Investigating gene-gene and gene-environment interactions in the association between overnutrition and obesity-related phenotypes.

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A thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
in partial fulfillment of the requirements for the
M. Sc. degree in Epidemiology

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Abstract

Introduction – Animal studies suggested that *NFKB1*, *SOCS3* and *IKBKB* genes could be involved in the association between overnutrition and obesity. This study aims to investigate interactions involving these genes and nutrition affecting obesity-related phenotypes.

Methods – We used multifactor dimensionality reduction (MDR) and penalized logistic regression (PLR) to better detect gene/environment interactions in data from the Toronto Nutrigenomics and Health Study (n=1639) using dichotomized body mass index (BMI) and waist circumference (WC) as obesity-related phenotypes. Exposure variables included genotypes on 54 single nucleotide polymorphisms, dietary factors and ethnicity.

Results – MDR identified interactions between SOCS3 rs6501199 and rs4969172, and *IKBKB* rs3747811 affecting BMI in whites; SOCS3 rs6501199 and *NFKB1* rs1609798 affecting WC in whites; and SOCS3 rs4436839 and IKBKB rs3747811 affecting WC in South Asians. PLR found a main effect of SOCS3 rs12944581 on BMI among South Asians.

Conclusion – MDR and PLR gave different results, but support some results from previous studies.

Acknowledgements

I would like to express my gratitude to the following people who provided indispensable help in this project.

Dr Marie-Hélène Roy-Gagnon, my supervisor, for her dedicated support and constant guidance throughout the project. Merci de m'avoir fait découvrir l'épidémiologie génétique.

Dr Bénédicte Fontaine-Bisson, my co-supervisor, for generously sharing her knowledge in nutrigenomics and for providing me the opportunity to explore nutritional and genetic data.

Dr Lise Dubois, member of my Thesis Advisory Committee, for her expertise and for introducing me to nutritional epidemiology.

Jean-François Lefebvre, for his continuous technical and software support.

À Marylène Charette, pour son amour et son soutien inconditionnel à travers la maîtrise.

À Laure Tessier, pour son aide précieuse et pour m'avoir permis de découvrir l'épidémiologie.

À mes parents, Andrée Forget et Gilles Tessier, pour m'avoir toujours encouragé à me dépasser et pour tout le soutient qu'ils m'ont procuré.

Andrew Tomayer and Cheng Wang, for their support and friendship.

Table of contents

Abstract ii

Acknowledgements iii

Table of contents iv

Contribution of authors vi

List of tables vii

List of figures x

List of abbreviations xi

Chapter 1: Introduction 1

1.1 Evolutionary Hypotheses for the Obesity Epidemic 2

1.1.1 Thrifty Gene Hypothesis 2

1.1.2 Drifty Gene Hypothesis 3

1.1.3 Thrifty Phenotype Hypotheses and the Thrifty Epigenome Hypothesis 4

1.1.4 Behavioral Switch Hypothesis 4

1.1.5 Importance of the Evolutionary Origins of the Obesity Epidemic 6

1.2 Genetic Epidemiology and the "Missing Heritability" 6

1.3 The Hypothalamic IKKβ/NF-κB Signaling Pathway 8

1.4. Genes of interest for this study 11

Chapter 2: Hypothesis and Objectives 12

Chapter 3: Methods 13

3.1 Study population 13

3.2 Dietary assessment and environmental exposure variables 14

3.3 Anthropometric measurements and outcome variables 15

3.4 Physical activity assessment 16

3.5 Selection of tagging SNPs and genotyping 17

3.6 Statistical analysis 17

3.6.1 Logistic regression 17

3.6.2 Multifactor dimensionality reduction 18

3.6.3 Penalized logistic regression 21

3.6.4 False Discovery Rate 22

3.6.5 Statistical analysis software 23

Chapter 4: Results 24

4.1 Results: Logistic regression models 25
4.2 Results: MDR models 28
4.2.1 Gene-gene interactions MDR models 28
4.2.2 Gene-environment interaction MDR models 31
4.3 Results: PLR models 32
Chapter 5: Discussion 34
5.1 Gene-gene interaction models 37
5.2 Gene-environment interaction models 39
5.3 Strengths and limitations 42
5.6 Conclusion 45
Tables 46
Figures 155
References 159
Appendix 1: Ottawa Health Science Network Research Ethics Board approval letter 165
Appendix 2: Ethics approval from the University of Toronto 166
Appendix 3: General health and lifestyle questionnaire 167
Appendix 4: Food frequency questionnaire 174
Appendix 5: FFQ instructions and serving sizes 199

Contribution of authors

The supervisors, Marie-Hélène Roy-Gagnon and Bénédicte Fontaine Bisson, designed the project with input from the student, François Tessier. The Toronto Nutrigenomics and Heath study database was accessed through a collaboration with Ahmed El-Sohemy (University of Toronto). François Tessier conducted all analyses. Jean-François Lefebvre, Dr. Roy-Gagnon's research assistant, provided guidance on the use of the required specialized statistical software.

