Sohemy 2014; Chao et al. 2008; Hietaranta-Luoma et al. 2014).

Overall, research in the area of nutrigenomics interventions and lifestyle behaviour change is highly variable regarding the follow-up time points, methods, intervention strategies, participants, and therefore nutrition-related outcomes. Perhaps the truly important research question is not broadly “*does* genetic testing motivate improvements in health behaviours?” with a simple ‘yes’ or ‘no’ answer, but rather, “*how* can we use genetic testing to motivate improvements in health behaviours?” Indeed, the former has been the focus of more recent systematic reviews (Hollands et al. 2016; French et al. 2017).

In terms of weight-related outcomes, further detailed in Chapter 4, previous research exploring the impact of nutrigenomics interventions on weight management have had mixed findings. Some research demonstrated effectiveness, while others reported no effect (Arkadianos et al. 2007; Celis-Morales et al. 2017; Frankwich et al. 2015). Study designs and nutrigenomics interventions have both been highly variable in the research that has been conducted to date. The NOW trial demonstrated that an actionable nutrigenomics-guided weight management intervention was effective at significantly reducing BFP after 3 and 6 months (Chapter 7). The first study assessing weight loss outcomes stemming from nutrigenomics interventions demonstrated an increased likelihood of maintaining some weight loss, with varying follow-up time points between 90 days and >365 days (Arkadianos et al. 2007). Later research in a sample of U.S. veterans, followed for 24 weeks, found that a nutrigenomics intervention had no impact on weight compared to general advice, but adherence to the nutrigenomics intervention was correlated with weight loss, whereas adherence to the standard diet was not (Frankwich et al. 2015). More recently, Celis-Morales et al. (2017) found that, compared to the provision of other levels of personalization, there was no beneficial impact of communicating genotype-related information and advice on weight and waist circumference in a 6-month follow-up study.

Therefore, the NOW trial adds promise to the body of literature with respect to short-term and moderate-term reductions in BFP in a nutrigenomics-guided intervention, above and beyond BFP changes demonstrated in a highly regarded public health weight management program. However, over the long-term there were no significant differences in weight-related outcomes between groups (Chapter 7). This is curious, given the long-term significant differences in dietary change and adherence, whereby the nutrigenomics-guided intervention group made greater dietary changes and better adhered to the dietary guidelines compared to the standard intervention group. There are some plausible explanations for this, as discussed previously in Chapter 7. It is possible that participants noticed weight regain occurring from 6 until 12 months, and thus at 12 months, became increasingly motivated to follow their genetic-based dietary guidelines. It is also possible that established biological adaptations occurring with weight loss could help to explain these diverging findings. This topic warrants further discussion, below.

8.5 Biological Challenges of Long-Term Weight Loss and Maintenance

Over time, physiological mechanisms including adipose cellularity, endocrine function, energy metabolism and neural responsivity promote weight regain after a period of weight loss (Ochner et al. 2013). Decades of research have demonstrated that increased energy (calorie) intake can lead to increased fat cell size and fat cell number (Martinsson 1969; Hirsch and Batchelor 1976; Tchoukalova et al. 2010), and while weight loss may reduce the size of fat cells, it is unlikely to reduce the number of fat cells (Martinsson 1969; Björntorp et al. 1975; Hirsch and Han 1969; Arner and Spalding 2010; Gurr et al. 1982; Löfgren et al. 2005). Furthermore, while not well-established, preliminary research has demonstrated that this could encourage weight regain following periods of weight loss due to a reduction in the rate of fat oxidation and

increased retention of ingested energy (MacLean et al. 2006; Jackman et al. 2008; Knittle and Hirsch 1968; Kelley et al. 1999; Berggren et al. 2008). Changes in leptin (the satiety hormone) levels can also impact weight regain with research indicating that compared to a control, formerly obese individuals who had lost weight had reduced serum leptin levels despite having the same BFP (Löfgren et al. 2005). Several studies have shown a greater reduction in leptin levels following weight loss than one would expect (Arner and Spalding 2010; Löfgren et al. 2005; Rosenbaum et al. 1997). Leptin depletion can lead to decreased metabolic rate (energy expenditure) and physical activity (Rosenbaum et al. 2010) as well as increased hunger and energy (calorie) intake (Kissileff et al. 2012). Peptide YY and cholecystokinin are other satiety-promoting hormones, while ghrelin is a hunger-inducing hormone and changes in levels of these hormones have also been observed following periods of weight loss (Wren et al. 2001; Batterham et al. 2002; Sumithran et al. 2011; Lien et al. 2009). Therefore, weight loss could lead to both reduced satiety, and increased hunger, resulting in overeating and thus weight regain (Rosenbaum et al. 1997). Additionally, research has demonstrated a decrease in thyroid function (and thus, a decrease in metabolic rate) after weight loss in individuals with obesity (Rosenbaum et al. 2000; Kozłowska and Rosołowska-Huszcz 2004; Moreno et al. 2008). Moreover, the activity of hypothalamic-pituitary-adrenal axis, which regulates cortisol levels, is heightened following weight loss and this can lead to increased appetite and fat accumulation (Björntorp 2001).

In terms of changes in metabolic rate, a decrease in fat mass and lean mass will both lead to reductions in energy output/expenditure (Leibel, Rosenbaum, and Hirsch 1995; Gallagher et al. 1996). While a reduction in metabolic rate is normal and expected, studies have demonstrated that weight loss occurring from lifestyle interventions (behavioural weight loss) results in

‘metabolic adaptation’ (Leibel, Rosenbaum, and Hirsch 1995; Gallagher et al. 1996; Astrup et al. 1999; Rosenbaum and Leibel 2010; Johannsen et al. 2012; Camps, Verhoef, and Westerterp 2013; Tremblay and Chaput 2009). *Metabolic adaptation* refers to a greater reduction in metabolic rate than would be expected based on an individual’s body composition (Leibel, Rosenbaum, and Hirsch 1995; Gallagher et al. 1996; Astrup et al. 1999; Rosenbaum and Leibel 2010; Johannsen et al. 2012; Camps, Verhoef, and Westerterp 2013; Tremblay and Chaput 2009). This decrease in resting metabolic rate following weight loss leads to biological challenges with weight maintenance. The classic Minnesota semi-starvation experiment was one of the first studies to demonstrate a reduced resting metabolic rate during a period of weight regain following weight loss (Keys 1950). A number of studies have corroborated these findings following the publication of the Minnesota semi-starvation experiment (Leibel, Rosenbaum, and Hirsch 1995; Astrup et al. 1999; Rosenbaum and Leibel 2010; Johannsen et al. 2012; Camps, Verhoef, and Westerterp 2013; Tremblay and Chaput 2009). Weight cycling can also negatively affect resting metabolic rate, with research demonstrating that the fat-to-lean mass ratio of weight regained is greater than the fat-to-lean mass ratio of weight lost. Therefore, weight cycling can result in the body favouring fat mass over lean mass (Lahti-Koski et al. 2005). With lean mass having a greater contribution to energy expenditure compared to fat mass, over time multiple bouts of weight cycling can have a considerable impact on metabolic rate (Prentice et al. 1992).

Long-term weight loss is further challenged by neural responsivity. Specifically, neural systems include: the homeostatic system, which functions to respond to caloric needs to maintain energy balance; the reward-related system, which functions to promote eating based on dopamine signalling, thus driving the perception of the reward-value of food; and the inhibitory

system, which functions to inhibit excessive food intake (Le et al. 2006). With caloric restriction, the homeostatic system upregulates the reward-related system, thus leading to greater consumption of high-calorie foods compared to low-calorie foods. This upregulation appears to persist during the period following weight loss (Kissileff et al. 2012; Murdaugh et al. 2012), which can result in weight regain (LaBar et al. 2001; Berthoud 2011). Indeed, research demonstrates that individuals crave “forbidden foods” during periods of dietary restriction (Soetens et al. 2008).

Ultimately, there are several biological mechanisms leading the body to resist weight loss, and drive weight regain. This could explain why results from the NOW trial demonstrated weight regain trends occurring from 6-month to 12-month follow-up in both the GLB and GLB+NGx groups (Chapter 7). It is intriguing to notice the continued trend towards decreasing BFP (but not weight) in the GLB group only. It is hypothesized that the faster rate of BFP loss experienced in the GLB+NGx group led to an earlier onset of the biological responses promoting weight regain. Indeed, research supports this notion (MacLean et al. 2011). Additionally, considering the nutrition-related findings presented in Chapter 6, taken together with the weight-related findings from Chapter 7, it is likely that the drivers of weight and fat mass regain in the GLB+NGx group were related more to metabolic adaptation, endocrine function, energy metabolism and adipose cellularity than to neural responsivity and hormonal changes associated with increased energy intake, such as changes in peptide YY, cholecystokinin and ghrelin. Overall, biological adaptations to weight loss will remain a challenge for researchers in the field of pragmatic nutrigenomics for weight loss.

8.6 Participant Retention in Weight Loss Research

With these biological and behavioural challenges associated with sustaining weight loss long-term, it is not surprising to find higher dropout rates in weight loss studies compared to studies of other health-related outcomes. While the target dropout rate for an RCT is <20% (National Institutes of Health n.d.), studies demonstrate that this is typically challenging for long-term weight loss studies (Hillmer et al. 2017; Truby et al. 2006; Jebb et al. 2011; Wadden et al. 2004; Gill et al. 2012; Foster et al. 2003). Thus, the dropout rate of 46% in the NOW trial was not remarkable. Reasons for reduced participant retention could include scheduling conflicts, dissatisfaction with treatment, and lack of time to meet the study requirements (Wadden et al. 2004). Having a lower education level, a higher level of obesity, and higher stress levels are also risk factors for dropping out of weight loss programs/studies (Michelini et al. 2014; Ortner Hadžiabdić et al. 2015). Many of these factors contributed to participant dropout in the NOW trial as further indicated in Chapter 7: Figure 7.1 and Table 7.1, and Chapter 6: Table 6.2. Notably, research has previously been conducted within the GLB program at the EEFHT and five other Ontario primary care locations. In this previous study, the program was offered during a 9-month period, and dropout rates throughout the study were 26.8% at 3-months, 46.8% at 6-months, and 63.0% at 9-months (Hillmer et al. 2017). This is the most comparable study to the NOW trial, in terms of dropout rate, given the similarities in the intervention and setting. The addition of nutrigenetic information in the NOW trial may have helped achieve a higher retention rate (over a longer period of time) than this previous research.

8.7 Future Directions

Future research evaluating the impact of genetic testing on health behaviours should consider validated behaviour change theory, such as the TPB. Not only would this help to ensure important possible confounders of behaviour change are considered, but it would also help to inform high-quality, detailed results from future systematic reviews on this topic. Perhaps genetic testing for personalized nutrition helps to motivate health behaviour change only when attitudes and/or subjective norms and/or behavioural control and/or behavioural intentions are high? For example, participants in the NOW trial had highly positive attitudes towards changing their nutritional habits, with neutral subjective norms and behavioural control, and strong intentions to make changes to their nutritional intake. These participants successfully made long-term changes to their total fat and saturated fat intake. If this study was repeated in a sample of participants with negative attitudes and weak intentions towards changing their nutritional habits, results may demonstrate no changes in nutritional intake even if behavioural control and/or subjective norms are positive in terms of encouraging behaviour change. Future studies should seek to test this concept. Additional TPB research should determine if, over time, genetic testing for personalized nutrition and physical activity positively affects one or more of the intermediates of behaviour change: attitudes, subjective norms, and/or perceived behavioural control. Overall, our understanding of the impact of genetic testing on health behaviour change is complex and knowledge is only in its infancy.

Future research should further seek to evaluate the impact of pragmatic nutrigenomics interventions on other indicators of health such as blood pressure, cholesterol, blood glucose, insulin, and others. In terms of weight management, assessing the impact of nutrigenomics interventions in samples of patients who may benefit from short-term and moderate-term

reductions in BFP would be beneficial. These specific patient populations are further outlined in Chapter 7. Ideally, an RCT methodology should be employed, with the consideration of validated behaviour change theory to guide both the genetic-based and the standard interventions as well as the statistical analyses. Given the established difficulties associated with long-term weight loss including biological adaptations to adipose cellularity, endocrine function, energy metabolism, and neural responsivity (Ochner et al. 2013), it appears to be of great importance for researchers to focus on obesity-prevention. Nonetheless, the present work did not seek to specifically explore if biological mechanisms were responsible for long-term challenges with maintaining weight loss and fat mass loss from a genetic-based intervention, and thus future research should aim to replicate the NOW trial while exploring this phenomenon.

CHAPTER 9: CONCLUSION

In the areas of nutrigenomics, health behaviour change, overweight/obesity and their interrelations, there is much that remains to be understood. The NOW trial provided an intriguing and insightful analysis of these topics, contributing to our overall understanding of the interplay between nutrition, genetics, health behaviours and health-related outcomes. The findings from the present dissertation generated strong insights for the focus of future research. As we continue to gain knowledge in the fields of nutrigenomics, health behaviour change, overweight/obesity and their interrelations, we are not only contributing greatly to the scientific community, but more importantly, to the health and wellbeing of individuals through the development of more precise and personalized health strategies.

REFERENCES

- 23andMe. c2019. "23andMe." Accessed August 12, 2019. <https://www.23andme.ca>.
- Abusabha R, Peacock J, and Achterberg C. 1999. "How to Make Nutrition Education More Meaningful through Facilitated Group Discussions." *Journal of the American Dietetic Association* 99 (1): 72-76.
- Adan RAH, Tiesjema B, Hillebrand JJG, Fleur SE, Kas MJH, and De Krom M. 2006. "The MC4 Receptor and Control of Appetite." *British Journal of Pharmacology* 149: 815–27. <https://doi.org/10.1038/sj.bjp.0706929>.
- Ahmad T, Chasman DI, Mora S, Paré G, Cook NR, Buring JE, Ridker PM, and Lee IM. 2010. "The Fat-Mass and Obesity-Associated (FTO) Gene, Physical Activity, and Risk of Incident Cardiovascular Events in White Women." *American Heart Journal* 160 (6): 1163–69. <https://doi.org/10.1016/j.ahj.2010.08.002>.
- Ahmetov II, Kulemin NA, Popov DV, Naumov VA, Akimov EB, Bravy YR, Egorova ES, et al. 2015. "Genome-Wide Association Study Identifies Three Novel Genetic Markers Associated with Elite Endurance Performance." *Biology of Sport* 32 (1): 3–9. <https://doi.org/10.5604/20831862.1124568>.
- Ahmetov II, Druzhevskaya AM, Lyubaeva EV, Popov DV, Vinogradova OL, and Williams AG. 2011. "The Dependence of Preferred Competitive Racing Distance on Muscle Fibre Type Composition AndACTN3genotype in Speed Skaters." *Experimental Physiology* 96 (12): 1302–10. <https://doi.org/10.1113/expphysiol.2011.060293>.
- Ajzen I. c2019. "Constructing a Theory of Planned Behavior Questionnaire." <https://people.umass.edu/aizen/pdf/tpb.measurement.pdf>.
- Ajzen I. 1991. "The Theory of Planned Behavior." *Organizational Behavior and Human Decision Making Processes* 51: 179–211.
- Ajzen I. 2006. "Icek Ajzen: Theory of Planned Behavior." 2006. <http://people.umass.edu/aizen/tpb.html>.
- Ajzen I. 2011. "The Theory of Planned Behaviour: Reactions and Reflections." *Psychology & Health* 26 (9): 1113–27. <https://doi.org/10.1080/08870446.2011.613995>.
- Aller E, Larsen TM, Claus H, Lindroos AK, Kafatos A, Pfeiffer A, Martinez JA, et al. 2014. "Weight Loss Maintenance in Overweight Subjects on Ad Libitum Diets with High or Low Protein Content and Glycemic Index: The DIOGENES Trial 12-Month Results." *International Journal of Obesity* 38 (12): 1511–17. <https://doi.org/10.1038/ijo.2014.52>.
- Alva ML. 2019. "How Much Does Attendance Impact Weight Loss and Health Care Spending in a Diabetes Prevention Program Serving Older Adults?" *American Journal of Health Promotion* 33 (7): 1067–72. <https://doi.org/10.1177/0890117119848985>.
- Alva ML, Romaine M, and Acquah J. 2019. "Impact of Financial Incentives on Diabetes Prevention Class Attendance and Program Completion: Evidence From Minnesota, Montana, and New York." *American Journal of Health Promotion* 33 (4): 601–5.

<https://doi.org/10.1177/0890117118794087>.

Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, et al. 2016. "Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult." *Can J Cardiol* 32(11): 1263-82.

Andreasen CH, Stender-Peterson KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, Nielsen AL, et al. 2008. "Low Physical Activity Accentuates the Effect of the FTO Rs9939609 Polymorphism on Body Fat Accumulation." *Diabetes* 57: 95–101.

Andrew BJ, Mullan BA, De Wit JBF, Monds LA, Todd J, Kothe EJ. 2016. "Does the Theory of Planned Behaviour Explain Condom Use Behaviour Among Men Who Have Sex with Men ? A Meta-Analytic Review of the Literature." *AIDS and Behavior* 20 (12): 2834–44. <https://doi.org/10.1007/s10461-016-1314-0>.

Annan J, Clement N, Macpherson GJ, Brenkel IJ, Ballantyne JA, and Dunstan E. 2018. "Body Mass Index, Hip Function and Surgeon Volume Are Independent Predictors of Dislocation: An Analysis of 4334 Total Hip Replacements." *European Journal of Orthopaedic Surgery and Traumatology* 28 (5): 899–905. <https://doi.org/10.1007/s00590-017-2078-6>.