List of tables

Table 1. General characteristics of study participants by high/low BMI and high/low WC categories (n=1512)

Table 2. General characteristics of study participants using alternate BMI cut-offs (n=1512)

Table 3. Allele frequencies stratified by population

Table 4. Allele frequencies stratified by population and BMI

Table 5. Allele frequencies stratified by population and WC

Table 6. Allele frequencies stratified by population and alternative BMI

Table 7. Odds ratios from logistic regression models of dichotomized BMI unadjusted and adjusted for covariates

Table 8. Odds ratios from logistic regression models of dichotomized WC unadjusted and adjusted for covariates

Table 9. Odds ratios of logistic regression models of alternate dichotomized BMI unadjusted and adjusted for covariates

Table 10. Odds ratios from logistic regression models of dichotomized BMI unadjusted and adjusted for age and sex only

Table 11. Main effect logistic regression models of dichotomized BMI

Table 12. Main effect logistic regression models of dichotomized WC

Table 13. Main effect logistic regression models of alternate dichotomized BMI

Table 14. Gene-gene interaction logistic regression models of dichotomized BMI

Table 15. Gene-gene interaction logistic regression models of dichotomized WC

Table 16. Gene-gene interaction logistic regression models of alternate dichotomized BMI

Table 17. Gene-gene interaction logistic regression models of dichotomized BMI considering only whites

Table 18. Gene-gene interaction logistic regression models of dichotomized BMI considering only East Asians

Table 19. Gene-gene interaction logistic regression models of alternative dichotomized BMI considering only South Asians

Table 20. Gene-gene interaction logistic regression models of dichotomized WC considering only whites

Table 21. Gene-gene interaction logistic regression models of dichotomized WC considering only East Asians

Table 22. Gene-gene interaction logistic regression models of dichotomized WC considering only South Asians

Table 23. Gene-gene interaction logistic regression models of alternate dichotomized BMI considering only whites

Table 24. Gene-gene interaction logistic regression models of alternate dichotomized BMI considering only East Asians

Table 25. Gene-gene interaction logistic regression models of alternate dichotomized BMI considering only South Asians

Table 26. Gene-environment interaction logistic regression models of dichotomized BMI

Table 27. Gene-environment interaction logistic regression models of dichotomized WC

Table 28. Gene-environment interaction logistic regression models of alternate dichotomized BMI

Table 29. ORs of the most significant gene-gene interaction with logistic regression

Table 30. ORs of the most significant gene-environment interaction with logistic regression

Table 31. MDR models of two- and three-fold gene-gene interactions considering all ethnicities

Table 32. MDR models of two- and three-fold gene-gene interactions considering only whites (n=665)

Table 33. MDR models of two- and three-fold gene-gene interactions considering only East Asians (n=450)

Table 34. MDR models of two- and three-fold gene-gene interactions considering only South Asians (n=149)

Table 35. MDR models of two- and three-fold gene-environment interactions considering all ethnicities

Table 36. MDR models of two- and three-fold gene-environment interactions considering only whites (n=660)

Table 37. MDR models of two- and three-fold gene-environment interactions considering only East Asians (n=448)

Table 38. MDR models of two- and three-fold gene-environment interactions considering only South Asians (n=144)

List of figures

Figure 1. Diagram of the hypothalamic regulation of satiety and hunger

Figure 2. MDR contingency table of the 3-fold gene-gene interaction model of high/low BMI (whites only)

Figure 3. MDR contingency table of the 2-fold gene-gene interaction model of high/low WC (whites only)

Figure 4. MDR contingency table of the best 2-fold gene-gene interaction model of high/low WC (South Asians only)

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List of abbreviations

BMI: Body mass index

CV: Cross-validation

GWAS: Genome-wide association studies

HWE: Hardy-Weinberg equilibrium

MDR: Multifactor dimensionality reduction

OR: Odds ratio

PLR: Penalized logistic regression

SNP: Single nucleotide polymorphism

WC: Waist circumference

WHO: World Health Organization

Chapter 1: Introduction

In January 2016, the World Health Organization (WHO) published the report entitled *Ending Childhood Obesity*, stating that the obesity rate had nearly doubled since 1990 in African countries. (1) This report raised the troubling fact that the obesity epidemic – once thought of being a burden of developed countries – is now affecting developing countries. (1) Adding to the concerning situation, another recent study investigating data from 19.2 million adult participants indicates that, if the current trends of obesity prevalence worldwide continue, the global prevalence of obesity will surpass 18% in men, and 21% in women by 2025. (2) As for Canada, 20.2% of Canadians aged 18 and older were classified as obese in 2014, according to Statistics Canada based on the results of the Canadian Community Health Survey. (3) Furthermore, the rate of obesity among men has dramatically increased since 2003, jumping from 16.0% to 21.8% in 2014. (3) Canadian women have also seen an increased in their obesity rate since 2003, rising from 14.5% to 18.7% in 2014. (3)

These alarming reports illustrate the gravity of the obesity epidemic's fallout on public health systems worldwide, and how a better understanding of obesity pathogenesis could help to improve public health interventions. (4) Obesity is often described as the result of an energy imbalance between energy intake and energy expenditure. (5,6) However, this simplified explanation of obesity disregards the complex pathogenesis of this common disease, which includes multiple factors of biological, behavioral and sociological nature. (4,6,7) Thus, there is no simple solution to address this burden, and there is no consensus on the strategy to follow to properly manage this epidemic. (4,7) However, recent advances in genetics might offer promising new approaches on targeted interventions. (8)

This research project explores the involvement of genes that might offer promising leads for the development of new interventions and treatments against obesity pathogenesis. In this introduction, we will present a summary of the evolutionary hypotheses of the obesity epidemic, discuss the progress of genetic studies on obesity, explain the role of the hypothalamus and the IKKβ/NF-κB signaling pathway in the pathogenesis of obesity, introduce the genes of interest of this study, and present the study hypothesis and objectives.

1.1 Evolutionary Hypotheses for the Obesity Epidemic

1.1.1 Thrifty Gene Hypothesis

The most popular and accepted hypothesis of the evolutionary origins of the obesity epidemic by researchers is the thrifty gene hypothesis. (9,10) However, presently there is little research supporting this hypothesis with convincing evidence. (9) The thrifty gene hypothesis was first proposed by geneticist James Neel in 1962. (11) This hypothesis suggests that obesity (or other metabolic syndrome related traits, such as diabetes) is an adaptive trait that became a "side effect" of human evolution with the advent of industrialization and modern lifestyles. (5,9) It is based on the assumption that during the vast majority of human history, people were living under alternating periods of feast and famine. (5,9,12) Hence, evolution would have selected individuals with genes enabling better storage of fat to face these famines. (5,9,11) After the second agricultural revolution (coinciding with the Industrial Revolution), the lifestyle of developed countries changed drastically, resulting in a lifestyle where food is easy to access and very little energy is expended for its procurement. (5,12) Thus, the environment changed, but not the thrifty genes that are still contributing to energy storage, preparing for a famine that may never come. (9,11)

The thrifty gene hypothesis has many criticisms (e.g. it doesn't explain the heterogeneity of obesity between and within populations). (9) One of the most important criticisms states that if the feast/famine cycle was really an evolutionary driving force throughout humankind history, then the vast majority of humans should be obese by now. (9,13) This argument, supported by statistical models, was proposed by biologist John Speakman. (13) He argues that thriftiness is a post-agricultural adaptation and not enough time has passed for it to be the explanation of the obesity epidemic. (9,13) Based on this argument, Speakman has suggested a counter hypothesis of the obesity epidemic called the drifty gene hypothesis. (9,14)

1.1.2 Drifty Gene Hypothesis

This hypothesis is based on the assumption that human ancestors were subject to strong predation pressure, and that a reduced body size (thus a reduced energy intake) was an advantage in the presence of predators. (9,14,15) This idea comes from evidence that predation has an effect on weight regulation in prey animals. (14) Prey mammals have been observed to have reduced body size and foraging time in the presence of predators. (9,14,15) However, for modern humans, since predation no longer has an important selective pressure on being lean, genes controlling the upper limit of body weight are no longer a disadvantage. (9,14) Thus, these genes were freed from predation selective pressure, and subject to genetic drift. (9,14)

Supporters of the thrifty gene hypothesis have criticized Speakman's hypothesis, particularly emphasizing the fact that he failed to take into consideration the effect of famine on women's fertility. (9) They suggested that the thrifty gene hypothesis could still be viable if we consider that metabolic thriftiness could have been driven by the effect of starvation on female fertility, and not solely mortality as proposed before. (9) This argument is supported by historical events observed

in modern day Gambia and Bangladesh where the fertility decreased from 30 to 50 percent following a normal famine season. (9,16)

1.1.3 Thrifty Phenotype Hypotheses and the Thrifty Epigenome Hypothesis

Other hypotheses have adopted the idea of thriftiness to explain the obesity epidemic. (9) The thrifty phenotype hypotheses (many variations of this idea exist) and the thrifty epigenome hypothesis are both related to the thrifty gene hypothesis, and they tend to complete each other. (9) Briefly, the thrifty phenotype hypotheses suggest that the thriftiness is due to the fetus development: the future adult phenotype is the result of the predicted adult environment through fetal environment signals (mostly through intrauterine nutritional signals). (9) The thrifty epigenome hypothesis is basically the link bringing together the thrifty gene and thrifty phenotype hypotheses: the phenotypic expression of humans' thrifty genotypes is the result of epigenetic factors in relation to their environment, mostly intrauterine signals (9) Epigenetics are the mechanisms which modify gene expression, without changing the genetic code itself. (17) Examples of these mechanisms are DNA methylation and histone modifications. (17) The thrifty epigenome hypothesis was developed by Stöger (2008) as a way to understand the complex gene-environment interactions underlying obesity and type 2 diabetes . (17)