Appleton KM. 2016. "Barriers to and Facilitators of the Consumption of Animal-Based Protein-Rich Foods in Older Adults." *Nutrients* 8(4).

Arena R, McNeil A, Sagner M, and Hills AP. 2017. "The Current Global State of Key Lifestyle Characteristics: Health and Economic Implications." *Progress in Cardiovascular Diseases Arena Ross Progress in Cardiovascular Diseases* 9. <https://doi.org/10.1016/j.pcad.2017.02.002>.

Arkadianos I, Valdes AM, Marinos E, Florou A, Gill RD, and Grimaldi KA. 2007. "Improved Weight Management Using Genetic Information to Personalize a Calorie Controlled Diet." *Nutrition Journal* 6: 29. <https://doi.org/10.1186/1475-2891-6-29>.

Arksey H, and O'Malley L. 2005. "Scoping Studies: Towards a Methodological Framework." *International Journal of Social Research Methodology* 8 (1): 19–32.

Armitage CJ and Conner M. 2001. "Efficacy of the Theory of Planned Behaviour: A Meta-Analytic Review." *British Journal of Social Psychology* 40: 471–99. <https://doi.org/10.1348/014466601164939>.

Arner P and Spalding KL. 2010. "Fat Cell Turnover in Humans." *Biochemical and Biophysical Research Communications* 396 (1): 101–4. <https://doi.org/10.1016/j.bbrc.2010.02.165>.

Astrup A, Gøtzsche PC, Van De Werken K, Ranneries C, Toubro S, Raben A, and Buemann B. 1999. "Meta-Analysis of Resting Metabolic Rate in Formerly Obese Subjects." *American Journal of Clinical Nutrition* 69 (6): 1117–22. <https://doi.org/10.1093/ajcn/69.6.1117>.

Athletigen. 2018. "Nutrition Report." 2018. <https://athletigen.com/products/nutrition-report/>.

Audrain J, Boyd NR, Roth J, Main D, Caporaso NE, and Lerman C. 1997. "Genetic Susceptibility Testing in Smoking-Cessation Treatment: One-Year Outcomes of a Randomized Trial." *Addictive Behaviors* 22 (6): 741–51. [https://doi.org/10.1016/S0306-4603\(97\)00060-9](https://doi.org/10.1016/S0306-4603(97)00060-9).

- Azuma K, Rádiková Z, Mancino J, Toledo FGS, Thomas E, Kangani C, Man CD, et al. 2008. "Measurements of Islet Function and Glucose Metabolism with the Dipeptidyl Peptidase 4 Inhibitor Vildagliptin in Patients with Type 2 Diabetes." *Journal of Clinical Endocrinology and Metabolism* 93 (2): 459–64. <https://doi.org/10.1210/jc.2007-1369>.
- Bandura A. 1991. "Social Cognitive Theory of Self-Regulation." *Organ Behav Hum Dec* 50 (2): 248–87.
- Banks NF, Tomko PM, Colquhoun RJ, Muddle TWD, Emerson SR, and Jenkins NDM. 2019. "Genetic Polymorphisms in ADORA2A and CYP1A2 Influence Caffeine's Effect on Postprandial Glycaemia." *Scientific Reports* 9 (1): 1–9. <https://doi.org/10.1038/s41598-019-46931-0>.
- Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wrem AM, et al. 2002. "Gut Hormone PYY 3-36 Physiologically Inhibits Food Intake." *Nature* 418 (August): 728–30.
- Berezowska AF, Ronteltap ARH, Kuznesof A, Macready S, Fallaize A, van Trijp R. 2014. "Understanding Consumer Evaluations of Personalised Nutrition Services in Terms of the Privacy Calculus: A Qualitative Study." *Public Health Genomics* 17 (3): 127–40.
- Bedogni G, Agosti F, De Col A, et al. 2013. "Comparison of dual energy X-ray absorptiometry, air displacement plethysmography and bioelectrical impedance analysis for the assessment of body composition in morbidly obese women." *European Journal of Clinical Nutrition* 67(11):1129-32.
- Berggren JR, Boyle KE, Chapman WH, and Houmard JA. 2008. "Skeletal Muscle Lipid Oxidation and Obesity: Influence of Weight Loss and Exercise." *American Journal of Physiology - Endocrinology and Metabolism* 294 (4): 726–32. <https://doi.org/10.1152/ajpendo.00354.2007>.
- Berthoud HR. 2011. "Metabolic and Hedonic Drives in the Neural Control of Appetite: Who's the Boss?" *Current Opinions in Neurobiology* 21 (6): 889–96. <https://doi.org/10.1038/jid.2014.371>.
- Best D, Avenell A, and Bhattacharya S. 2017. "How Effective Are Weight-Loss Interventions for Improving Fertility in Women and Men Who Are Overweight or Obese? A Systematic Review and Meta-Analysis of the Evidence." *Human Reproduction Update* 23 (6): 681–705. <https://doi.org/10.1093/humupd/dmx027>.
- Best RL and Appleton KM. 2013. "The Consumption of Protein-Rich Foods in Older Adults: An Exploratory Focus Group Study." *Journal of Nutrition Education and Behavior* 45(6):751-5.
- Björntorp P. 2001. "Do Stress Reactions Cause Abdominal Obesity and Comorbidities?" *Obesity Reviews* 2 (2): 73–86. <https://doi.org/10.1046/j.1467-789x.2001.00027.x>.
- Björntorp P, Carlgren G, Isaksson B, Krokiewski M, Larsson B, and Sjöström L. 1975. "Effect of an Energy- Reduced Dietary Regimen in Relation to Adipose Tissue Cellularity in Obese Women." *American Journal of Clinical Nutrition* 28: 445–52.
- Blackburn R, Osborn D, Walters K, Falcaro M, Nazareth I, and Petersen I. 2017. "Statin

- Prescribing for People with Severe Mental Illnesses : A Staggered Cohort Study of ‘ Real-World ’ Impacts.” <https://doi.org/10.1136/bmjopen-2016-013154>.
- Bloss CS, Schork NJ, and Topol EJ. 2011. “Effect of Direct-to-Consumer Genomewide Profiling to Assess Disease Risk.” *The New England Journal of Medicine* 364 (6): 524–34. <https://doi.org/10.1056/NEJMoa1011893>.
- Bloss CS, Wineinger NE, Darst BF, Schork NJ, and Topol EJ. 2013. “Impact of Direct-to-Consumer Genomic Testing at Long Term Follow-Up.” *Journal of Medical Genetics* 50 (6): 393–400. <https://doi.org/10.1136/jmedgenet-2012-101207>.
- BodyStat. 2017. "Professional Body Composition and Nutrition Analysis: BodyStat 1500MDD Touch Screen." BodyStat, c2017.
- Boeldt DL, Schork NJ, Topol EJ and Bloss CS. 2015. “Influence of Individual Differences in Disease Perception on Consumer Response to Direct-to-Consumer Genomic Testing.” *Clinical Genetics* 87 (3): 225–32. <https://doi.org/10.1111/cge.12419>.
- Bookman JS, Schwarzkopf R, Rathod P, Iorio R, and Deshmukh AJ. 2018. “Obesity: The Modifiable Risk Factor in Total Joint Arthroplasty.” *Orthop Clin North Am* 49 (3): 291–96.
- Boschmann M, Engeli S, Dobberstein K, Budziarek P, Strauss A, Boehnke J, Sweep FC, et al. 2009. “Dipeptidyl-Peptidase-IV Inhibition Augments Postprandial Lipid Mobilization and Oxidation in Type 2 Diabetic Patients.” *Journal of Clinical Endocrinology and Metabolism* 94 (3): 846–52. <https://doi.org/10.1210/jc.2008-1400>.
- Bouwman L, Molder H, and Hiddink G. 2009. “Patients, Evidence and Genes: An Exploration of GPs’ Perspectives on Gene-Based Personalized Nutrition Advice.” *Family Practice* 25 (SUPPL. 1): 116–22. <https://doi.org/10.1093/fampra/cmn067>.
- Branson R, Potoczna N, Kral JG, Lentos K-U, Hoehe MR, and Horber FF. 2003. “Binge Eating as a Major Phenotype of Melanocortin 4 Receptor Gene Mutations.” *New England Journal of Medicine* 348 (12): 1096–1103. <https://doi.org/10.1056/nejmoa021971>.
- Brock DW, Chandler-Laney PC, Alvarez JA, Gower BA, Gaesser GA, and Hunter GR. 2010. “Perception of Exercise Difficulty Predicts Weight Regain in Formerly Overweight Women” 18 (5): 982–86. <https://doi.org/10.1038/oby.2009.318>.Perception.
- Brownell KD. 2005. “Does a ‘Toxic’ Environment Make Obesity Inevitable?” *Obesity Management* 1 (2): 52–55. <https://doi.org/10.1089/obe.2005.1.52>.
- Buchholz AC, Bartok C, Schoeller DA. 2004. “The validity of bioelectrical impedance models in clinical populations.” *Nutrition in Clinical Practice* 19(5):433-446.
- Camps SG, Verhoef SPM, and Westerterp KR. 2013. “Weight Loss, Weight Maintenance, and Adaptive Thermogenesis.” *American Journal of Clinical Nutrition* 97 (5): 990–94. <https://doi.org/10.3945/ajcn.112.050310>.
- Carpenter MJ, Strange C, Jones Y, Dickson MR, Carter C, Moseley MA, and Gilbert GE. 2007. “Does Genetic Testing Result in Behavioral Health Change? Changes in Smoking Behavior Following Testing for Alpha-1 Antitrypsin Deficiency.” *Annals of Behavioral Medicine* 33 (1): 22–28. https://doi.org/10.1207/s15324796abm3301_3.

- Casas-Agustench P, Arnett DK, Smith CE, Lai C-Q, Parnell LD, Borecki IB, Allison M, et al. 2013. “Saturated Fat Intake Modulates the Association between a Genetic Risk Score of Obesity and BMI in Two US Populations Patricia.” *J Acad Nutr Diet* 18 (9): 1199–1216. <https://doi.org/10.1016/j.micinf.2011.07.011>.Innate.
- Caulfield T and McGuire AL. 2012. “Direct-to-Consumer Genetic Testing: Perceptions, Problems, and Policy Responses.” *Annual Review of Medicine* 63 (1): 23–33. <https://doi.org/10.1146/annurev-med-062110-123753>.
- CDC. 2016. “Chronic Disease Overview.” 2016. <https://www.cdc.gov/chronicdisease/overview/>.
- Celis-Morales C, Livingstone KM, Marsaux CFM, Forster H, O'Donovan CB, Woolhead C, Macready AL, et al. 2015. “Design and Baseline Characteristics of the Food4Me Study: A Web-Based Randomised Controlled Trial of Personalised Nutrition in Seven European Countries.” *Genes and Nutrition* 10 (1). <https://doi.org/10.1007/s12263-014-0450-2>.
- Celis-Morales C, Livingstone KM, Woolhead C, Forster H, O'Donovan CB, Macready AL, Fallaize R, et al. 2015. “How Reliable Is Internet-Based Self-Reported Identity, Socio-Demographic and Obesity Measures in European Adults?” *Genes and Nutrition* 10 (5): 1–10. <https://doi.org/10.1007/s12263-015-0476-0>.
- Celis-Morales C, Marsaux CFM, Livingstone KM, Navas-Carretero S, San-Cristobal R, O'Donovan CB, Forster H, et al. 2016. “Physical Activity Attenuates the Effect of the FTO Genotype on Obesity Traits in European Adults: The Food4Me Study.” *Obesity* 24 (4): 962–69. <https://doi.org/10.1002/oby.21422>.
- Celis-Morales C, Marsaux CFM, Livingstone KM, Navas-Carretero S, San-Cristobal R, Fallaize R, Macready AL, et al. 2017. “Can Genetic-Based Advice Help You Lose Weight ? Findings from The Food4Me European randomized controlled trial.” *American Journal of Clinical Nutrition*. 105: 1204–13. <https://doi.org/10.3945/ajcn.116.145680.1>.
- Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, et al. 2013. “SPIRIT 2013 Explanation and Elaboration: Guidance for Protocols of Clinical Trials.” *BMJ (Clinical Research Ed.)* 346: 1–42. <https://doi.org/10.1136/bmj.e7586>.
- Chao SJ, Roberts S, Marteau TM, Silliman R, Cupples LA, and Green RC. 2008. “Health Behavior Changes After Genetic Risk Assessment for Alzheimer Disease: The REVEAL Study.” *Alzheimer Dis Assoc Disord*. 100 (2): 130–34. <https://doi.org/10.1016/j.pestbp.2011.02.012>.Investigations.
- Cheung SF and Chan DKS. 2000. “The Role of Perceived Behavioral Control in Predicting Human Behavior: A Meta-Analytic Review of Studies on the Theory of Planned Behavior.” *Unpublished Manuscript, Chinese University Hong Kong*.
- Clausen ES, Frankel C, Palmer SM, Snyder LD, and Smith PJ. 2018. “Pre-Transplant Weight Loss and Clinical Outcomes after Lung Transplantation.” *Journal of Heart and Lung Transplantation* 37 (12): 1443–47. <https://doi.org/10.1016/j.healun.2018.07.015>.
- Coletta AM, Sanchez B, Connor AO, Dalton R, Springer A, Koozehchian MS, Murano PS, Woodman CR, Rasmussen C, and Richard B. 2018. “Alignment of Diet Prescription to Genotype Does Not Promote Greater Weight Loss Success in Women with Obesity

- Participating in an Exercise and Weight Loss Program.” *Obesity Science and Practice*. <https://doi.org/10.1002/osp4.305>.
- Collins J, Bertrand B, Hayes V, Li SX, Thomas J, Truby H, and Whelan K. 2013. “The Application of Genetics and Nutritional Genomics in Practice: An International Survey of Knowledge, Involvement and Confidence among Dietitians in the US, Australia and the UK.” *Genes and Nutrition* 8 (6): 523–33. <https://doi.org/10.1007/s12263-013-0351-9>.
- Conway JM, Ingwersen LA, Vinyard BT, and Moshfegh AJ. 2003. “Effectiveness of the US Department of Agriculture 5-Step Multiple-Pass Method in Assessing Food Intake in Obese and Nonobese Women.” *American Journal of Clinical Nutrition* 77 (5): 1171–78.
- Cooke R, Dahdah M, Norman P, and French DP. 2016. “How Well Does the Theory of Planned Behaviour Predict Alcohol Consumption ? A Systematic Review and Meta-Analysis.” *Health Psychology Review* 0 (0): 1–20. <https://doi.org/10.1080/17437199.2014.947547>.
- Corella D, Peloso G, Arnett DK, Demissie S, Cupples A, Tucker K, Lai CQ, et al. 2009. “APOA2, Dietary Fat, and Body Mass Index: Replication of a Gene-Diet Interaction in 3 Independent Populations” 169 (20): 1897–1906.
- Corella D, Tai ES, Sorli JV, Chew SK, Coltell O, Sotos-Prieto M, Garcia-Rios A, Estruch R, and Ordovas JM. 2011. “Association between the APOA2 Promoter Polymorphism and Body Weight in Mediterranean and Asian Populations : Replication of a Gene – Saturated Fat Interaction” 35: 666–75. <https://doi.org/10.1038/ijo.2010.187>.
- Corella D, Ortega-Azorín C, Sorlí JV, Covas MI, Carrasco P, Salas-Salvadó J, Martínez-González MA, et al. 2012. “Statistical and Biological Gene-Lifestyle Interactions of MC4R and FTO with Diet and Physical Activity on Obesity: New Effects on Alcohol Consumption.” *PLoS ONE* 7 (12). <https://doi.org/10.1371/journal.pone.0052344>.
- Corella D, Peloso G, Arnett DK, Cupples LA, Tucker K, Lai C-Q, Parnell LF, Coltell O, Lee Y-C, and Jose M. 2010. “APOA2, Dietary Fat and Body Mass Index: Replication of a Gene-Diet Interacton in Three Independent Populations.” *Archives of Internal Medicine* 169 (20): 1897–1906. <https://doi.org/10.1001/archinternmed.2009.343.APOA2>.
- Cormier H, Tremblay BL, Paradis AM, Garneau V, Desroches S, Robitaille J, and Vohl M-C. 2014. “Nutrigenomics - Perspectives from Registered Dietitians: A Report from the Quebec-Wide e-Consultation on Nutrigenomics among Registered Dietitians.” *Journal of Human Nutrition and Dietetics* 27 (4): 391–400. <https://doi.org/10.1111/jhn.12194>.
- Cornelis MC, El-Sohemy A, Kabagambe EK, and Campos H. 2006. “Coffee, CYP1A2 Genotype, and Risk of Myocardial Infarction.” *Journal of the American Medical Association*. <https://doi.org/10.1001/jama.295.10.1135>.
- Critical Appraisal Skills Programme. 2017. “CASP Qualitative Research Checklist.” 2017.
- Dallal GE. 2017. “Randomization.com.” 2017. www.randomization.com.
- de Viron S, van der Heyden J, Ambrosino E, Arbyn M, Brand A, and van Oyen H. 2012. “Impact of Genetic Notification on Smoking Cessation: Systematic Review and Pooled-Analysis.” *PLoS ONE* 7 (7). <https://doi.org/10.1371/journal.pone.0040230>.