1.1.4 Behavioral Switch Hypothesis

The behavioral switch hypothesis argues that insulin resistance is a sociological adaptation playing the role of mediator for two phenotypic transitions. (18) The first is a transition in reproductive strategy from the "r" to the "K" strategy. (18) The "r" reproductive strategy means

that individuals have a large number of offspring, but have little time to invest in them. (18) The "K" reproductive strategy means the opposite; the individuals have a smaller number of offspring, but have more time to invest in each. (18) The second transition is one of lifestyle: it is a transition from "stronger to smarter", or "soldier to diplomat". In other words, it is a transition from a lifestyle depending on muscle tissue to a lifestyle depending on the brain. (18) In order for these transitions to take place, they both need a common switch that is the byproduct of a socio-economic adaptation. (18) This common switch is thought to be insulin resistance. (18) The authors of this hypothesis argue that insulin resistance is the common switch, because it plays the role of energy allocation in different tissues. (18)

Succinctly, the pathogenesis starts when intense "diplomat" lifestyles – such as in developed countries lifestyles – create a high insulin sensitivity, due to the large amount of energy intake and little energy output (highly accessible food and sedentary lifestyle). (9,18) Therefore, the body achieved unprecedented levels of stimuli, which exaggerates the biological response and leads to pathology. (18) Among others, the outcome of this exaggerated biological response is a slowed wound healing and an increase in inflammatory responses that both contribute to the pathogenesis of the metabolic syndrome and obesity. (9,18) The strengths of this hypothesis is that it explains some of the physiological mechanism and epidemiological patterns that the thriftiness hypothesis was not able to explain. (18) It is also an answer to the review of all known genes predisposing to obesity by O'Rahilly and Farooqi, who concluded that predisposition for obesity was more neuro-behavioral than metabolic. (18,19)

1.1.5 Importance of the Evolutionary Origins of the Obesity Epidemic

The hypotheses of the obesity epidemic's evolutionary origins described above are among the most cited ones, but others exist. (13,20–22) Until now, none of these hypotheses has been entirely confirmed by researchers. (9) In addition, they are not necessarily incompatible with each other, and they might contribute to obesity pathogenesis on different levels. (9) Understanding the evolutionary origins of the obesity epidemic implies a better understanding of the pathogenesis of the disease, consequently of its underlying genetics. (8,9) The genes explored in this project could potentially be involved in any of these obesity epidemic hypotheses – based on their biological involvement explained in section 1.3 – and understanding their mechanisms might give new perspectives for public health interventions by a better identification of at risk individuals, and by opening new horizons for new clinical treatment of obesity.

1.2 Genetic Epidemiology and the "Missing Heritability"

Genetic factors are known to be partly responsible for the pathogenesis of obesity, and they have been highly investigated in order to confirm the evolutionary origin of obesity, but also to better understand the biological mechanisms involved and to develop treatments. (23) Genetic factors contribution to obesity pathogenesis is hypothesized to influence the metabolism and the control of appetite. (23) With the introduction of genome-wide association studies (GWAS) in 2005, many studies have been conducted on obesity and related traits, resulting in the identification of 32 loci in association with body mass index (BMI), and 14 loci with BMI-adjusted waist-to-hip ratio in populations of European descent. (8) GWAS also found loci near key hypothalamic regulators of energy balance associated with BMI, suggesting that genetic variation in the central control of metabolism plays an important role in the obesity risk. (24) However, GWAS of obesity-

related traits have been disappointing, giving effect sizes of the associated loci smaller than anticipated. The combined effect of the identified risk alleles explained only ~1.45% of the heritability of BMI. (8) Of all the genes, the largest effect identified has been from the *FTO* gene (0.34%). (8,25) Homozygotes for the at-risk *FTO* allele have 1.67 times the risk of being obese compared to the homozygotes for the normal allele. (25) In 2013, Karra et al. found that the *FTO* gene is associated with obesity by regulating ghrelin, a hormone playing a significant role in the regulation of appetite. (26)

Unsatisfactory results of GWAS studies related to complex disease have been speculatively explained by the so-called "missing heritability", which means that the risk of a disease might be generated by more than just the combined additive effect of the risk alleles. (8) One potential mechanism underlying the "missing heritability" are gene-gene and gene-environment interactions. (8) The primary goal of this project is to explore gene-gene and gene-environment interactions of candidate genes implicated in the hypothalamic IKKβ/NF-κB signaling pathway in the association between overnutrition and obesity-related traits.

In order to detect interactions between multiple genes, or with environmental factors, several methods and software packages have been developed during the last decade. (27,28) The main reason for developing these new methods is because standard statistical methods cannot handle high order interactions or lack power to detect their effect. For instance, logistic regression suffers from such limitations when a large number of potential interaction terms are considered. It can create overfitting problems, possible correlation between factors (when many candidate loci are involved), and interaction terms resulting in empty or small number categories. Also, because a larger number of variables are usually assessed in genetic epidemiology studies, conservative adjustment for multiple comparisons have to be used, such as Bonferroni correction. (29) The

purposes of these alternative statistical methods are to increase power to detect statistical interactions between loci or environmental factors, and to help underpin the biological or biochemical pathway of complex disease. (27,28) Because of the large number of new methods and software packages developed, it is often common that some have not been applied to real data. In this research project, we decided to investigate gene-gene and gene-environment interactions using two alternative methods, multifactor dimensionality reduction (MDR) and penalized logistic regression (PLR).