- Dean E and Söderlund A. 2015. "What Is the Role of Lifestyle Behaviour Change Associated with Non-Communicable Disease Risk in Managing Musculoskeletal Health Conditions with Special Reference to Chronic Pain?" *BMC Musculoskeletal Disorders* 16 (1): 1–7. <https://doi.org/10.1186/s12891-015-0545-y>.
- Delgado-Lista J, Perez-Jimenez F, Tanaka T, Perez-Martinez P, Jimenez-Gomez Y, Marin C, Ruano J, Parnell L, Ordovas JM and Lopez-Miranda J. 2018. "An Apolipoprotein A-II Polymorphism (-265T/C, Rs5082) Regulates Postprandial Response to a Saturated Fat Overload in Healthy Men." *The Journal of Nutrition* 137 (9): 2024–28. <https://doi.org/10.1093/jn/137.9.2024>.
- Denison FC, Weir Z, Carver H, Norman JE, and Reynolds RM. 2015. "Physical Activity in Pregnant Women with Class III Obesity : A Qualitative Exploration of Attitudes and Behaviours." *Midwifery* 31 (12): 1163–67. <https://doi.org/10.1016/j.midw.2015.08.006>.
- Devito NJ, French L, and Goldacre B. 2018. "Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age , 2007-2008 to 2015-2016" 319 (16): 2016–18.
- Diabetes Canada. c2019. "Are You at Risk?" <https://www.diabetes.ca/about-diabetes/risk-factors/are-you-at-risk>.
- Diabetes Prevention Program Research Group. 2002. "Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin." *The New England Journal of Medicine* 346 (6): 393.
- Dimatteo MR, Giordani PJ, Lepper HS, and Thomas W. 2002. "Patient Adherence and Medical Treatment Outcomes A Meta-Analysis Published by : Lippincott Williams & Wilkins Stable URL : [Http://Www.Jstor.Org/Stable/3768145](http://www.jstor.org/stable/3768145)." *Medical Care* 40 (9): 794–811. <https://doi.org/10.1097/01.MLR.0000024612.61915.2D>.
- Downie L, Donoghue S, and Stutterd C. 2017. "Advances in Genomic Testing" 46 (4): 200–204.
- Drabsch T and Holzapfel C. 2019. "A scientific perspective of personalised gene-based dietary recommendations for weight management." *Nutrients* 11(3): 1-14.
- Edelman R, Hesselink JR, Zlatkin MB, Cruess JV. *Clinical Magnetic Resonance Imaging*. (2006); Saunders, Philadelphia, PA.
- Edwards H, Simpson JAR, Bushholz AC. 2011. "Air Displacement Plethysmography For Fat-mass Measurement in Healthy Young Women." *Can J Diet Pract Res*, 72(2):85-7.
- Egglestone C, Morris A, and O'Brien A. 2013. "Effect of Direct-to-Consumer Genetic Tests on Health Behaviour and Anxiety: A Survey of Consumers and Potential Consumers." *Journal of Genetic Counseling* 22 (5): 565–75. <https://doi.org/10.1007/s10897-013-9582-6>.
- Eldridge SM, Chan CL, Campbell MJ, Bond CM, and Hopewells. 2016. "CONSORT 2010 Statement: Extension to Randomised Pilot and Feasibility Trials The Consolidated Standards of Reporting Trials (CONSORT) Statement Reporting of Randomised Controlled an Extension to That Statement For." *BMJ: British Medical Journal* 355: 1–29. <https://doi.org/10.1136/bmj.i5239>.
- Eller LK, Ainslie PN, Poulin MJ, and Reimer RA. 2008. "Differential Responses of Circulating

- Amylin to High-Fat vs. High-Carbohydrate Meal in Healthy Men.” *Clinical Endocrinology* 68 (6): 890–97. <https://doi.org/10.1111/j.1365-2265.2007.03129.x>.
- Elo S and Kyngäs H. 2008. “The Qualitative Content Analysis Process.” *Journal of Advanced Nursing* 62 (1): 107–15. <https://doi.org/10.1111/j.1365-2648.2007.04569.x>.
- Eriksson J, Forsén T, Osmond C, and Barker D. 2003. “Obesity from Cradle to Grave.” *International Journal of Obesity* 27 (6): 722–27. <https://doi.org/10.1038/sj.ijo.0802278>.
- Evans D. 2003. “Hierarchy of Evidence: A Framework for Ranking Evidence Evaluating Healthcare Interventions.” *Journal of Clinical Nursing* 12 (1): 77–84. <https://doi.org/10.1046/j.1365-2702.2003.00662.x>.
- Eynon J, Duarte JA, Oliveira J, Sagiv M, Yamin C, Meckel Y, Sagiv M, and Goldhammer E. 2009. “ACTN3 R577X Polymorphism and Israeli Top-Level Athletes.” *International Journal of Sports Medicine* 30 (9): 695–98. <https://doi.org/10.1055/s-0029-1220731>.
- Fallaize R, Macready AL, Butler LT, Ellis JA, and Lovegrove JA. 2013. “An Insight into the Public Acceptance of Nutrigenomic-Based Personalised Nutrition.” *Nutrition Research Reviews* 26 (1): 39–48. <https://doi.org/10.1017/S0954422413000024>.
- Fields DA, Higgins PB, Hunter GR. 2004. “Assessment of body composition by air-displacement plethysmography: influence of body temperature and moisture.” *Dynamic Medicine* 3:3.
- Feinman RD. 2009. “Intention-to-Treat. What is the Question?” *Nutrition and Metabolism* 6 (1): 1-7.
- Fenech M. 2008. “Genome Health Nutrigenomics and Nutrigenetics - Diagnosis and Nutritional Treatment of Genome Damage on an Individual Basis.” *Food and Chemical Toxicology* 46 (4): 1365–70. <https://doi.org/10.1016/j.fct.2007.06.035>.
- Ferguson LR and Barnett MPG. 2012. “Research in Nutrigenomics and Potential Applications to Practice.” *Nutrition and Dietetics* 69 (3): 198–202. <https://doi.org/10.1111/j.1747-0080.2012.01623.x>.
- Field A, Camargo C, and Ogino S. 2013. “The Merits of Subtyping Obesity One Size Does Not Fit All.” *JAMA* 02115: 4–5. <https://doi.org/10.1038/onc.2013.244.4>.
- Finkelstein EA, Ruhm CJ, and Kosa KM. 2005. “Economic Causes and Consequences of Obesity.” *Annual Review of Public Health* 26 (1): 239–57. <https://doi.org/10.1146/annurev.publhealth.26.021304.144628>.
- Fishbein M and Ajzen I. 2010. *Predicting and Changing Behavior: The Reasoned Action Approach*. New York: Taylor & Francis.
- Flint A, Raben A, Astrup A, and Holst JJ. 1998. “Glucagon-like Peptide 1 Promotes Satiety and Suppresses Energy Intake in Humans.” *Journal of Clinical Investigation* 101 (3): 515–20. <https://doi.org/10.1172/JCI990>.
- Food4Me. n.d. “Food4Me: Scientific Publications.” Accessed April 11, 2017. <http://food4me.org/scientific-publications>.

- Food4Me. 2011. "Food4Me: Aims and Objectives." <http://food4me.org/about/aims-and-objectives>.
- Fosbol MO and Zerahn B. 2015. "Contemporary methods of body composition measurement." *Clin Physiol Funct Imaging* 35:81-97.
- Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, and Klein S. 2003. "A Randomized Trial of a Low-Carbohydrate Diet for Obesity." *The New England Journal of Medicine* 348 (21): 2082–90. <https://doi.org/10.1056/NEJMoa022207>.
- Frankwich KA, Egnatios J, Kenyon ML, Rutledge TR, Liao PS, Gupta S, Herbst KL, and Zarrinpar A. 2015. "Differences in Weight Loss Between Persons on Standard Balanced vs Nutrigenetic Diets in a Randomized Controlled Trial." *Clinical Gastroenterology and Hepatology* 13 (9): 1625–32. <https://doi.org/10.1016/j.cgh.2015.02.044>.
- French DP, Cameron E, Benton JS, Deaton C, and Harvie M. 2017. "Can Communicating Personalised Disease Risk Promote Healthy Behaviour Change? A Systematic Review of Systematic Reviews." *Annals of Behavioral Medicine* 51 (5): 718–29. <https://doi.org/10.1007/s12160-017-9895-z>.
- Ford I, Norrie J. 2016. "Pragmatic trials." *New England Journal of Medicine* 375(5):454-63.
- Gallagher D, Visser M, Wang Z, Harris T, Pierson RN, and Heymsfield SM. 1996. "Metabolically Active Component of Fat-Free Body Mass: Influences of Age, Adiposity, and Gender." *Metabolism: Clinical and Experimental* 45 (8): 992–97. [https://doi.org/10.1016/S0026-0495\(96\)90269-3](https://doi.org/10.1016/S0026-0495(96)90269-3).
- Gao H, Wang X, Zhang Z, Yang Y, Yang J, Li X, and Ning G. 2007. "GLP-1 Amplifies Insulin Signaling by up-Regulation of IR β , IRS-1 and Glut4 in 3T3-L1 Adipocytes." *Endocrine* 32 (1): 90–95. <https://doi.org/10.1007/s12020-007-9011-4>.
- Garaulet M, Smith CE, Hernández-González T, Lee YC, and Ordovás JM. 2011. "PPAR γ Pro12Ala Interacts with Fat Intake for Obesity and Weight Loss in a Behavioural Treatment Based on the Mediterranean Diet." *Molecular Nutrition and Food Research* 55 (12): 1771–79. <https://doi.org/10.1002/mnfr.201100437>.
- Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, Desai M, and King AC. 2018. "Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion The DIETFITS Randomized Clinical Trial." *JAMA* 319 (17): 667–79. <https://doi.org/10.1001/jama.2018.0245>.
- Gene Cards. n.d. "UCP1 Gene." Accessed July 8, 2019. <https://www.genecards.org/cgi-bin/carddisp.pl?gene=UCP1>.
- Gibney MJ, and Walsh MC. 2013. "The Future Direction of Personalised Nutrition: My Diet, My Phenotype, My Genes." *The Proceedings of the Nutrition Society* 72 (2): 219–25. <https://doi.org/10.1017/S0029665112003436>.
- Gill RS, Karmali S, Hadi G, Al-Adra DP, Shi X, and Birch DW. 2012. "Predictors of Attrition in a Multidisciplinary Adult Weight Management Clinic." *Canadian Journal of Surgery* 55

(4): 239–43. <https://doi.org/10.1503/cjs.035710>.

- Gilliland JA, Rangel CY, Healy MA, Tucker P, Loebach JE, Hess PM, He M, Irwin JD, and Wilk P. 2012. “Linking Childhood Obesity to the Built Environment: A Multi-Level Analysis of Home and School Neighbourhood Factors Associated With Body Mass Index.” *Canadian Journal of Public Health*: S15-21.
- Giner V, Poch E, Bragulat E, Oriola J, González D, Coca A, and de la Sierra A. 2012. “Renin-Angiotensin System Genetic Polymorphisms and Salt Sensitivity in Essential Hypertension.” *Hypertension* 35 (1): 512–17. <https://doi.org/10.1161/01.hyp.35.1.512>.
- Goossens GH. 2017. "The metabolic phenotype in obesity: Fat mass, body fat distribution, and adipose tissue function." *Obesity Facts* 10:207-215.
- Government of Canada. 2019. “Social Determinants of Health and Health Inequalities.” 2019. <https://www.canada.ca/en/public-health/services/health-promotion/population-health/what-determines-health.html>.
- Grau K, Cauchi S, Holst C, Astrup A, Martinez JA, Saris WHM, Blaak EE, et al. 2010. “TCF7L2 Rs7903146-Macronutrient Interaction in Obese Individuals’ Responses to a 10-Wk Randomized Hypoenergetic Diet.” *American Journal of Clinical Nutrition* 91 (2): 472–79. <https://doi.org/10.3945/ajcn.2009.27947>.
- Grimaldi KA, van Ommen B, Ordovas JM, Parnell LD, Mathers JC, Bendik I, Brennan L, et al. 2017. “Proposed Guidelines to Evaluate Scientific Validity and Evidence for Genotype-Based Dietary Advice.” *Genes and Nutrition* 12 (1): 1–12. <https://doi.org/10.1186/s12263-017-0584-0>.
- Gudivaka R, Schoeller DA, Kushner RF, Bolt MJ. 1999. "Single and multifrequency models for bioelectrical impedance analysis of body water compartments." *J Appl Physiol* 87:1087-96.
- Guo SS, Zeller C, Chumlea WC, Siervogel RM. 1999. “Aging, body composition, and lifestyle: the Fels Longitudinal Study.” *Am J Clin Nutr* 70:405–411.
- Gupta SK. 2011. "Intention-to-Treat Concept: A Review." *Perspect Clin Res*. 2 (3): 109-112.
- Gurr MI, Jung RT, Robinson MP, and James WP. 1982. “Adipose Tissue Cellularity in Man: The Relationship between Fat Cell Size and Number, the Mass and Distribution of Body Fat and the History of Weight Gain and Loss.” *International Journal of Obesity* 6: 419–36.
- Hall S, Weinman J, and Marteau TM. 2004. “The Motivating Impact of Informing Women Smokers of a Link Between Smoking and Cervical Cancer: The Role of Coherence.” *Health Psychology* 23 (4): 419–24. <https://doi.org/10.1037/0278-6133.23.4.419>.
- Hayakawa T, Nagai Y, Taniguchi M, Yamashita H, Takamura T, Abe T, Nomura G, and Kobayashi KI. 1999. “Phenotypic Characterization of the B3-Adrenergic Receptor Mutation and the Uncoupling Protein 1 Polymorphism in Japanese Men.” *Metabolism: Clinical and Experimental* 48 (5): 636–40. [https://doi.org/10.1016/S0026-0495\(99\)90063-X](https://doi.org/10.1016/S0026-0495(99)90063-X).
- He, Z., Yang Hu, L. Feng, Y. Lu, C. Liu, Y. Xi, L. Wen, and L. R. McNaughton. 2007. “NRF2 Genotype Improves Endurance Capacity in Response to Training.” *International Journal of Sports Medicine* 28 (9): 717–21. <https://doi.org/10.1055/s-2007-964913>.

- He Z, Hu Y, Feng L, Lu Y, Liu G, Xi Y, Wen L, and McNaughton LR. 2006. "NRF2 Genotype Improves Endurance Capacity in Response to Training." *International Journal of Sports Medicine* 28: 717–21.
- Health Canada. 2010. "Dietary Reference Intakes." Accessed November 4, 2019 http://www.canada.ca/content/dam/hc-sc/migration/hc-sc/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/dri_tables-eng.pdf
- Heesch KC, Brown DR, and Blanton CJ. 2000. "Perceived Barriers to Exercise and Stage of Exercise Adoption in Older Women of Different Racial/Ethnic Groups." *Women and Health* 30 (4): 61–76. https://doi.org/10.1300/J013v30n04_05.
- Heilbronn LK, Kind KL, Pancewicz E, Morris AM, Noakes M, and Clifton PM. 2000. "Association of -3826 G Variant in Uncoupling Protein-1 with Increased BMI in Overweight Australian Women." *Diabetologia* 43: 242–44.
- Helds DA and Allison DB. 2012. "Air displacement plethysmography pediatric option in 2-6 years old using the four-compartment model as a criterion method." *Obesity* 20:1732-37.
- Hendershot CS, Otto JM, Collins SE, Liang T, and Wall TL. 2010. "Evaluation of a Brief Web-Based Genetic Feedback Intervention for Reducing Alcohol-Related Health Risks Associated with ALDH2." *Annals of Behavioral Medicine* 40 (1): 77–88. <https://doi.org/10.1007/s12160-010-9207-3>.
- Hietaranta-Luoma HL, Tahvonen R, Iso-Touru T, and Puolijoki H. 2014. "An Intervention Study of Individual, ApoE Genotype-Based Dietary and Physical-Activity Advice: Impact on Health Behavior." *Lifestyle Genomics* 7 (3): 161–74.
- Hillmer M, Sandoval GA, Elliott JA, Barker T, Prisniak A, Astley S, and Rosella L. 2017. "Diabetes Risk Reduction in Primary Care: Evaluation of the Ontario Primary Care Diabetes Prevention Program." *Canadian Journal of Public Health* 108 (2): e176–84.
- Hirsch J, and Batchelor B. 1976. "Adipose Tissue Cellularity in Human Obesity." *Clin Endocrinol Metab.* 5 (2): 299–311.
- Hirsch J, and Han PW. 1969. "Cellularity of Rat Adipose Tissue: Effects of Growth, Starvation, and Obesity." *Journal of Lipid Research* 10: 77–82.
- Hishida A, Terazawa T, Mamiya T, Ito H, Matsuo K, Tajima K, and Hamajima N. 2010. "Efficacy of Genotype Notification to Japanese Smokers on Smoking Cessation-An Intervention Study at Workplace." *Cancer Epidemiology* 34 (1): 96–100. <https://doi.org/10.1016/j.canep.2009.11.008>.
- Hoffer EC, Meador CK, Simpson DC. 1969. "Correlation of whole-body impedance with total body water volume." *J Appl Physiol* 27:531–534.
- Hogarth S, Javitt G, and Melzer D. 2008. "The Current Landscape for Direct-to-Consumer Genetic Testing: Legal, Ethical, and Policy Issues." *Annual Review of Genomics and Human Genetics* 9: 161–82. <https://doi.org/10.1146/annurev.genom.9.081307.164319>.
- Hollands GJ, French DP, Griffin SJ, Prevost AT, Sutton S, King S, and Marteau TM. 2016. "The Impact of Communicating Genetic Risks of Disease on Riskreducing Health Behaviour:

- Systematic Review with Meta-Analysis.” *BMJ* 352: I1102.
<https://doi.org/10.1136/bmj.i1102>.
- Hollands GJ, Whitwell SCL, Parker RA, Prescott NJ, Forbes A, Sanderson J, Mathew CG, et al. 2012. “Effect of Communicating DNA Based Risk Assessments for Crohn’s Disease on Smoking Cessation: Randomised Controlled Trial.” *BMJ* 345 (7870).
<https://doi.org/10.1136/bmj.e4708>.
- Horne J, Gilliland J, Madill J, Shelley J. A critical examination of legal and ethical considerations of nutrigenetic testing with recommendations for improving regulation in Canada: From science to consumer. *Journal of Law and the Biosciences*. 2020 [in press].
- Horne J, Madill J, and O’Connor C. 2016. “Exploring Knowledge and Attitudes of Personal Nutrigenomics Testing among Dietetic Students and Its Value as a Component of Dietetic Education and Practice.” *Canadian Journal of Clinical Nutrition* 4 (6): 50–62.
<https://doi.org/10.7897/2277-4343.04323>.
- Horne J, Gilliland J, O’Connor C, Seabrook J, Hannaberg P, and Madill J. 2019. “Study Protocol of a Pragmatic Randomized Controlled Trial Incorporated into the Group Lifestyle Balance™ Program: The Nutrigenomics, Overweight/Obesity and Weight Management Trial (the NOW Trial).” *BMC Public Health* 19 (1): 1–10. <https://doi.org/10.1186/s12889-019-6621-8>.
- Horne J, Madill J, O’Connor C, Shelley J, and Gilliland J. 2018. “A Systematic Review of Genetic Testing and Lifestyle Behaviour Change : Are We Using High-Quality Genetic Interventions and Considering Behaviour Change Theory?” *Lifestyle Genomics*, 1–15.
<https://doi.org/10.1159/000488086>.
- Horne J, Madill J, and Gilliland J. 2017. “Incorporating the ‘ Theory of Planned Behavior ’ into Personalized Healthcare Behavior Change Research: A Call to Action.” *Personalized Medicine* 14 (6): 521–29.
- Humphries SE, Gable D, Cooper JA, Ireland H, Stephens JW, Hurel SJ, Li KW, et al. 2006. “Common Variants in the TCF7L2 Gene and Predisposition to Type 2 Diabetes in UK European Whites, Indian Asians and Afro-Caribbean Men and Women.” *Journal of Molecular Medicine* 84 (12): 1–10. <https://doi.org/10.1007/s00109-006-0108-7>.
- Imboden MT, Welch WA, Swartz AM, Montoye AHK, Finch HW, Harber MP, and Kaminsky LA. 2017. “Reference Standards for Body Fat Measures Using GE Dual Energy X-Ray Absorptiometry in Caucasian Adults.” *PLoS ONE* 12 (4): e0175110.
- Ito H, Matsuo K, Wakai K, Saito T, Kumimoto H, Okuma K, Tajima K, and Hamajima N. 2006. “An Intervention Study of Smoking Cessation with Feedback on Genetic Cancer Susceptibility in Japan.” *Preventive Medicine* 42 (2): 102–8.
<https://doi.org/10.1016/j.ypmed.2005.10.006>.
- Jackman MR, Steig A, Higgins JA, Johnson GC, Fleming-Elder BK, Bessesen DH, and MacLean PS. 2008. “Weight Regain after Sustained Weight Reduction Is Accompanied by Suppressed Oxidation of Dietary Fat and Adipocyte Hyperplasia.” *American Journal of Physiology - Regulatory Integrative and Comparative Physiology* 294 (4): 1117–29.
<https://doi.org/10.1152/ajpregu.00808.2007>.

- Jebb SA, Ahern AL, Olson AD, Aston LM, Holzapfel C, Stoll J, Amann-Gassner U, et al. 2011. “Primary Care Referral to a Commercial Provider for Weight Loss Treatment versus Standard Care: A Randomised Controlled Trial.” *The Lancet* 378 (9801): 1485–92. [https://doi.org/10.1016/S0140-6736\(11\)61344-5](https://doi.org/10.1016/S0140-6736(11)61344-5).
- Jeffers KS, Castellon-Lopez Y, Grotts J, Mangione CM, Moin T, Tseng C-H, Turk N, et al. 2019. “Diabetes Prevention Program Attendance Is Associated with Improved Patient Activation: Results from the Prediabetes Informed Decisions and Education (PRIDE) Study.” *Preventive Medicine Reports* 16: 100961. <https://doi.org/10.1016/j.pmedr.2019.100961>.
- Jenkins NDM, Colquhoun RJ, Tomko PM, Gradnigo T, Magrini MA, Muddle TWD, Fleming S, Ferrell M, and El-Sohemy A. 2018. “Genetic Variant in the B2-Adrenergic Receptor (Arg16Gly) Influences Fat-Free Mass, Muscle Strength and Motor Unit Behaviour in Young Men.” *Experimental Physiology* 103 (12): 1645–55. <https://doi.org/10.1113/EP087145>.
- Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, et al. 2014. “A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society.” *Circulation* 129 (25 SUPPL. 1): 102–41. <https://doi.org/10.1161/01.cir.0000437739.71477.ee>.
- Jensen MD, Ryan DH, Donato KA, Apovian CM, Ard JD, Comuzzie AG, Hu FB, et al. 2014. “Guidelines (2013) for the Management of Overweight and Obesity in Adults.” *Obesity* 22: S1–410. <https://doi.org/10.1002/oby.20821>.
- Johannsen DL, Knuth ND, Huizenga R, Rood JC, Ravussin E, and Hall KD. 2012. “Metabolic Slowing with Massive Weight Loss despite Preservation of Fat-Free Mass.” *Journal of Clinical Endocrinology and Metabolism* 97 (7): 2489–96. <https://doi.org/10.1210/jc.2012-1444>.
- Jorge AS, Jorge GC, Paraíso AF, Franco RM, Vieira LJ, Hilzenderger AM, Guimarães AL, Andrade JM, De-Paula AM, and Santos SH. 2017. “Brown and White Adipose Tissue Expression of IL6, UCP1 and SIRT1 Are Associated with Alterations in Clinical, Metabolic and Anthropometric Parameters in Obese Humans.” *Experimental and Clinical Endocrinology and Diabetes* 125 (3): 163–70.
- Josse AR, Da Costa LA, Campos H, and El-Sohemy A. 2012. “Associations between Polymorphisms in the AHR and CYP1A1-CYP1A2 Gene Regions and Habitual Caffeine Consumption.” *American Journal of Clinical Nutrition* 96 (3): 665–71. <https://doi.org/10.3945/ajcn.112.038794>.
- Julve J, Escolà-Gil JC, Rotllan N, Fiévet C, Vallez E, De La Torre C, Ribas V, Sloan JH, and Blanco-Vaca F. 2010. “Human Apolipoprotein A-II Determines Plasma Triglycerides by Regulating Lipoprotein Lipase Activity and High-Density Lipoprotein Proteome.” *Arteriosclerosis, Thrombosis, and Vascular Biology* 30 (2): 232–38. <https://doi.org/10.1161/ATVBAHA.109.198226>.
- Karger. 2019. “Lifestyle Genomics.” 2019. <https://www.karger.com/Journal/Details/232009>.
- Katsanis SH, and Katsanis N. 2016. “Molecular Genetic Testing and the Future of Clinical

- Genomics.” *Genomic and Precision Medicine: Foundations, Translation, and Implementation: Third Edition* 14 (June): 263–82. <https://doi.org/10.1016/B978-0-12-800681-8.00018-9>.
- Kattel S, Onyekwelu T, Brown S-A, Jouni H, Austin E, and Kullo IJ. 2017. “Motivation, Perception, and Treatment Beliefs in the Myocardial Infarction Genes (MI-GENES) Randomized Clinical Trial.” *Journal of Genetic Counseling*. <https://doi.org/10.1007/s10897-017-0092-9>.
- Kaufman DJ, Bollinger JM, Dvoskin RL, and Scott JA. 2012. “Risky Business: Risk Perception and the Use of Medical Services among Customers of DTC Personal Genetic Testing.” *Journal of Genetic Counseling* 21 (3): 413–22. <https://doi.org/10.1007/s10897-012-9483-0>.
- Kelley DE, Goodpaster B, Wing RR, and Simoneau JA. 1999. “Skeletal Muscle Fatty Acid Metabolism in Association with Insulin Resistance, Obesity, and Weight Loss.” *American Journal of Physiology - Endocrinology and Metabolism* 277 (6 40-6). <https://doi.org/10.1152/ajpendo.1999.277.6.e1130>.
- Keys A. 1950. *The Biology of Human Starvation*. Minneapolis: University of Minnesota Press.
- Kikuchi N, Miyamoto-Mikami E, Murakami H, Nakamura T, Min SK, Mizuno M, Naito H, Miyachi M, Nakazato K, and Fuku N. 2016. “ACTN3 R577X Genotype and Athletic Performance in a Large Cohort of Japanese Athletes.” *European Journal of Sport Science* 16 (6): 694–701. <https://doi.org/10.1080/17461391.2015.1071879>.
- Kilpeläinen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, Ahmad T, et al. 2011. “Physical Activity Attenuates the Influence of FTO Variants on Obesity Risk: A Meta-Analysis of 218,166 Adults and 19,268 Children.” *PLoS Medicine* 8 (11). <https://doi.org/10.1371/journal.pmed.1001116>.
- Kissileff HR, Thornton JC, Torres MI, Pavlovich K, Mayer LS, Kalari V, Leibel RL, and Rosenbaum M. 2012. “Leptin Reverses Declines in Satiety in Weight-Reduced Obese Humans.” *American Journal of Clinical Nutrition* 95 (2): 309–17. <https://doi.org/10.3945/ajcn.111.012385>.
- Knittle JL, and Hirsch J. 1968. “Effect of Early Nutrition on the Development of Rat Epididymal Fat Pads: Cellularity and Metabolism.” *The Journal of Clinical Investigation* 47 (9): 2091–98. <https://doi.org/10.1172/JCI105894>.
- Knoll G, Cockfield S, Blydt-Hansen T, Baran D, Kiberd B, Landsberg D, Rush D, and Cole E. 2005. “Canadian Society of Transplantation Consensus Guidelines on Eligibility for Kidney Transplantation.” *CMAJ* 173 (10): S1–25. <https://doi.org/10.1254/fpj.108.160>.
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, and Nathan DM. 2002. “Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin.” *New England Journal of Medicine* 346 (6): 393–403. <https://doi.org/10.1056/NEJMoa012512>.
- Kozłowska L, and Rosołowska-Huszcz D. 2004. “Leptin, Thyrotropin, and Thyroid Hormones in Obese/Overweight Women before and after Two Levels of Energy Deficit.” *Endocrine* 24 (2): 147–53. <https://doi.org/10.1385/ENDO:24:2:147>.

- Kramer MK, Kriska AM, Venditti EM, Semler LN, Miller RG, McDonald T, Siminerio LM, and Orchard TJ. 2010. "A Novel Approach to Diabetes Prevention: Evaluation of the Group Lifestyle Balance Program Delivered via DVD." *Diabetes Research and Clinical Practice* 90 (3): e60–63. <https://doi.org/10.1016/j.diabres.2010.08.013>.
- Krause AJ, Simon EB, Mander BA, Greer SM, Saletin JM, Goldstein-Piekarski AN, and Walker MP. 2017. "The Sleep-Deprived Human Brain." *Nature Reviews Neuroscience*. <https://doi.org/10.1038/nrn.2017.55>.
- LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, and Mesulam MM. 2001. "Hunger Selectively Modulates Corticolimbic Activation to Food Stimuli in Humans." *Behavioral Neuroscience* 115 (2): 493–500. <https://doi.org/10.1037/0735-7044.115.2.493>.
- Lahti-Koski, Männistö S, Pietinen P, and Vartiainen E. 2005. "Prevalence of Weight Cycling and Its Relation to Health Indicators in Finland." *Obesity Research* 13 (2): 333–41. <https://doi.org/10.1038/oby.2005.45>.
- Lakdawalla D, and Philipson T. 2009. "The Growth of Obesity and Technological Change." *Economics and Human Biology* 7 (3): 283–93. <https://doi.org/10.1016/j.ehb.2009.08.001>.
- Le, Duc SNT, Pannacciulli N, Chen K, Del Parigi A, Salbe AD, Reiman EM, and Krakoff J. 2006. "Less Activation of the Left Dorsolateral Prefrontal Cortex in Response to a Meal: A Feature of Obesity." *American Journal of Clinical Nutrition* 84 (4): 725–31. <https://doi.org/10.1093/ajcn/84.4.725>.
- Lee HJ, Kim IK, Kang JH, Ahn Y, Han BG, Lee JY, and Song J. 2010. "Effects of Common FTO Gene Variants Associated with BMI on Dietary Intake and Physical Activity in Koreans." *Clinica Chimica Acta* 411 (21–22): 1716–22. <https://doi.org/10.1016/j.cca.2010.07.010>.
- Lee RD and Nieman DC. 2013. "Anthropometry." In: Lee RD, Nieman DC, eds. *Nutritional Assessment*: 6th ed. New York, NY: McGraw-Hill 166-220.
- Lee SY, Gallagher D. 2008. "Assessment methods in human body composition." *Curr Opin Clin Nutr Metab Care* 11(5):566–572. doi:10.1097/MCO.0b013e32830b5f23.
- Legenthal H, Benyamini Y, Brownlee S, et al. 1997. "Illness Representations: Theoretical Foundations." In *Perceptions of Health and Illness: Current Research and Applications*, edited by K Petrie and J Weinman, 19–45. Amsterdam.
- Leibel RL, Rosenbaum M, and Hirsch J. 1995. "Changes in Energy Expenditure Resulting from Altered Body Weight." *New England Journal of Medicine* 332 (10): 621–28. <https://doi.org/10.1056/NEJM199503093321001>.
- Li SX, Ye Z, Whelan K, and Truby H. 2016. "The Effect of Communicating the Genetic Risk of Cardiometabolic Disorders on Motivation and Actual Engagement in Preventative Lifestyle Modification and Clinical Outcome: A Systematic Review and Meta-Analysis of Randomised Controlled Trials." *The British Journal of Nutrition*, 1–11. <https://doi.org/10.1017/S0007114516002488>.
- Lien LF, Haqq AM, Arlotto M, Slentx CA, Muehlbauer MJ, McMahan RL, Rochon J, et al. 2009. "The STEDMAN Project: Biophysical, Biochemical and Metabolic Effects of a

- Behavioral Weight Loss Intervention during Weight Loss, Maintenance and Regain.” *OMICS A Journal of Integrative Biology* 13 (1): 21–35.
- Lifton RP. 1996. “Molecular Genetics of Human Blood Pressure Variation.” *Science* Vol 272: 676-680.
- Löfgren P, Andersson I, Adolfsson B, Leijonhufvud BM, Hertel K, Hoffstedt J, and Arner P. 2005. “Long-Term Prospective and Controlled Studies Demonstrate Adipose Tissue Hypercellularity and Relative Leptin Deficiency in the Postobese State.” *Journal of Clinical Endocrinology and Metabolism* 90 (11): 6207–13. <https://doi.org/10.1210/jc.2005-0596>.
- Loos RJF, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, Inouye M, et al. 2008. “Common Variants near MC4R Are Associated with Fat Mass, Weight and Risk of Obesity.” *Nature Genetics* 40 (6): 768–75. <https://doi.org/10.1038/ng.140>.
- Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, and Zwarenstein M. 2015. “The PRECIS-2 Tool: Designing Trials That Are Fit for Purpose.” *BMJ* 350: 1-11. <https://doi.org/10.1136/bmj.h2147>.
- Luis DA, Aller R, and Pacheco D. 2015. “Role of Rs9939609 FTO Gene Variant in Weight Loss, Insulin Resistance and Metabolic Parameters after a High Monounsaturated vs a High Polyunsaturated Fat Hypocaloric Diets.” *Nutr Hosp* 32 (1): 175–81. <https://doi.org/10.3305/nh.2015.32.1.9169>.
- Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. 1985. “Validation of tetrapolar bioelectrical impedance method to assess human body composition.” *J Appl Physiol* 60:1327–32.
- Lutz W, Sanderson W, Scherbov S. 2008. “The coming acceleration of global population ageing.” *Nature* 451:716–719.
- Ma F, Yang Y, Li X, Zhou F, Gao C, Li M, and Gao L. 2013. “The Association of Sport Performance with ACE and ACTN3 Genetic Polymorphisms: A Systematic Review and Meta-Analysis.” *PLoS ONE* 8 (1): 1–9. <https://doi.org/10.1371/journal.pone.0054685>.
- MacLean PS, Higgins JA, Jackman MR, Johnson GC, Fleming-Elder BK, Wyatt HR, Melanson EL, and Hill JO. 2006. “Peripheral Metabolic Responses to Prolonged Weight Reduction That Promote Rapid, Efficient Regain in Obesity-Prone Rats.” *American Journal of Physiology - Regulatory Integrative and Comparative Physiology* 290 (6). <https://doi.org/10.1152/ajpregu.00810.2005>.
- MacLean PS, Bergouignan A, Cornier MA, and Jackman MR. 2011. “Biology’s Response to Dieting: The Impetus for Weight Regain.” *American Journal of Physiology - Regulatory Integrative and Comparative Physiology* 301 (3): R581–600.
- Madill J. 2016. “Nutrigenomics, Overweight/Obesity and Weight Management Trial (NOW Trial).” *Clinicaltrials.gov*. 2016. <https://clinicaltrials.gov/ct2/show/NCT03015012?term=the+NOW+trial&rank=2>.
- Maina G, Albert U, Salvi V, and Bogetto F. 2004. “Weight Gain during Long-Term Treatment of Obsessive-Compulsive Disorder: A Prospective Comparison between Serotonin Reuptake Inhibitors.” *Journal of Clinical Psychiatry* 65 (10): 1365–71. <https://doi.org/10.4088/JCP.v65n1011>.