1.3 The Hypothalamic IKKβ/NF-κB Signaling Pathway

The hypothalamus is a structure of the brain located below the thalamus, and has a central role in energy homeostasis. (10,30,31) Regulation of energy homeostasis is mostly done by specialized neurons in the mediobasal hypothalamus. (30) These neurons control the secretion of neuropeptides that are crucial for normal energy balance – hence, prevention of obesity – through long-term regulation of appetite. (30,31) Their secretions are regulated by the levels of two hormones in the hypothalamus: leptin and insulin. (30,31)

Leptin is a hormone produced by adipocytes, and its role is to regulate long-term appetite signals, depending on the fat reserves available. (10,31) It is secreted in response to an increase in fat levels in the body and serves as an indicator to inform the hypothalamus about the quantity of available energy. (31) High leptin levels suppress hunger through the inhibition of orexins secretion in the lateral hypothalamus area, and stimulate satiety through the stimulation of corticotropin-releasing hormone secretion in the ventromedial nucleus of the hypothalamus. (10,31) Hence, high leptin levels contribute by extension to reduce food intake, and increase energy expenditure. (10,31) Low leptin levels (which are normally obtained when adipocytes are

low in fat) increase the appetite by not inhibiting the secretion of orexins, and thus also contribute to an increase in food intake, and reduce energy expenditure. (10,31) Dysfunction of leptin can therefore contribute to obesity pathogenesis; studies on mice have shown that mutants for the *ob* gene, which codes for leptin, were not able to produce sufficient amount of leptin, and gained weight. (10)

Insulin is a hormone secreted by beta cells of the pancreas, and its role is to assist the body cells with the consumption of glucose when glucose blood levels are elevated. (10) Insulin, like leptin, also contributes to the long-term control of appetite. (31) Both hormones inhibit the secretion of neuropeptide Y in the arcuate nucleus of the hypothalamus, a peptide that participates in the stimulation of hunger by stimulating the secretion of orexins, and by stimulating the secretion of melanocortins. (31,32) However, insulin is thought to have less effect than leptin on the inhibition of appetite. (31) Thus, if leptin and insulin are blocked or absent in the neurons of the mediobasal hypothalamus, it will result in an increase in appetite. (31,32) Figure 1 shows a diagram of insulin/leptin role in long-term regulation of appetite.

Genetic mouse models have revealed that the loss of insulin or leptin in the hypothalamus contributes to the pathogenesis of obesity and type 2 diabetes. (32–37) In individuals affected by obesity or type 2 diabetes, researchers have observed hyperlipidemia, hyperinsulinemia, but also high insulin and leptin levels in their cerebrospinal fluid, meaning that they are also suffering from leptin and insulin resistance in the hypothalamus. Furthermore, other studies have dissociated overnutrition from obesity, showing that overnutrition alone decreases the hypothalamic sensibility to leptin and insulin – even before the onset of obesity. (32,38,39)

In summary, hypothalamic insulin and leptin resistance contributes to the pathogenesis of obesity, which can be triggered by overnutrition. (9,16,30,40,41)

Overnutrition and obesity are known to be associated with inflammation, which will also contribute to the insulin and leptin resistance. (30,41) Indeed, studies have demonstrated that overnutrition induces an inflammation reaction in peripheral metabolic tissues, contributing to health problems related to type 2 diabetes. (32,40,41) IKKβ/NF-κB signaling pathway is a mediator of the metabolic inflammation participating in this peripheral reaction, and it was also studied for its involvement in immunologic responses. (42) In its latent form, NF-κB, a transcription factor, is linked to its inhibitors in the cytoplasm, IκB proteins. (32,42) When activated, IKKβ phosphorylates these inhibitors (the IκB proteins) and enables NF-κB to translocate to the cell's nucleus, and allows the transcription of multiple genes coding for proteins involved in immune or inflammatory response and cell growth. (32,42) In peripheral metabolic tissues, it was also found that IKKβ/NF-κB affected the metabolism of glucose and proteins in specific tissues. (43–45) More recently, Zhang et al. (2008) have shown that the IKKβ/NF-κB pathway is also implicated in the central nervous system, and contributes to the pathogenesis of obesity. (32) They found that neurons in the hypothalamus were enriched with inactive IKKβ/NF-κB. (32) However, overnutrition seems to activate hypothalamic IKKβ/NF-κB, which contributes to inhibiting insulin and leptin signaling. (32) Hence, activation of hypothalamic IKKβ/NF-κB pathway creates insulin/leptin resistance, which contributes to the pathogenesis of obesity by disrupting the normal appetite inhibition (Figure 1). (32) They also found that the inhibition of IKKβ (which allows activation of the NF-κB complex) in the brain or specifically in the mediobasal hypothalamus had a protective effect against glucose intolerance and obesity pathogenesis. (32) They established that the effect of the hypothalamic IKKβ/NF-κB pathway on obesity was also accomplished through the activation of SOCS3, an inhibitor of insulin and leptin signaling. (32)

1.4. Genes of interest for this study

The three genes of interest for this study are *nuclear factor kappa B subunit 1* (*NFKB1*), *inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta* (*IKBKB*), and *suppressor of cytokine signaling 3* (*SOCS3*). They are all part of the obesogenic IKKβ/NF-κB hypothalamic signaling pathway previously described. *NFKB1* codes for the subunit 1 of the NF-κB protein complex. (46) *IKBKB* codes for the IKKβ protein that phosphorylates the inhibitor of the NF-κB complex, allowing it to be activated. (47) The downstream gene of the IKKβ/NF-κB hypothalamic signaling pathway, *SOCS3*, codes for a protein of the same name acting as an inhibitor of insulin and leptin signaling. (32)

The role of these three genes through the IKKβ/NF-κB hypothalamic signaling pathway in obesity pathogenesis have only been shown in mouse models. (32) In humans, only *SOCS3* has been investigated, and few studies have found evidence of an association with obesity-related phenotypes. (48,49) While *NFKB1* and *IKBKB* have been associated with various types of cancer, they have not been investigated in the context of obesity-related phenotypes. (42) Because evidence for genetic effects have been detected in animal and human models, we will focus on identifying the potential causal SNPs of these three genes involved in interactions.

Chapter 2: Hypothesis and Objectives

We hypothesized that polymorphisms in genes involved in the hypothalamic IKKβ/NF-κB signaling pathway (*NFKB1*, *SOCS3*, *IKBKB*), alone or in interaction with nutrients, are associated with energy imbalance and obesity pathogenesis in humans. Furthermore, we hypothesize that these interactions will be better detected using alternative, machine learning approaches. The objectives of this study are to:

1) Investigate gene-gene and gene-environment interaction involving *NFKB1*, *IKBKB*, and *SOCS3* in the association between overnutrition and obesity-related phenotypes.
2) Use alternative approaches, such as MDR, and PLR models to better detect interactions than standard logistic regression.

Chapter 3: Methods

3.1 Study population

The present study is a secondary analysis of data from the Toronto Nutrigenomics and Health Study. Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board (Appendix 1) and from the University of Toronto (Appendix 2). Study population and data collection were previously described (50,51). In brief, participants were from the Toronto Nutrigenomics and Health Study, a multiethnic cohort composed of 1639 young adults aged 20-29 years. Subjects were recruited on the University of Toronto campus through postings and advertisements between September 2004 and July 2009. (50) Participants completed a general health and lifestyle questionnaire (Appendix 3), and a food frequency questionnaire (FFQ) (Appendix 4). (50) Individuals who may have underreported (<800 kcal/day) or overreported (>3500 kcal/day for women, >4000 kcal/day for men) their daily energy intakes were excluded (n=124). These daily energy intake cut-offs are based on biological limits used in previous studies using the Toronto Nutrigenomics and Health Study data. (50,51) Participants with missing data for the outcome variables were also excluded (n=3). After exclusions, 1512 participants remained (1033 women, and 479 men).

Subjects were asked an open-ended question to determine their ethnocultural status. (51) Then, they were classified into 4 ethnocultural groups based on their self-reported status: 733 whites (237 men, 496 women), 509 East Asians (142 men, 367 women), 160 South Asians (65 men, 95 women), and 110 others (35 men, 75 women). Whites included European, Middle Eastern, and Hispanic. East Asians were composed of Chinese, Japanese, Korean, Filipino, Vietnamese, Thai, and Cambodian. South Asians comprised Bangladeshi, Indian, Pakistani, and Sri Lankan. The "other" group was composed of participants belonging to ≥ 2 of the 4 ethnocultural groups,

or First Nations Canadians or Afro-Caribbeans. These 4 ethnocultural group definitions were used in the previous investigations using the Toronto Nutrigenomics and Health Study data. (50,51)

3.2 Dietary assessment and environmental exposure variables

Dietary intake was assessed using a modified Willett FFQ. This questionnaire is a 196 items semi-quantitative "Toronto-modified" Willett questionnaire, developed to improve the assessment of foods that contribute to glycemic index and caffeine. (51) Each subject was given instructions on how to complete the FFQ (Appendix 5), and asked to choose one of several frequency options corresponding to their usual monthly intake of different types of food, beverages and dietary supplements. To help the participants, a commonly used portion size (e.g. half a cup) was given to each item. The macronutrient intakes were then estimated in kilocalories using the USDA Nutrient Database for Standard Reference, and daily estimates of total calories, carbohydrates, fat, protein and alcohol intakes were derived from each participant. (51,52)

In order to adjust each macronutrient (carbohydrate, fat, protein, and alcohol) for a total energy intake, we used the residual method as proposed by Willett and Stampfer. (53) This method simply uses the residual of the regression of the macronutrient intake of interest on total caloric intake, which gives a measure of the nutrient intake that is independent of the total energy intake. (53,54) This adjustment is particularly important to do when energy intake is associated with the disease of interest. We used the residuals of the macronutrients on total caloric intake as environmental exposure variables in all analysis.