- Marsaux CFM, Celis-Morales C, Livingstone KM, Fallaize R, Kolossa S, Hallmann J, San-Cristobal R, et al. 2016. "Changes in Physical Activity Following a Genetic-Based Internet-Delivered Personalized Intervention: Randomized Controlled Trial (Food4Me)." *Journal of Medical Internet Research* 18 (2): 1–15. <https://doi.org/10.2196/jmir.5198>.
- Marsaux CFM, Celis-Morales C, Fallaize R, Macready AL, Kolossa S, Woolhead C, O'Donovan CB, et al. 2015. "Effects of a Web-Based Personalized Intervention on Physical Activity in European Adults: A Randomized Controlled Trial." *Journal of Medical Internet Research* 17 (10): 1–22. <https://doi.org/10.2196/jmir.4660>.
- Marteau T, Senior V, Humphries SE, Bobrow M, Cranston T, Crook MA, Day L, et al. 2004. "Psychological Impact of Genetic Testing for Familial Hypercholesterolemia within a Previously Aware Population: A Randomized Controlled Trial." *American Journal of Medical Genetics. Part A* 128A (3): 285–93. <https://doi.org/10.1002/ajmg.a.30102>.
- Martin P, DiMartini PA, Feng S, Brown R, and Fallon M. 2014. "Evaluation for Liver Transplantation in Adults: 2013 Practice Guidelines by the American Association for the Study of Liver Disease and the American Society of Transplantation." *Hepatology* 59 (3): 1144–65. <https://doi.org/10.1002/hep.26972>.
- Martinsson A. 1969. "Hypertrophy and Hyperplasia of Human Adipose Tissue in Obesity." *Pol Arch Med Wewn* 42: 481–86.
- Mattei J, Qi Q, Hu FB, Sacks FM, and Qi L. 2012. "TCF7L2 Genetic Variants Modulate the Effect of Dietary Fat Intake on Changes in Body Composition during a Weight-Loss Intervention." *American Journal of Clinical Nutrition* 96 (5): 1129–36. <https://doi.org/10.3945/ajcn.112.038125>.
- Mayer-Davis EJ, Sparks KC, Hirst K, Costacou T, Lovejoy JC, Regensteiner JG, et al. 2004. "Dietary Intake in the Diabetes Prevention Program Cohort: Baseline and 1-Year Post-Randomization." *Ann Epidemiol* 14(10): 763-72.
- Mcbride CM, Bepler G, Lipkus IM, Lyna P, Samsa G, Albright J, Datta S, and Rimer BK. 2002. "Incorporating Genetic Susceptibility Feedback into a Smoking Cessation Program for African-American Smokers with Low Income Incorporating Genetic Susceptibility Feedback into a Smoking Cessation Program for African-American Smokers with Low Income 1" 11 (June): 521–28.
- Mcdermott MS, Oliver M, Simnadis T, Beck EJ, Coltman T, Iverson D, Caputi P, and Sharma R. 2015. "The Theory of Planned Behaviour and Dietary Patterns: A Systematic Review and Meta-Analysis" 81: 150–56.
- Mceachan R, Hons BA, Taylor N, Gardner P, and Conner M. 2016. "Meta-Analysis of the Reasoned Action Approach (RAA) to Understanding Health Behaviors." *Annals of Behavioral Medicine*, 592–612. <https://doi.org/10.1007/s12160-016-9798-4>.
- McEachan RRC, Conner M, Taylor NJ, and Lawton RJ. 2011. "Prospective Prediction of Health-Related Behaviours with the Theory of Planned Behaviour: A Meta-Analysis." *Health Psychology Review* 5 (2): 97–144. <https://doi.org/10.1080/17437199.2010.521684>.
- McMorrow L, Ludbrook A, Macdiarmid JI, and Olajide D. 2017. "Perceived Barriers towards

- Healthy Eating and Their Association with Fruit and Vegetable Consumption.” *Journal of Public Health (United Kingdom)* 39 (2): 330–38. <https://doi.org/10.1093/pubmed/fdw038>.
- McTigue KM, Conroy MB, Bigi L, Murphy C, and McNeil M. 2009. “Weight Loss Through Living Well: Translating an Effective Lifestyle Intervention into Clinical Practice.” *Diabetes Educator* 35 (2): 199–208. <https://doi.org/10.1177/0145721709332815>.
- Mehra MR, Jessup M, Gronda E, and Costanzo MR. 2006. “Rationale and Process: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates-2006.” *Journal of Heart and Lung Transplantation* 25 (9): 1001–2. <https://doi.org/10.1016/j.healun.2006.06.006>.
- Meichenbaum D and Turk DC. 1987. *Facilitating Treatment Adherence: A Practitioner’s Guide*. New York: Plenum Press.
- Meisel SF, Beeken RJ, Van Jaarsveld CHM, and Wardle J. 2015. “Genetic Susceptibility Testing and Readiness to Control Weight: Results from a Randomized Controlled Trial.” *Obesity* 23 (2): 305–12. <https://doi.org/10.1002/oby.20958>.
- Memisoglu A, Hu FB, Hankinson SE, Manson JAE, De Vivo I, Willett WC, and Hunter DJ. 2003. “Interaction between a Peroxisome Proliferator-Activated Receptor γ Gene Polymorphism and Dietary Fat Intake in Relation to Body Mass.” *Human Molecular Genetics* 12 (22): 2923–29. <https://doi.org/10.1093/hmg/ddg318>.
- Menzo EL, Hinojosa M, Carbonell A, Krpata D, Carter J, and Rogers AM. 2018. “American Society for Metabolic and Bariatric Surgery and American Hernia Society Consensus Guideline on Bariatric Surgery and Hernia Surgery.” *Surgery for Obesity and Related Diseases* 14 (9): 1221–32. <https://doi.org/10.1016/j.soard.2018.07.005>.
- Merritt DC, Jamnik J, and El-sohemy A. 2018. “FTO Genotype , Dietary Protein Intake, and Body Weight in a Multiethnic Population of Young Adults : A Cross-Sectional Study.” *Genes and Nutrition* 13 (4): 1–10.
- Michellini I, Falchi AG, Muggia C, Grecchi I, Montagna E, De Silvestri A, and Tinelli C. 2014. “Early Dropout Predictive Factors in Obesity Treatment.” *Nutrition Research and Practice* 8 (1): 94–102. <https://doi.org/10.4162/nrp.2014.8.1.94>.
- Middlemass J, Davy Z, Cavanagh K, Linehan C, Morgan K, Lawson S, and Siriwardena AN. 2012. “Integrating Online Communities and Social Networks with Computerised Treatment for Insomnia :,” no. December. <https://doi.org/10.3399/bjgp12X659321>.
- Middleton KR, Anton SD, and Perri MG. 2013. “Long-Term Adherence to Health Behavior Change.” *Am J Lifestyle Med* 7 (6): 395–404. <https://doi.org/10.1016/j.physbeh.2017.03.040>.
- Miura J, Arai K, Tsukahara S, Ohno M, and Ikeda Y. 1989. “The Long Term Effectiveness of Combined Therapy by Behavior Modification and Very Low Calorie Diet: 2 Years Follow-Up.” *International Journal of Obesity* 13: 73–77.
- Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, Atkins D, et al. 2009. “Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.” *PLoS Medicine* 6 (7): e1000097.

- <https://doi.org/doi:10.1371/journal.pmed1000097>.
- Moore S, Hall JN, Harper S, and Lynch JW. 2010. "Global and National Socioeconomic Disparities in Obesity, Overweight, and Underweight Status." *Journal of Obesity* 2010. <https://doi.org/10.1155/2010/514674>.
- Moreno M, De Lange P, Lombardi A, Silvestri E, Lanni A, and Goglia F. 2008. "Metabolic Effects of Thyroid Hormone Derivatives." *Thyroid* 18 (2): 239–53. <https://doi.org/10.1089/thy.2007.0248>.
- Morin K. 2009. "Knowledge and Attitudes of Canadian Consumers and Health Care Professionals Regarding Nutritional Genomics." *OMICS A Journal of Integrative Biology* 13 (1): 37–41. <https://doi.org/10.1089/omi.2008.0047>.
- Most J, Marlatt KL, Altazan AD, Redman LM. 2018. "Advances in assessing body composition during pregnancy." *European Journal of Clinical Nutrition* 72(5):645–656.
- Murdaugh DL, Cox JE, Cook EW, and Weller RE. 2012. "fMRI Reactivity to High-Calorie Food Pictures Predicts Short- and Long-Term Outcome in a Weight-Loss Program." *NeuroImage* 59 (3): 2709–21. <https://doi.org/10.1016/j.neuroimage.2011.10.071>.
- Musali U, Kuchnia AJ, Cole AJ, Earthman CP. 2015. "Bioimpedance at the bedside: Current applications, limitations and opportunities." *Nutrition in Clinical Practice* 30(2):180-93.
- MyDNA. 2019. "My Diet Report." 2019. <https://www.mydna.life/wp-content/uploads/Example-Report-Wellness-Nutrition-Diet.pdf>.
- Naderpoor N, Shorakae N, Joham A, Boyle J, De Courten B, and Teede HJ. 2015. "Obesity and Polycystic Ovary Syndrom." *Minerva Endocrinol* 40 (1): 37–51.
- Nagai N, Sakane N, Tsuzaki K, and Moritani T. 2011. "UCP1 Genetic Polymorphism (-3826 A/G) Diminishes Resting Energy Expenditure and Thermoregulatory Sympathetic Nervous System Activity in Young Females." *International Journal of Obesity* 35 (8): 1050–55. <https://doi.org/10.1038/ijo.2010.261>.
- National Institutes of Health. n.d. "Study Quality Assessment Tools." Accessed July 11, 2019. <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>.
- National Institute for Health Research. 2014. "Procedure for measuring bioelectrical impedance using the BodyStat 1500." <https://www.uhs.nhs.uk/Media/Southampton-Clinical-Research/Procedures/BRCProcedures/Procedure-for-bioimpedance-with-Bodystat-1500.pdf>.
- National Institutes of Health. 1994. Bioelectrical impedance analysis in body composition measurement. Available from: <https://consensus.nih.gov/1994/1994bioelectricimpedancebodyta015pdf.pdf>
- National Institutes of Health. 2015. "The Human Genome Project." 2015. <https://www.genome.gov/10001772/all-about-the--human-genome-project-hgp/>.
- National Institutes of Health. 2018. "Diet History Questionnaire: Web-Based DHQ." 2018. <https://epi.grants.cancer.gov/DHQ/webquest/index.html>.

- Newcastle University. 2016. "Strategies for Personalised Nutrition (Food4Me)." 2016. <https://clinicaltrials.gov/ct2/show/NCT01530139>.
- Nielsen DE and El-Sohehy A. 2012. "A Randomized Trial of Genetic Information for Personalized Nutrition." *Genes and Nutrition* 7 (4): 559–66. <https://doi.org/10.1007/s12263-012-0290-x>.
- Nielsen DE and El-Sohehy A. 2014. "Disclosure of Genetic Information and Change in Dietary Intake: A Randomized Controlled Trial." *PLoS ONE* 9 (11): e112665. <https://doi.org/10.1371/journal.pone.0112665>.
- Nielsen DE, and El-Sohehy A. 2014. "Perceptions of Genetic Testing for Personalized Nutrition: A Randomized Trial of DNA-Based Dietary Advice." *Journal of Nutrigenetics and Nutrigenomics* 7(2): 94–104.
- NIH: Genetics Home Reference. 2018. "What Are the Risks and Limitations of Genetic Testing?" 2018.
- North KN, Yang N, Wattanasirichaigoon D, Mills M, Eastel S, and Beggs AH. 1999. "A Common Nonsense Mutation Results in Alpha-Actinin-3 Deficiency in the General Population." *Nature*.
- Notani A. 1998. "Moderators of Perceived Behavioral Control's Predictiveness in the Theory of Planned Behavior: A Meta-Analysis." *Journal of Consumer Psychology* 7 (3): 247–71. https://doi.org/10.1207/s15327663jcp0703_02.
- Notani AS. 1998. "Moderators of Perceived Behavioral Control's Predictiveness in the Theory of Planned Behavior: A Meta-Analysis." *Journal of Consumer Psychology* 7 (3): 247–71. https://doi.org/10.1207/s15327663jcp0703_02.
- Nutrigenomix. 2019. "For Practitioners." 2019. <https://www.nutrigenomix.com/for-practitioners>.
- Nutrigenomix Inc. n.d. "Downloads." <https://www.nutrigenomix.com/downloads>.
- Nuttall FQ. 2015. "Body Mass Index: Obesity, BMI, and Health: A Critical Review." *Nutrition Today* 50 (3): 117–28. <https://doi.org/10.1097/NT.0000000000000092>.
- Nyboer J. Electrical Impedance Plethysmography: The Electrical Resistive Measure of the Blood Pulse Volume. Springfield, IL: Charles C. Thomas; 1959.
- O'Donovan CB, Walsh MC, Gibney MJ, Brennan L, and Gibney ER. 2017. "Knowing Your Genes: Does This Impact Behaviour Change?" *Proceedings of the Nutrition Society*, no. July 2016: 1–10. <https://doi.org/10.1017/S0029665116002949>.
- O'Neil ISC, Kaufman E, DeMarco T, Peshkin BN, McKenna K, Shelby R, Valdimarsdottir H, Rispoli J, and Schwartz MD. 2008. "Changes in Diet and Physical Activity Following BRCA1/2 Testing." *Journal of Psychosocial Oncology* 26 (3): 63–80. <https://doi.org/10.1080/07347330802116051>.
- Ochner CN, Barrios DM, Lee CD, and Pi-Sunyer FX. 2013. "Biological Mechanisms That Promote Weight Regain Following Weight Loss in Obese Humans." *Physiology and Behavior* 120: 106–13. <https://doi.org/10.1016/j.physbeh.2013.07.009>.

- Ontario Ministry of Health and Long-Term Care. 2018. "Schedule M Program Description: Primary Care Diabetes Prevention Program 2017-2018."
- Ortner H, Mucalo I, Hrabač P, Matić T, Rahelić D, and Božikov V. 2015. "Factors Predictive of Drop-out and Weight Loss Success in Weight Management of Obese Patients." *Journal of Human Nutrition and Dietetics* 28 (s2): 24–32. <https://doi.org/10.1111/jhn.12270>.
- Ozenoglu A, Ugurlu S, Can G, Hatemi H. 2009. "Reference values of body composition for adult females who are classified as normal weight, overweight or obese according to body mass index." *Endocrine regulations* 43:29-37.
- Paniagua JA, de la Sacristana AG, Sánchez E, Romero I, Pérez-Martinez P, López-Miranda J, Pérez-Jiménez F, et al. 2007. "A MUFA-Rich Diet Improves Postprandial Glucose, Lipid and GLP-1 Responses in Insulin-Resistant Subjects." *Journal of the American College of Nutrition* 26 (5): 434–44. <https://doi.org/10.1080/07315724.2007.10719633>.
- Pathway Genomics. n.d. "Pathway Genomics." <https://www.pathway.com/>.
- Perri MG, Limacher MC, Durning PE, Janicke DM, Lutes LD, Bobroff LB, Dale MS, Daniels MJ, Radcliff TA, and Martin AD. 2008. "Extended-Care Programs for Weight Management in Rural Communities." *Archives of Internal Medicine* 168 (21): 2347. <https://doi.org/10.1001/archinte.168.21.2347>.
- Petticrew M and Roberts H. 2006. *Systematic Reviews in the Social Sciences: A Practical Guide*. Oxford, Malden, MA: Blackwell Publishing.
- Phillips CM, Kesse-Guyot E, McManus R, Hercberg S, Lairon D, Planells R, and Roche HM. 2012. "High Dietary Saturated Fat Intake Accentuates Obesity Risk Associated with the Fat Mass and Obesity-Associated Gene in Adults." *Journal of Nutrition* 142 (5): 824–31. <https://doi.org/10.3945/jn.111.153460>.
- Piatt GA, Seidel MC, Chen HY, Powell RO, and Zgibor JC. 2012. "Two-Year Results of Translating the Diabetes Prevention Program Into an Urban, Underserved Community." *The Diabetes Educator* 38 (6): 798–804. <https://doi.org/10.1177/0145721712458834>.
- Pickering C and Kiely J. 2017. "ACTN3: More than Just a Gene for Speed." *Frontiers in Physiology*. Frontiers Media S.A. <https://doi.org/10.3389/fphys.2017.01080>.
- Poch, Esteban, Daniel González, Vicente Giner, Ernesto Bragulat, Antonio Coca, and Alejandro de la Sierra. 2007. "Molecular Basis of Salt Sensitivity in Human Hypertension." *Hypertension* 38 (5): 1204–9. <https://doi.org/10.1161/hy1101.099479>.
- Poinhos R, Van Der Lans IA, Rankin A, Fischer ARH, Bunting B, Kuznesof S, Stewart-Knox B, and Frewer LJ. 2014. "Psychological Determinants of Consumer Acceptance of Personalised Nutrition in 9 European Countries." *PLoS ONE* 9 (10). <https://doi.org/10.1371/journal.pone.0110614>.
- Popova L. 2012. "The Extended Parallel Process Model: Illuminating the Gaps in Research." *Health Education and Behaviour* 39(4): 455-73.
- Prentice AM, Jebb SA, Goldberg GR, Coward WA, Murgatroyd PR, Poppitt SD, and Cole TJ. 1992. "Effects of Weight Cycling on Body Composition." *American Journal of Clinical*