3.3 Anthropometric measurements and outcome variables

Anthropometric measurements were taken by trained personnel with the participants dressed in light clothing without shoes. (51) Waist circumference (WC) was measured between the lowest rib and the iliac crest, and was measured twice to the nearest 0.1 cm. The mean of the two measurements was then calculated. If the difference between the two measurements was ≥1 cm, a third measurement was taken. Then, the two WC measurements with the smallest difference were taken to calculate the mean WC. Weight was measured to the nearest 0.1 kg using a digital scale (model Bellissima 841, Seca Corporation, Hanover, MD), and height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (model Seca 206, Seca Corporation, Hanover, MD). Subsequently, BMI (kg/m^2) was calculated for each participant.

BMI and WC were used to define outcome variables related to obesity phenotypes. Both were dichotomized in order to compare the standard MDR methods, which can only handle a binary outcome, to logistic regression and PLR. (55) BMI was dichotomized into a high BMI category, composed of participants considered as overweight and obese (BMI $\geq$ 25.0 kg/m^2), and a low BMI category, composed of participants with a normal BMI and underweight (BMI < 25.0 kg/m^2). This dichotomized BMI is based on the BMI cut-off points recommended by WHO and the National Institutes of Health. (56,57) However, since it is now well known that standard BMI threshold might not be appropriate for individuals of East Asian and South Asian ethnicity, an alternate BMI definition was used to make a comparison with the standard BMI definition in a sensitivity analysis. This alternate BMI definition uses the dichotomized BMI threshold stated before for white individuals, but categorizes East Asian and South Asian individuals in the high BMI group if BMI $\geq$ 23.0 kg/m^2, and in the low BMI group if BMI < 23.00 kg/m^2. This alternate BMI is based on a WHO expert consultation which recommended BMI cut-off points for the Asian

population. (58) They have identified a lower BMI cut-off point for overweight individuals (23.0 $kg/m^2 \leq BMI < 27.5\ kg/m^2$), and obese ($BMI \geq 27.5\ kg/m^2$), among others on the continuum of BMI. However, WHO experts recommend to still use the current WHO BMI cut-off points, particularly in countries with concurrent problems of undernutrition and overnutrition, since the new cut-off points are still up to debate, and more research is needed on this matter.

For WC, WHO's definition of a high WC was not used since very few participants were considered having high WC. This is probably because participants were young; maybe the hypothetical biological effect of genes under study was just starting to have some real effect on these young adults, and they were only starting to gain weight. Therefore, we used the last quartile of the WC distribution to define a high WC group. Since the usual WC cut-offs are different for men and women, we stratified the WC distributions by sex. Hence, participants with high WC for men were defined as $WC \geq 85.25$ cm, and otherwise they were considered as low WC. High WC for women included participants with $WC \geq 74.73$ cm, and otherwise they were categorized in the low WC group. As with BMI, alternate WC cut-off points have been proposed for Asian populations. (59) However, we do not have enough participants that would fit the high WC definition (< 30) to appropriately apply the multifactor dimensionality reduction method in this study; using the standard WC definition would have resulted in numerous empty or nearly empty cells, and thus numerous invalid MDR models. Hence, we used only one definition of high WC, i.e., the last quartile stratified by sex definition as described above.

3.4 Physical activity assessment

Physical activity levels were assessed using the general health and lifestyle questionnaire and expressed as modifiable metabolic equivalent of task (MET) hours per week. (51) Specifically,

the questionnaire aimed to estimate the total hours spent in light, moderate, and vigorous physical activity on a typical weekday and weekend day over the past month. (60) This measure represents leisure and occupational activity, but not sedentary hours of sleeping or sitting. (51) One MET is equivalent to 1 kcal spent per kilogram of body weight per hour of sitting at rest. (61)

3.5 Selection of tagging SNPs and genotyping

Tag SNP selection was made using HapMap release 27 and Haploview 4.2, and Multiplex genotyping was performed using Sequenom at Princess Margaret Hospital. An initial 54 single-nucleotide polymorphisms (SNPs) were selected among the three genes of interest: 27 for *SOCS3*, 18 for *NFKB1*, and 9 for *IKBKB*. First, we tested for Hardy-Weinberg equilibrium (HWE). All tag SNPs were in HWE (HWE test p-value > 0.01). Afterwards, we excluded 30 SNPs with minor allele frequency <5%. Finally, 4 SNPs were excluded because they were in high linkage disequilibrium ($R^2 > 0.8$). The final SNPs selection was 8 for *SOCS3*, 9 for *NFKB1*, and 3 for *IKBKB*. SNPs effects were coded as an additive effect for logistic regression models, but were considered as discrete variables for MDR (since it can only handle discrete variables) and PLR. (62)

3.6 Statistical analysis

3.6.1 Logistic regression

Logistic regression was used to investigate genetic main effects, environment (macronutrients) main effects, two-fold gene-gene interactions, and two-fold gene-environment interactions. Genetic main effect, and gene-gene interaction models were adjusted for age,

ethnocultural groups, and sex. Environment main effect, and gene-environment interaction models were adjusted for age, ethnocultural group, physical activity, and sex.