- Nutrition* 56: 209S-16S. <https://doi.org/10.1093/ajcn/56.1.209S>.
- Prochaska JO and Velicer WF. 1997. "The Transtheoretical Model of Health Behavior Change." *Am J Health Promot* 12 (1): 38–48.
- Public Health Agency of Canada. 2016. "Social Determinants of Health." 2016. <http://cbpp-pcpe.phac-aspc.gc.ca/public-health-topics/social-determinants-of-health/>.
- Qi L, Kraft P, Hunter DJ, and Hu FB. 2008. "The Common Obesity Variant near MC4R Gene Is Associated with Higher Intakes of Total Energy and Dietary Fat , Weight Change and Diabetes Risk in Women." *Human Molecular Genetics* 17 (22): 3502–8. <https://doi.org/10.1093/hmg/ddn242>.
- Quach J, Porter K, Leventhal H, and Kelly KM. 2009. "Health Behaviors among Ashkenazi Jewish Individuals Receiving Counseling for BRCA1 and BRCA2 Mutations." *Familial Cancer* 8 (3): 241–50. <https://doi.org/10.1007/s10689-009-9235-y>.
- Ramis JM, Luis González-Sánchez J, Proenza AM, Martínez-Larrad MT, Fernández-Pérez C, Palou A, and Serrano-Ríos M. 2004. "The Arg64 Allele of the β 3 -Adrenoceptor Gene but Not the -3826G Allele of the Uncoupling Protein 1 Gene Is Associated with Increased Leptin Levels in the Spanish Population." *Metabolism: Clinical and Experimental* 53 (11): 1411–16. <https://doi.org/10.1016/j.metabol.2004.06.006>.
- Rampersaud E, Mitchell BD, Pollin TI, Fu M, Shen H, O'Connell JR, Ducharme JL, et al. 2008. "Physical Activity and the Association of Common FTO Gene Variants with Body Mass Index and Obesity." *Archives of Internal Medicine* 168 (16): 1791–97. <https://doi.org/10.1001/archinte.168.16.1791>.
- Rankin A, Buntin BP, Poinho R, van der Lans IA, Fischer ARH, Kuznesof S, et al. 2018. "Food Choice Motives, Attitudes Towards and Intention to Adopt Personalised Nutrition." *Public Health Nutrition* 21(14): 2606-16.
- Rees G, Gaff C, Young MA, and Martin PR. 2007. "Health Beliefs and Behaviors of Women Who Have Received Genetic Counseling for Breast Cancer." *Journal of Genetic Counseling* 16 (4): 457–68. <https://doi.org/10.1007/s10897-006-9079-7>.
- Rhee E-J. 2017. "Weight Cycling and Its Cardiometabolic Impact." *Journal of Obesity & Metabolic Syndrome* 26 (4): 237–42. <https://doi.org/10.7570/jomes.2017.26.4.237>.
- Rich A, Brandes K, Mullan B, Hagger MS, and Rich A. 2015. "Theory of Planned Behavior and Adherence in Chronic Illness : A Meta-Analysis." *J Behav Med* 38: 673–88. <https://doi.org/10.1007/s10865-015-9644-3>.
- Rief W, Conradt M, Dierk JM, Rauh E, Schlumberger P, Hinney A, and Hebebrand J. 2007. "Is Information on Genetic Determinants of Obesity Helpful or Harmful for Obese People? - A Randomized Clinical Trial." *Journal of General Internal Medicine* 22 (11): 1553–59. <https://doi.org/10.1007/s11606-007-0353-7>.
- Rivis A and Sheeran P. 2003. "Descriptive Norms as an Additional Predictor in the Theory of Planned Behaviour: A Meta-Analysis." *Current Psychology* 22: 218–33. <https://doi.org/10.1007/s12144-003-1018-2>.

- Rogerson D, Soltani H, and Copeland R. 2016. “The Weight-Loss Experience: A Qualitative Exploration.” *BMC Public Health* 16 (1): 1–12. <https://doi.org/10.1186/s12889-016-3045-6>.
- Roke K, Walton K, Klingel S, Harnett A, Subedi S, Haines J, and Mutch D. 2017. “Evaluating Changes in Omega-3 Fatty Acid Intake after Receiving Personal FADS1 Genetic Information: A Randomized Nutrigenetic Intervention.” *Nutrients* 9 (3): 240. <https://doi.org/10.3390/nu9030240>.
- Rosenbaum M and Leibel RL. 2010. “Adaptive Thermogenesis in Humans.” *International Journal of Obesity* 34: S47–55.
- Rosenbaum M, Hirsch J, Murphy E, and Leibel RL. 2000. “Effects of Changes in Body Weight on Carbohydrate Metabolism, Catecholamine Excretion, and Thyroid Function.” *American Journal of Clinical Nutrition* 71 (6): 1421–32. <https://doi.org/10.1093/ajcn/71.6.1421>.
- Rosenbaum M, Kissileff HR, Mayer LES, Hirsch J, and Leibel RL. 2010. “Energy Intake in Weight-Reduced Humans.” *Brain Research* 1350: 95–102. <https://doi.org/10.1016/j.brainres.2010.05.062>.
- Rosenbaum M, Nicolson M, Hirsch J, Murphy E, Chu F, and Leibel RL. 1997. “Effects of Weight Change on Plasma Leptin Concentrations and Energy Expenditure.” *Journal of Clinical Endocrinology and Metabolism* 82 (11): 3647–54. <https://doi.org/10.1210/jc.82.11.3647>.
- Ross R, Janssen I. 2005. Computed tomography and magnetic resonance imaging. In: Human Body Composition (eds. Heymsfield, SB, Lohman, TG, Wang, Z, Going, SB), pp 89-108. Human Kinetics, Champaign, IL.
- Roth GA, Johnson C, Abajobir A, Foad Abd-Allah, Semaw Ferede Abera, Gebre Abyu, Muktar Ahmed, et al. 2017. “Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015.” *Journal of the American College of Cardiology* 70 (1): 1–25. <https://doi.org/10.1016/j.jacc.2017.04.052>.
- San-Cristobal R, Milagro FI, and Martínez JA. 2013. “Future Challenges and Present Ethical Considerations in the Use of Personalized Nutrition Based on Genetic Advice.” *Journal of the Academy of Nutrition and Dietetics* 113 (11): 1447–54. <https://doi.org/10.1016/j.jand.2013.05.028>.
- Sanderson SC, Humphries SE, Hubbart C, Hughes E, Jarvis MJ, and Wardle J. 2008. “Psychological and Behavioural Impact of Genetic Testing Smokers for Lung Cancer Risk: A Phase II Exploratory Trial.” *Journal of Health Psychology* 13 (4): 481–94. <https://doi.org/10.1177/1359105308088519>.
- Santiago C, Ruiz JR, Buxens A, Artieda M, Arteta D, González-Freire M, Rodríguez-Romo G, et al. 2011. “Trp64Arg Polymorphism in ADRB3 Gene Is Associated with Elite Endurance Performance.” *British Journal of Sports Medicine* 45 (2): 147–49. <https://doi.org/10.1136/bjsm.2009.061366>.
- Santos I, Sniehotta FF, Marques MM, Carraça EV, and Teixeira PJ. 2017. “Prevalence of Personal Weight Control Attempts in Adults: A Systematic Review and Meta-Analysis.” *Obesity Reviews* 18 (1): 32–50. <https://doi.org/10.1111/obr.12466>.

- Sarma S, Zaric GS, Campbell MK, and Gilliland J. 2014. "Economics and Human Biology The Effect of Physical Activity on Adult Obesity : Evidence from the Canadian NPHS Panel." *Economics and Human Biology* 14: 1–21. <https://doi.org/10.1016/j.ehb.2014.03.002>.
- Saukko P. 2013. State of Play in Direct-To-Consumer Genetic Testing for Lifestyle-Related Riseases: Market, Marketing Content, User Experiences and Regulation. *Proc Nutr Soc* 72(1):53-60.
- Scharfetter H, Schlager T, Stollberger R, Felsberger R, Hutten H, Hinghofer-Szalkay H. 2001. Assessing abdominal fatness with local bioimpedance analysis: basics and experimental findings. *Int J Obes Relat Metab Disord* 25:502–511. doi: 10.1038/sj.ijo.0801556.
- Scherme A, Mendoza J, Henson S, Dukeshire S, Pasut L, Emrich TE, Lou W, Qi Y, and L'Abbé MR. 2014. "Canadians' Perceptions of Food, Diet, and Health - A National Survey." *PLoS ONE* 9 (1). <https://doi.org/10.1371/journal.pone.0086000>.
- Schulze R and Wittmann WW. 2003. *A Meta-Analysis of the Theory of Reasoned Action and the Theory of Planned Behavior: The Principle of Compatibility and Multidimensionality of Beliefs as Moderators*. In: *Meta-Analysis: New Developments and Applications in Medical and Social Sciences*. Edited by D. Schulze, R. Holling, H. Bohning. Seattle, WA: Hogrefe & Huber.
- Schutzer KA and Graves BS. 2004. "Barriers and Motivations to Exercise in Older Adults." *Preventive Medicine* 39 (5): 1056–61. <https://doi.org/10.1016/j.ypmed.2004.04.003>.
- Scott RA, Bailey MES, Moran CN, Wilson RH, Fuku N, Tanaka M, Tsiokanos A, et al. 2010. "FTO Genotype and Adiposity in Children: Physical Activity Levels Influence the Effect of the Risk Genotype in Adolescent Males." *European Journal of Human Genetics* 18 (12): 1339–43. <https://doi.org/10.1038/ejhg.2010.131>.
- Seabrook JA and Avison WR. 2010. "Social Science & Medicine Genotype – Environment Interaction and Sociology : Contributions and Complexities." *Social Science & Medicine* 70 (9): 1277–84. <https://doi.org/10.1016/j.socscimed.2010.01.016>.
- Seabrook JA and Avison WR. 2012. "Socioeconomic Status and Cumulative Disadvantage Processes Across the Life Course: Implication for Health Outcomes." *Canadian Review of Sociology* 49(1): 50-68.
- Seguin R, Connor L, Nelson M, Lacroix A, and Eldridge G. 2014. "Understanding Barriers and Facilitators to Healthy Eating and Active Living in Rural Communities." *Journal of Nutrition and Metabolism* 2014: 23–25. <https://doi.org/10.1155/2014/146502>.
- Sheean P, Gonzalez C, Prado CM, McKeever L, Hall AM, Braunschweig CA. 2020. "ASPEN Clinical Guidelines: The validity of body composition assessment in clinical populations." *JPEN* 44(1).
- Shepherd J, Ng B, Sommer M, Heymsfield SB. 2017. "Body composition by DXA." *Bone* 104:101-105.
- Shim J-S, Oh K, Kim H. 2014. "Dietary Assessment Methods in Epidemiological Studies." *Epidemiol Health* 7(2):302-4.

- Siero FW. 2000. "Impact of Group Nutrition Education and Surplus Value of Prochaska-Based Stage-Matched Information on Health-Related Cognitions and on Mediterranean Nutrition Behavior." *Health Education Research* 15 (5): 635–47.
<https://doi.org/10.1093/her/15.5.635>.
- Siscovick DS, Barringer TA, Fretts AM, Wu JHY, Lichtenstein AH, Costello RB, Kris-Etherton PM, et al. 2017. "Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory from the American Heart Association." *Circulation* 135 (15): e867–84.
<https://doi.org/10.1161/CIR.0000000000000482>.
- Sladjana R, Milivoj D, Marina D-N, Nadja V, et al. 2019. "Profile and reference values for body fat and skeletal muscle mass percent at females, aged from 18.0 to 69.9, measured by multichannel segmental bioimpedance method: Serbian population study." *Int J Morphol* 37(4):1286-93.
- Smilowitz JT, Wiest MM, Watkins SM, Teegarden D, Zemel MB, German JB, and Van Loan MD. 2009. "Lipid Metabolism Predicts Changes in Body Composition during Energy Restriction in Overweight Humans 1 – 3," 1–8. <https://doi.org/10.3945/jn.108.095364>.and.
- Smith CE, Ordovás JM, Sánchez-Moreno C, Lee YC, and Garaulet M. 2012. "Apolipoprotein A-II Polymorphism: Relationships to Behavioural and Hormonal Mediators of Obesity." *International Journal of Obesity* 36 (1): 130–36. <https://doi.org/10.1038/ijo.2011.24>.
- Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. 2004. "Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study." *Int J Obes Relat Metab Disord* 28:402–409.
- Soetens B, Braet C, Van Vlierberghe L, and Roets A. 2008. "Resisting Temptation: Effects of Exposure to a Forbidden Food on Eating Behaviour." *Appetite* 51 (1): 202–5.
<https://doi.org/10.1016/j.appet.2008.01.007>.
- Soleymani T, Daniel S, and Garvey WT. 2016. "Weight Maintenance: Challenges, Tools and Strategies for Primary Care Physicians." *Obesity Reviews* 17 (1): 81–93.
<https://doi.org/10.1111/obr.12322>.
- Sonestedt E, Gullberg B, Ericson U, Wirfält E, Hedblad B, and Orho-Melander M. 2011. "Association between Fat Intake, Physical Activity and Mortality Depending on Genetic Variation in FTO." *International Journal of Obesity* 35 (8): 1041–49.
<https://doi.org/10.1038/ijo.2010.263>.
- Sonestedt E, Roos C, Gullberg B, Ericson U, Wirfält E, and Orho-Melander M. 2009. "Fat and Carbohydrate Intake Modify the Association between Genetic Variation in the FTO Genotype and Obesity." *American Journal of Clinical Nutrition* 90 (5): 1418–25.
<https://doi.org/10.3945/ajcn.2009.27958>.
- Speakman JR. 2015. "The 'Fat Mass and Obesity Related' (FTO) Gene: Mechanisms of Impact on Obesity and Energy Balance." *Current Obesity Reports* 4 (1): 73–91.
<https://doi.org/10.1007/s13679-015-0143-1>.
- Srivastava A, Mittal B, Prakash J, Narain VS, Natu SM, and Srivastava N. 2014. "Evaluation of

- MC4R [Rs17782313, Rs17700633], AGRP [Rs3412352] and POMC [Rs1042571] Polymorphisms with Obesity in Northern India.” *Oman Medical Journal* 29 (2): 114–18.
- Statistics Canada. 2014. “Overweight and Obese Adults (Self-Reported), 2014.” 2014. <http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14185-eng.htm>.
- Stewart-Knox BJ, Bunting BP, Gilpin S, Parr HJ, Pinhão S, Strain J, de Almeida MDV, and Gibney M. 2009. “Attitudes toward Genetic Testing and Personalised Nutrition in a Representative Sample of European Consumers.” *British Journal of Nutrition* 101 (7): 982–89. <https://doi.org/10.1017/S0007114508055657>.
- Stewart-Knox B, Kuznesof S, Robinson J, Rankin A, Orr K, Duffy M, Poínhos R, et al. 2013. “Factors Influencing European Consumer Uptake of Personalised Nutrition. Results of a Qualitative Analysis.” *Appetite* 66: 67–74. <https://doi.org/10.1016/j.appet.2013.03.001>.
- Stutzmann F, Cauchi S, Durand E, Calvacanti-Proença C, Pigeyre M, Hartikainen AL, Sovio U, et al. 2009. “Common Genetic Variation near MC4R Is Associated with Eating Behaviour Patterns in European Populations.” *International Journal of Obesity* 33 (3): 373–78. <https://doi.org/10.1038/ijo.2008.279>.
- Subbiah MT. 2008. “Understanding the Nutrigenomic Definitions and Concepts at the Food–Genome Junction.” *OMICS A Journal of Integrative Biology* 12 (4): 229–35.
- Sui Z, Raman J, Han B, Burchell T, Coogan SCP, Brennan B, and Sartoretto A. 2019. “Recent Trends in Intensive Treatments of Obesity: Is Academic Research Matching Public Interest?” *Surgery for Obesity and Related Diseases* 15 (5): 766–76. <https://doi.org/10.1016/j.soard.2019.01.009>.
- Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, and Proietto J. 2011. “Long-Term Persistence of Hormonal Adaptations to Weight Loss.” *New England Journal of Medicine* 365 (17): 1597–1604. <https://doi.org/10.1056/NEJMoa1105816>.
- Svetkey LP, Stevens VJ, Brantley PJ, Appel LJ, Hollis JF, Loria CM, Vollmer WM, et al. 2008. “Comparison of Strategies for Sustaining Weight Loss.” *Journal of the American Medical Association* 299 (10): 1139–48.
- Wadden TA, Foster GD, Sarwer DB, Anderson DA, Gladis M, Sanderson RS, Letchak RV, Berkowitz RI, and Phelan S. 2004. “Dieting and the Development of Eating Disorders in Obese Women: Results of a Randomized Controlled Trial.” *American Journal of Clinical Nutrition* 80 (3): 560–68. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L41115518>.
- Taylor JY, Wu CY. 2010. “Effects of Genetic Counseling for Hypertension on Changes in Lifestyle Behaviors among Africa-American Women.” *Journal Natl Black Nurses Assoc*.
- Tchoukalova YD, Votruba SB, Tchkonja T, Giorgadze N, Kirkland JL, and Jensen MD. 2010. “Regional Differences in Cellular Mechanisms of Adipose Tissue Gain with Overfeeding.” *Proceedings of the National Academy of Sciences of the United States of America* 107 (42): 18226–31. <https://doi.org/10.1073/pnas.1005259107>.
- The Cochrane Collaboration. 2011. *Cochrane Handbook for Systematic Reviews of*

Interventions. Edited by J Higgins and S Green. V5.1.0.

- Tremblay A and Chaput JP. 2009. "Short Communication: Adaptive Reduction in Thermogenesis and Resistance to Lose Fat in Obese Men." *British Journal of Nutrition* 102 (4): 488–92. <https://doi.org/10.1017/S0007114508207245>.
- Trent RJ. 2013. "Direct-to-Consumer Genetic Testing - Clinical Considerations." *Medical Journal of Australia* 198 (9): 496–98. <https://doi.org/10.5694/mja12.11019>.
- Truby H, Baic S, DeLooy A, Fox KR, Livingstone MBE, Logan CM, Macdonald IA, Morgan LM, Taylor MA, and Millward DJ. 2006. "Randomised Controlled Trial of Four Commercial Weight Loss Programmes in the UK: Initial Findings from the BBC 'Diet Trials.'" *British Medical Journal* 332 (7553): 1309–11. <https://doi.org/10.1136/bmj.38833.411204.80>.
- University of Pittsburgh. c2017. "DPP Group Lifestyle Balance Curriculum."
- University of Pittsburgh. c2019. "GLB Program Locations." <https://www.diabetesprevention.pitt.edu/index.php/for-the-public/glb-program-locations-unitedstates/>.
- University of Pittsburgh. 2017. "2017 Diabetes Prevention Program Group Lifestyle Balance™ Materials." 2017. <http://www.diabetesprevention.pitt.edu/index.php/group-lifestyle-balance-materials/>.
- UNOS Transplant Living. c2019. "Finding a Living Donor." Accessed October 30, 2019. <https://transplantliving.org/kidney/who-are-living-donors/>.
- Vallée Marcotte B, Cormier H, Garneau V, Robitaille J, Desroches S, and Vohl M-C. 2019. "Nutrigenetic Testing for Personalized Nutrition: An Evaluation of Public Perceptions, Attitudes, and Concerns in a Population of French Canadians." *Lifestyle Genomics*. <https://doi.org/10.1159/000499626>.
- Verdich C, Flint A, Gutzwiller J-P, Naslund E, Beglinger C, Hellstrom PM, et al. 2001. "A Meta-Analysis of the Effect of Glucagon-Like Peptide-1 (7-36) Amide on Ad Libitum Energy Intake in Humans." <https://academic.oup.com/jcem/article-abstract/86/9/4382/2848979>.
- Vernarelli JA, Roberts JS, Hiraki S, Chen CA, Cupples LA, and Green RC. 2010. "Effect of Alzheimer Disease Genetic Risk Disclosure on Dietary Supplement Use." *American Journal of Clinical Nutrition* 91 (5): 1402–7. <https://doi.org/10.3945/ajcn.2009.28981>.
- Vickery CE and Cotugna N. 2005. "Incorporating Human Genetics into Dietetics Curricula Remains a Challenge." *Journal of the American Dietetic Association* 105 (4): 583–88. <https://doi.org/10.1016/j.jada.2005.01.007>.
- Vimaleswaran KS, Li S, Zhao JH, Luan J, Bingham SA, Khaw KT, Ekelund U, Wareham NJ, and Loos RJF. 2009. "Physical Activity Attenuates the Body Mass Index-Increasing Influence of Genetic Variation in the FTO Gene." *American Journal of Clinical Nutrition* 90 (2): 425–28. <https://doi.org/10.3945/ajcn.2009.27652>.
- Voils CI, Coffman CJ, Grubber JM, Edelman D, Sadeghpour A, Maciejewski ML, Bolton J, Cho

- A, Ginsburg GS, and Yancy WS. 2015. "Does Type 2 Diabetes Genetic Testing and Counseling Reduce Modifiable Risk Factors? A Randomized Controlled Trial of Veterans." *Journal of General Internal Medicine* 30 (11): 1591–98. <https://doi.org/10.1007/s11606-015-3315-5>.
- Wadden TA, Foster GD, Sarwer DB, Anderson DA, Gladis M, Sanderson RS, Letchak RV, Berkowitz RI, and Phelan S. 2004. "Dieting and the Development of Eating Disorders in Obese Women: Results of a Randomized Controlled Trial." *American Journal of Clinical Nutrition* 80: 560–68.
- Wadden TA and DB Sarwer. 1999. "Behavioral Treatment of Obesity: New Approaches to an Old Disorder." In *The Management of Eating Disorders and Obesity*.
- Walker KZ, O’Dea K, Gomez M, Girgis S, and Colagiuri R. 2010. "Diet and Exercise in the Prevention of Diabetes." *Journal of Human Nutrition and Dietetics* 23 (4): 344–52. <https://doi.org/10.1111/j.1365-277X.2010.01061.x>.
- Walsh TP, Arnold JB, Evans AM, Yaxley A, Damarell RA, Shanahan EM. 2018. "The association between body fat and musculoskeletal pain: a systematic review and meta-analysis." *BMC Musculoskelet Disord* 19(1):233.
- West S, King V, Carey TS, Lohr KN, McKoy N, Sutton SF, and Lux L. 2002. "Systems to Rate the Strength of Scientific Evidence." *Evidence Resports/Technology Assessments*. Rockville, MD.
- Williamson DA, Bray GA, and Ryan DH. 2015. "Is 5 % Weight Loss a Satisfactory Criterion to Define Clinically Significant Weight Loss ?" 23 (12): 2319–20. <https://doi.org/10.1002/oby.21358>.
- Wing RR, Tate DF, Gorin AA, Raynor HA, and Fava JL. 2006. "A Self-Regulation Program for Maintenance of Weight Loss." *New England Journal of Medicine* 355 (15): 1563–71. <https://doi.org/10.1056/NEJMoa061883>.
- Witte K, Meyer G, and Martell D. 2001. *Effective Health Risk Messages: A Step-By-Step Guide*. SAGE Publications, Inc.
- Wren AM, Seal LJ, Cohen MA, Bryne AE, Frost GS, Murphy KG, Dhillo WS, Ghatei MA, and Bloom SR. 2001. "Ghrelin Enhances Appetite and Increases Food Intake in Humans." *Journal of Clinical Endocrinology and Metabolism* 86 (12): 5992–95.
- Wu Y, Zhai L, and Zhang D. 2014. "Sleep Duration and Obesity among Adults: A Meta-Analysis of Prospective Studies." *Sleep Medicine* 15 (12): 1456–62.
- Xi B, Wang C, Wu L, Zhang M, Shen Y, Zhao X, Wang X, and Mi J. 2011. "Influence of Physical Inactivity on Associations between Single Nucleotide Polymorphisms and Genetic Predisposition to Childhood Obesity." *American Journal of Epidemiology* 173 (11): 1256–62. <https://doi.org/10.1093/aje/kwr008>.
- Xiao L, Yank V, Wilson SR, Lavori PW, and Ma J. 2013. "Two-Year Weight-Loss Maintenance in Primary Care-Based Diabetes Prevention Program Lifestyle Interventions." *Nutrition and Diabetes* 3 (JUNE): 17–19. <https://doi.org/10.1038/nutd.2013.17>.

- Yang N, MacArthur DG, Gulbin JP, Hahn AG, Beggs AH, Eastal S, and North K. 2003. "ACTN3 Genotype Is Associated with Human Elite Athletic Performance." *The American Journal of Human Genetics* 73 (3): 627–31. <https://doi.org/10.1086/377590>.
- Yang Q, Xiao T, Guo J, and Su Z. 2017. "Complex Relationship between Obesity and the Fat Mass and Obesity Locus." *International Journal of Biological Sciences*. Ivyspring International Publisher. <https://doi.org/10.7150/ijbs.17051>.
- Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P Jr, Razak F, Sharma AM, Anand SS: Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study . *Lancet* 2005;366:1640–1649.
- Zarebska A, Jastrzebski Z, Kaczmarczyk M, Ficek K, Maciejewska-Karlowska A, Sawczuk M, Leońska-Duniec A, et al. 2014. "The GSTP1 c.313A>G Polymorphism Modulates the Cardiorespiratory Response to Aerobic Training." *Biology of Sport* 31 (4): 261–66. <https://doi.org/10.5604/20831862.1120932>.
- Zhang X, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, Bray GA, and Qi L. 2012. "FTO Genotype and 2-Year Change in Body Composition and Fat Distribution in Response to Weight-Loss Diets: The POUNDS LOST Trial." *Diabetes* 61 (11): 3005–11. <https://doi.org/10.2337/db11-1799>.
- Zhu B, Hershberger PE, Kapella MC, and Fritschi C. 2017. "The Relationship between Sleep Disturbance and Glycaemic Control in Adults with Type 2 Diabetes: An Integrative Review." *Journal of Clinical Nursing* 26 (23–24): 4053–64. <https://doi.org/10.1111/jocn.13899>.
- Zhu J, Loos RJF, Lu L, Zong G, Gan W, Ye X, Sun L, Li H, and Lin X. 2014. "Associations of Genetic Risk Score with Obesity and Related Traits and the Modifying Effect of Physical Activity in a Chinese Han Population." *PLoS ONE* 9 (3). <https://doi.org/10.1371/journal.pone.0091442>.
- Zobel DP, Andreasen CH, Grarup N, Eiberg H, Sørensen TIA, Sandbaek A, Lauritzen T, et al. 2009. "Variants near MC4R Are Associated with Obesity and Influence Obesity-Related Quantitative Traits in a Population of Middle-Aged People: Studies of 14,940 Danes." *Diabetes* 58 (3): 757–64. <https://doi.org/10.2337/db08-0620>.
- Zou ZC, Mao LJ, Shi YY, Chen JH, Wang LS, and Cai W. 2015. "Effect of Exercise Combined with Dietary Intervention on Obese Children and Adolescents Associated with the FTO Rs9939609 Polymorphism." *European Review for Medical and Pharmacological Sciences* 19 (23): 4569–75. <http://www.ncbi.nlm.nih.gov/pubmed/26698254>.
- Zwarentein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, Oxman AD, and Moher D. 2008. "Improving the Reporting of Pragmatic Trials: An Extension of the CONSORT Statement." *BMJ* 7 (4): 392–97. <https://doi.org/10.1136/bmj.a2390>.

APPENDIX A:

Selected TPB Survey Questions Included in Attrition Analysis

Attitudes/Behavioural Beliefs/Outcome Evaluations

Meeting the recommendation for **physical activity** outlined in my 1-page report will help me to better manage my weight.

Unlikely 1 2 3 4 5 6 7 Likely

Meeting the recommendation for **calories** outlined in my 1-page report will help me to better manage my weight.

Unlikely 1 2 3 4 5 6 7 Likely

Meeting the recommendation(s) for **fat (either total fat and/or different types of fat)** outlined in my 1-page report will help me to better manage my weight.

Unlikely 1 2 3 4 5 6 7 Likely

Meeting the recommendation for **protein** outlined in my 1-page report will help me to better manage my weight.

Unlikely 1 2 3 4 5 6 7 Likely

Subjective (Perceived) Norms/Injunctive Normative Beliefs/Motivation to Comply

My **friends** eat a generally healthy diet.

Disagree 1 2 3 4 5 6 7 Agree

My **family** eats a generally healthy diet.

Disagree 1 2 3 4 5 6 7 Agree

Perceived Behavioural Control/Control Beliefs/Power of Control Factors

For me, making beneficial changes to my **calorie intake** over the next three months will be:

Extremely Difficult 1 2 3 4 5 6 7 Extremely Easy

For me, making beneficial changes to my **fat intake (either total fat and/or different types of fat)** over the next three months will be:

Extremely Difficult 1 2 3 4 5 6 7 Extremely Easy

For me, making beneficial changes to my **protein intake** over the next three months will be:

Extremely Difficult 1 2 3 4 5 6 7 Extremely Easy

When it comes to making changes to your lifestyle (diet or physical activity), which sentence best describes your attitude:

- a. I do not believe that I need to make any changes to my lifestyle
- b. I might need to make some changes to my lifestyle
- c. I am determined to make changes to my lifestyle but haven't started to make any changes yet
- d. I have started making positive changes to my lifestyle over the past three months
- e. I have started making positive changes to my lifestyle, which I have sustained over the past 3-6 months
- f. I have started making positive changes to my lifestyle, which I have sustained for over 6 months

Actual Behavioural Control

What is your highest level of education?

1. Elementary School
2. Middle School (Grade 7/8)
3. High School
4. College
5. University

[Annual household income (CDN\$) taken from participant demographic questionnaire]

APPENDIX B:

BIA Data Collection Methods

The data collection methods detailed below were adapted with guidance from the National Institute for Health Research Biomedical Research Centre (National Institute for Health Research, 2014) and the BodyStat 1500MDD instruction manual (BodyStat, 2017). One researcher (JH) completed all BIA assessments with participants and therefore inter-rater reliability assessments were not needed. Before each BIA assessment, safety screening was conducted. Participants were asked if they had a pacemaker or any other implanted electrical device and if so, the BIA was not conducted ($n=2$). Participants were asked to remove all right-sided jewellery and were given the opportunity to void prior to the BIA assessment. They were then asked to remove their right shoe and sock and lay in a supine position while the researcher set up the BIA machine and input patient-specific data. The data that was input into the BIA device included: measured height and weight, age, gender, and physical activity level. Physical activity level was determined based on the participant's self-reported 7-day physical activity recall, which they completed immediately prior to completing the BIA assessment. Alcohol wipes were used to thoroughly clean the area of the skin where the electrodes would be attached. Two electrode pads were placed on the right foot, and two on the right hand and wrist as indicated in Image 1 and Image 2, below. Specifically, the current injection (red) electrodes were placed proximally to the phalangeal joints and the voltage detection (black) electrodes were placed at the pisiform prominence of the wrist and on the ankle, in between the medial and lateral malleoli. The process of setting up the BIA device took approximately 5 minutes, and this was completed while the patient was laying in the supine position.

Image 1

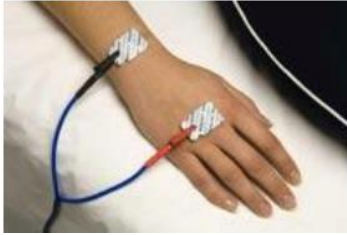


Image 2



Images taken from: National Institute for Health Research, 2014

It should be noted that some test violations occurred since dietary intake and physical activity data collection occurred at the same time period as body composition data collection. Participants were not asked: to avoid eating 4-5 hours before the test, to avoid caffeine and alcohol 24 hours before the test or to avoid exercise for 12 hours before the test.

There was one unexpected deviation from the protocol above, in the case of a participant who experienced extreme pain in the supine position and therefore the participant's BIA assessment was conducted in a seated position. This participant, however, only completed the baseline assessment and therefore their data was not included in the final analysis.

Curriculum Vitae

Justine Horne, MScFN, RD, PhD

Profile

- Registered dietitian experienced in clinical, community, industry and research settings with a passion for knowledge translation, research and teaching
- Proficient in both English (first language) and French (second language)

Education

- **Doctor of Philosophy (PhD) in Health and Aging:** September 2016 – March 2020, Western University, Health and Rehabilitation Sciences
 - **Supervisors:** Jason Gilliland, PhD; Janet Madill, PhD, RD
 - **Major Project:** The Nutrigenomics, Overweight/Obesity and Weight Management Trial (The NOW Trial): A pragmatic randomized controlled trial of personalized, genetic-based lifestyle advice
 - CIHR Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Research Award recipient (\$105,000)
- **Master of Science in Food and Nutrition (MScFN)** with Distinction: June 2015, Western University (Brescia University College)
 - **Supervisor:** Colleen O'Connor, PhD, RD
 - **Major Project:** Exploring knowledge and attitudes of personal nutrigenomics testing among dietetic students and its value as a component of dietetic education & practice.
 - MScFN Leadership Award recipient
- **Bachelor of Science (BSc) in Food and Nutrition – Honours Specialization in Nutrition and Dietetics** with Distinction: June 2013, Western University
 - Western Gold Medal recipient
- **Certificate in Practical French:** June 2013, Western University
 - Sir Wilfrid Laurier Memorial Prize recipient

Student Mentorship

- **Preceptor:** Diploma in Dietetic Education and Practical Training, Brescia University College (BUC), 2017 – present
 - Supervised 5 dietetic interns for their research placements
 - Supervised 3 dietetic interns for their community nutrition/public health placement
 - Supervised 1 dietetic intern for their clinical nutrition placement

- **Lead Coordinator:** The NOW Trial Experiential Learning Group, BUC, 2016 – January 2020
 - Oversee 50+ student volunteers involved in data collection for The NOW Trial
- **Undergraduate Independent Study Co-Advisor:** BUC Honours BScFN Program, 2019 – present
 - Co-advising undergraduate student with Janet Madill, PhD, RD
- **Preceptor:** MScFN Program, Brescia University College, 2015 – 2017
 - Supervised 4 dietetic interns for their clinical nutrition placements

Awards and Recognitions

- **Top Scoring Abstract, ASPEN Nutrition Science and Practice Conference:** March 2020 (complimentary conference registration)
- **CNS Graduate Student and Trainee Award – Poster Competition Finalist:** May 2019
- **Campus Collaboration Award** (the NOW Experiential Learning Group): April 2019
- **Canadian Institutes of Health Research (CIHR) – Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Research Award:** 2018 – present, CIHR (\$105,000)
- **Ontario Graduate Scholarship:** 2017-2018 (2018-2019: offered & declined), Government of Ontario (\$15,000)
- **Ontario Respiratory Care Society (ORCS) Fellowship Award:** 2017-2018, ORCS (\$9200)
- **Dean’s Honour List with Distinction:** 2009 – 2020, Western University
- **Dean’s Honour Roll of Teaching:** 2015 – 2018, Western University (Brescia University College)
- **TalentEdge Internship Grant:** 2015, Ontario Centres for Excellence (\$20,000)
- **MScFN Leadership Award:** 2015, Brescia University College
- **CIS Academic All-Canadian:** 2010-2014, Western University
- **Sir Wilfrid Laurier Memorial Prize:** 2013, Western University (\$375)
- **A.K. Knill Award:** 2013, Western University (Residence Staff)
- **Western Gold Medal:** 2013, Western University
- **Excellence in Leadership Award:** 2010-2011, Western University

Certifications

- **Registered Dietitian:** May 2015 – present, College of Dietitians of Ontario
- **Certified Lifestyle Coach:** May 2017 – present, Group Lifestyle Balance™/Diabetes Prevention Program
- **DELF Level B2 and DALF Level C1 French Bilingual Certification:** May 2013, French Ministry of Education

Professional Dietetics Experience

East Elgin Family Health Team: Registered Dietitian, and Health Programs & Research Co-ordinator, January 2017 – March 2020

Justine the RD & Associates - Personalized Nutrition Consulting: Owner, January 2016 – October 2018

Nutrigenomix Inc: Manager of Research & Education, May 2015 – Dec 2017

Nutrition Professionals of Canada: Consulting Dietitian, April 2016 – November 2016

Kitchener Downtown Community Health Centre: Registered Dietitian and Diabetes Educator, May 2015 – September 2015

Brescia University College: Dietetic Intern, May 2014 – April 2015

Teaching Experience

Brescia University College: Adjunct Faculty, January – April 2018

- Nutrition Through the Human Life Cycle, FN2241B
- Dean's Honour Roll of Teaching

Brescia University College: Adjunct Faculty, September 2015 – December 2016

- Clinical Nutrition 1, FN3351A
- Dean's Honour Roll of Teaching

Western University: Guest Lecturer, January 2014 – April 2018

- Health Policy, Law & Equity: MPH9009, Lecture Topic: Nutrigenomics: Genetic Testing for Personalized Nutrition (Graduate Level), April 2018
- Musculoskeletal Disorders in Rehabilitation Science: RS3360, Lecture Topic: Rehabilitation from the Nutrition Perspective (Undergraduate Level), March 2018
- Guidelines for Physical Activity and Exercise in Older Adults: KIN4474, Lecture Topic: Nutrition for Healthy Aging and Participation in Physical Activity (Undergraduate Level), February 2018
- Advances in Clinical Nutrition: FN9444B, Lecture Topics: 1. Long-Term Care; 2. Nutrigenomics: Genetic Testing for Personalized Nutrition (Graduate Level), January 2015
- Clinical Nutrition 1: FN3351A, Lecture Topic: Disordered Eating (Undergraduate Level), January 2014
- Nutrition Through the Human Life Cycle: FN2242, Lecture Topics: 1. Nutrition During Pregnancy; 2. Early Childhood Nutrition; 3. Adult Nutrition (Undergraduate Level), March - April 2014
- Clinical Nutrition III: FN4453A, Lecture Topic: Nutrigenomics: Genetic Testing for Personalized Nutrition (Undergraduate Level), January 2014/2015/2016/2017/2018

Western University: Teaching Assistant, September – December 2016

- Foundations of Mental Health, HS4620F: Supervisor – Louis Charland, PhD
- Population Health Interventions, HS4250A: Supervisor – Jean Samuel, PhD

Self-Employed: Private Tutor, April – June 2014

Brescia University College: Course Assistant, October 2013 – April 2014

- Clinical Nutrition 1, FN3351A and Nutrition Through the Human Life Cycle, FN2242: Supervisors – Colleen O'Connor, PhD, RD and Janet Madill, PhD, RD

Peer-Reviewed Publications

1. **Horne J**, Gilliland J, Madill J, Shelley J. A critical examination of legal and ethical considerations of nutrigenetic testing with recommendations for improving regulation in Canada: From science to consumer. *Journal of Law and the Biosciences*. 2020 [in press].
2. **Horne J**. Are we losing sight of the true meaning of “evidence-based nutrition?” *International Journal of Public Health*. 2020 [in press].
3. Guest NS, **Horne J**, Vanderhout S, El-Sohemy A. Sport nutrigenomics: Personalized nutrition for athletic performance. *Frontiers in Nutrition*. 2019;6:8.
4. Toth J, O'Connor C, Hartman B, Dworatzek P, **Horne J**. "Detoxify or Die": Qualitative assessments of Ontario nutritionists' and dietitians' blog posts related to detoxification diets. *Canadian Journal of Dietetic Practice and Research*. 2019;1-6.
5. **Horne J**, Gilliland J, O'Connor C, Seabrook J, Hannaberg P, Madill J. Study Protocol of a pragmatic randomized controlled trial incorporated into the Group Lifestyle Balance™ Program: The Nutrigenomics, Overweight/Obesity and Weight Management Trial (The NOW Trial). *BMC Public Health*. 2019;19(1):310.
6. **Horne J**, Madill J, O'Connor C, Shelley J, Gilliland J. A Systematic Review of Genetic Testing and Lifestyle Behaviour Change: Are We Using High-Quality Genetic Interventions and Considering Behaviour Change Theory? *Lifestyle Genomics*. 2018;11(1):49-63.
7. **Horne J**, Madill J, Gilliland J. Incorporating the 'Theory of Planned Behaviour' into personalized healthcare behavior change research: a call to action. *Personalized Medicine*. 2017;14(6):521–9.
8. Rinaldi S, **Horne J**, Madill J. An evolving understanding of modifiable risk factors for post-transplant mortality. [Letter to the Editor] *Transplant International*. 2017;30(5): 533-534.

9. **Horne J**, O'Connor C, Madill J, Rinaldi S, Gilliland J. Re: Polymorphisms of three genes (ACE, AGT and CYP11B2) in the renin-angiotensin-aldosterone system are not associated with blood pressure salt sensitivity: A systematic meta-analysis. [Letter to the Editor] *Blood Pressure*. 2016;26(4): 255-256.

10. **Horne J**, Madill J, O'Connor C. Exploring knowledge and attitudes of personal nutrigenomics testing among dietetic students and its value as a component of dietetic education and practice. *Canadian Journal of Clinical Nutrition*. 2016;4(1): 50-62.

Abstracts and Poster Presentations

1. **Horne J**, Gilliland J, Seabrook J, O'Connor C, Madill J. Change in weight, BMI, and body composition after 3, 6, and 12 months in a population-based intervention vs. genetic-based intervention: Results from the NOW randomized controlled trial. *ASPEN Nutrition Science and Practice Conference*. Tampa, United States. March 29, 2019 (**Top Scoring Abstract**). [International]

2. **Horne J**, Gilliland J, Seabrook J, O'Connor C, Madill J. Exploring the Canadian general public's attitudes towards genetic-based lifestyle advice for weight management: Results from the NOW randomized controlled trial. *ASPEN Nutrition Science and Practice Conference*. Tampa, United States. March 30, 2019. [International]

3. **Horne J**, Gilliland J, Seabrook J, O'Connor C, Madill J. Genetic-based lifestyle information and recommendations are superior to population-based guidelines for improving body composition after 3-month follow-up: Results from the NOW trial. *European Conference on Personalized Nutrition and Health*. Wageningen, Netherlands. October 8, 2019. [International]

4. **Horne J**, Gilliland J, Seabrook J, O'Connor C, Madill J. Exploring the Canadian general public's attitudes towards genetic-based lifestyle advice for weight management: Results from the NOW randomized controlled trial. *European Conference on Personalized Nutrition and Health*. Wageningen, Netherlands. October 8, 2019. [International]

5. **Horne J**, Gilliland J, Seabrook J, O'Connor C, Madill J. Genetic-based lifestyle information and recommendations are superior to population-based guidelines for improving body composition after 3-month follow-up: Results from the NOW trial. *Canadian Nutrition Society Annual Conference*. May 3-4, 2019 (**Poster Competition Finalist**). [National]

6. Veloce D, Fisher M, O'Connor C, Hartman B, **Horne J**. Does the Ontario public understand the difference between registered dietitians and nutritionists? A cross-sectional mixed methods study assessing public awareness and experiences with different nutrition providers. *Canadian Nutrition Society Annual Conference*. May 3-4, 2019. [National]

7. Hannaberg P, **Horne J**, Rinaldi S, Gilliland J, Madill J. Phase angle and malnutrition in Canadian community-dwelling adults: Preliminary results. *Dietitians of Canada National Conference*. Vancouver, BC. June 8, 2018. [National]
8. Rinaldi S, Kurowski C, **Horne J**, Hannaberg P, Brown C, Mura M, Mehta S, Madill J. Vitamin D intake and status in three patient populations: Interstitial lung disease, pulmonary hypertension and patients participating in the Group Lifestyle Balance™ weight management program. *ASPEN 2018: Nutrition Science & Practice Conference*. 2018:53-4. [International]
9. **Horne J**, Madill J, O'Connor C. Nutrigenomics: An evident need for education in the field of dietetics. *Canadian Journal of Dietetic Practice and Research*. 2015;76(3):9. [Oral Presentation by O'Connor C; National]
10. **Horne J**, Madill J, O'Connor C. Exploring knowledge and attitudes of personal nutrigenomics testing among dietetic students and its value as a component of dietetic education and practice. *Journal of Parenteral and Enteral Nutrition*. 2015:95. *ASPEN's Clinical Nutrition Week*, Long Beach, United States. [International]

Conference Presentations

Horne J. Change in weight, BMI, and body composition after 3, 6, and 12 months in a population-based intervention vs. genetic-based intervention: Results from the NOW randomized controlled trial. *ASPEN Nutrition Science and Practice Conference*. Tampa, United States. March 29, 2019. [Oral Presentation]

Horne J. Nutritional genomics: Where are we now and where do we go from here? Hamilton Health Sciences Annual Dietetics Meeting. Hamilton, Canada. June 11, 2019 [Invited Keynote]

Horne J and El-Sohemy A. Are we ready for nutritional genomics in clinical practice? Canadian Nutrition Society Annual Conference. Niagara Falls, Canada. May 4, 2019 [Invited Talk]

Horne J and Buccino J. Finding your advocacy passion and taking the first step. Dietitians of Canada: Ontario RD Networking Meeting. London, Canada. October 10, 2019 [Invited Keynote]

Caulfield T, El-Sohemy A, **Horne J**, MacKay D. Debate forum - Are we ready for personalized nutrition? International Society of Nutrigenetics and Nutrigenomics Annual Meeting, Winnipeg, Canada. October 3, 2018 [Invited Talk]

Horne J. Lifestyle genomics testing for obesity management in Canada: A critical review with implications for policy and legislation. Canadian Obesity Network: Student Meeting, London, Canada. June 22, 2018 [Oral Presentation]

Horne J. Nutrigenomics, behaviour change and The NOW Trial. Dietitians of Canada FHT Registered Dietitians and Primary Care Conference, Barrie, Canada. September 28, 2017 [Invited Talk]

Community Outreach (Oral Presentations)

Horne J. The NOW Trial Results. East Elgin Family Health Team Physician and Healthcare Professionals Meeting. Aylmer, Canada. February 13, 2020

Horne J. The NOW Trial Results. East Elgin Family Health Team Patients Meeting. Aylmer, Canada. February 13, 2020

Horne J. Nutrigenomics and the NOW Trial. SW Regional Diabetes Educators' Meeting. London, ON. June 7, 2019. [Keynote]

Veloce D, Buccino J, Sauvé A, **Horne J.** Protect "Nutritionist." Protect "Registered." Protect the Public. College of Dietitians of Ontario. Toronto, Canada. October 26, 2018.

Horne J. Nutrigenomics, Behaviour Change and The Nutrigenomics, Overweight/Obesity and Weight Management Trial. London Primary Care Dietitians' Meeting. London, Canada. December 7, 2017.

Horne J. The Group Lifestyle Balance Program and The Nutrigenomics, Overweight/Obesity and Weight Management Trial. Thames Valley FHT Quarterly Meeting. Canada. November 24, 2017.

Horne J and Madill J. The Nutrigenomics, Overweight/Obesity and Weight Management Trial. Canadian Society of Transplantation: Patient Meeting. Toronto, Canada. April 8, 2017.

Horne J. Nutrigenomics and Personalized Nutrition. Southwestern Ontario Regional Dietitians' Meeting. Woolwich, Canada. May 6, 2016.

Horne J. The Science of Nutrigenomics. RD Appreciation Day. Stratford, Canada. April 13, 2016.

Other Publications

Horne J. Nutrigenomics and weight management. Dietitians in Integrative and Functional Medicine Newsletter (Academy of Nutrition and Dietetics). *Invited.*

Horne J and O'Connor C. The truth about detox diets [guest blog post]. Weighty Matters Blog (Yoni Freedhoff). [2019]. *Invited.*

Horne J. Nutritional genomics: Genetic testing for personalized nutrition. Nutrition Nibbles (Hamilton Family Health Team). [2019]. *Invited.*

Horne J. What RDs Do. Something Nutrishus Blog. [2017]. Available from: <http://nutrishus.blogspot.com/2017/04/what-rds-do-justine-horne-msc-rd-phd.html>

Horne J and Cianfrini L. Integrating nutrigenomics into undergraduate dietetic education. Dietetic Educators' Network Newsletter (Dietitians of Canada). 2013. *Invited.*

Affiliations/Memberships

- Canadian Nutrition Society: 2018 – present
- Dietitians of Canada: 2013-2016, 2018 - present
- Ontario Respiratory Care Society: 2017 – present
- College of Dietitians of Ontario: 2015 – present
- Collegiate and Professional Sports Dietitians' Association: 2016 – 2017

Academic Conference Attendance

- ASPEN Nutrition Science and Practice Conference, Tampa, United States: March 2020
- European Conference on Personalized Nutrition and Health, Wageningen, Netherlands: October 2019
- Canadian Society of Nutrition Annual Conference, Niagara, Canada: May 2019
- International Society for Nutrigenetics and Nutrigenomics, Winnipeg, Canada: September 2018
- Canadian Obesity Network: Student Meeting, London, Canada: May 2018
- Association of Family Health Teams of Ontario Conference, Toronto, Canada: October 2017
- Dietitians of Canada Family Health Team and Primary Care RD Conference, Barrie, Canada: September 2017
- Low German Mennonite Networking Conference, Aylmer, Canada: May 2017
- Canadian Nutrition Society: Advances in Nutrition, Gut Health and the Microbiome, Toronto, Canada: January 2017
- Food and Nutrition Conference and Expo (Exhibitor), Nashville, United States: September 2015
- Canadian Association of Nephrology Dietitians National Meeting, Toronto, Canada: September 2015
- APSEN's Clinical Nutrition Week, Long Beach, United States: February 2015

Other Professional Development Activities

- Speaker, Dietitians of Canada Webinar, Nutrigenomics: Impact on Weight and Body Composition, 2020
- Intuitive Eating PRO Skills Training Course, 2019
- Speaker, Dietitians of Canada Learning on Demand course: The NOW Trial: Nutrigenomics, Overweight/Obesity and Weight Management, 2017
- Diabetes Prevention Program training, March 2017
- ASPEN pre-conference course: 'Taste Signaling – Impact on Food Selection, Intake, and Health,' February 2015
- Dietitians of Canada online courses completed:

- Critical Care Nutrition, 2015
- Population and Public Health Needs Assessment, 2014
- Herbal Supplements, 2013
- World Health Organization Growth Charts, 2012
- Crisis Prevention Institute's non-violent crisis intervention training, 2014
- Bridges Out of Poverty training, 2014
- Hope's Garden Eating Disorders Awareness Breakfast attendee, 2014

Journal Article Reviews

- *BMJ Open*, 2020: Number of works reviewed/refereed: 1
- *Medicine*, 2019: Number of works reviewed/refereed: 1
- *Lifestyle Genomics*, 2018, 2019: Number of works reviewed/refereed: 3
- *PLoS One*, 2018: Number of works reviewed/refereed: 1
- *Nutrition and Health*, 2017, 2019: Number of works reviewed/refereed: 2
- *Annals of Behavioural Medicine*, 2017: Number of works reviewed/refereed: 1