Logistic regression is a classic method for modelling effects and interactions for a binary outcome, but since this study includes a large number of potential interaction terms, this method may not be the most appropriate approach. (62,63) Including a large number of interactions in logistic regression models requires many parameters that can result in overfitting problems.(62,64) Other problems come from the possible correlation between factors (when many candidate loci are involved), and from interaction terms resulting in small or null frequencies. (62) For these reasons, we used the alternative methods below.

3.6.2 Multifactor dimensionality reduction

Multifactor dimensionality reduction (MDR) is a technique used for detecting gene-gene and gene-environment interactions in common, complex genetic diseases developed by Ritchie et al. (2001). (65) MDR is a nonparametric and model-free method that transforms a high-dimensional multilocus model (including genetic and/or environmental factors) to a one-dimensional model. (65) Hence, it offers an alternative method to overcome logistic regression's problems of sparse data cells. (65)

The MDR algorithm works with discrete genetic/environmental factors and a dichotomous disease status. (65) Its goal is to find the best interaction order *K* and the best set of *K* factors that determine disease status. (65) To find the best set of factors for each *K* fold interactions, MDR uses cross-validation (CV), by default a 10-fold CV. The following are the steps of the tenfold CV used to find the best set of factors:

1. Training and testing parts: MDR uses 9/10 of the data as the training part, and 1/10 as the testing part.
2. High-risk/low-risk contingency table: For every possible set of *K* factors, MDR creates in the training part (9/10) a contingency table based on the cases and the controls. Each cell of this table is then labelled as *high-risk* if the case/control ratio is greater than 1. The other cells are labelled *low-risk*.
3. Training error: MDR classifies the *high-risk* as cases, and the *low-risk* as controls. Based on this, it then computes the training error of the training part (9/10).
4. Prediction error: Using the testing part (1/10), MDR calculates the prediction error of the set of *K* factors with the lowest training error.

These 4 steps are repeated for each CV fold (as mentioned above, by default a tenfold CV). The steps above described the CV process; the following steps are the general steps of the MDR algorithm:

1. Tenfold CV for each *K*: A tenfold CV for each interaction order *K* is used to find the best set of *K* factors; this step corresponds to the 4 steps that we have just enumerated.
2. Prediction errors and consistencies comparison: For each different *K*, the prediction errors and the CV consistencies (how many times the best set of *K* factors was selected in the 10-fold CV) are compared.
3. Final multifactor model: The selection of the best multifactor model is done by selecting the *K* with the smallest prediction error and/or the largest CV consistency.

For MDR models with BMI and WC, the best models will be retained by evaluating two outputs of the MDR software: the average testing accuracy and the CV consistency. The average

testing accuracy and prediction error are interchangeable terms, where the testing accuracy is 1-prediction error. The testing accuracy can also be defined as:

$$(TP + TN)/(TP + TN + FP + FN)$$

where TP are true positives, TN are true negatives, FP are false positives and FN are false negatives. The models with the highest average testing accuracy (which is the proportion of individuals that are correctly classified as being a case or a control, averaged across all CV intervals) and CV consistency. The latter is usually used as a tie breaker, and to indicate a certain degree of bias in the average testing accuracy, since a CV consistency <10 indicates that at least one CV interval contributes to the average testing accuracy with a testing accuracy estimated from a different model (e.g. the factors selected are different). Therefore, models with an average testing accuracy under 55% will be considered as invalid, since an average testing accuracy of around 50% is what you would expect if the case-control status was determined by flipping a coin. In other words, these models are unlikely to generalize to independent data, and will not be retained as a best model. Another criterion to be selected as a best model is a CV consistency > 6, since low CV consistency means that the variables presented by MDR have only been selected a few times during the CV. Thus, the average testing accuracy of models with low CV consistency is calculated with models composed of different variables. Contingency tables of the selected best models will be evaluated to ensure that no empty cells or nearly empty cells are in the models.

Some strengths of this approach are its capacity to detect multiple genetic loci simultaneously and keeping false-positive rate low. (63) It is a model-free approach, which is advantageous when the mode of inheritance is unknown. The CV used in this method minimizes the false positives rate, and the power remains high with some genotyping error and/or missing

data (~5%). (63,65) Also, the number of interactions does not grow exponentially with every new variable added, which is one of the important problems with research covering epistatic interactions due to the exponential increase of interactions as the number of SNPs increases. (63–65) Regarding its limitations, the MDR method has reduced power when high phenocopy/genetic heterogeneity exists, it can be strongly influenced by missing data and it is computationally intensive when the number of genetic/environmental factors tested increases. (27,63) Also, MDR can be difficult to interpret, since it classifies genotypes/environmental factors into high risk and low risk, but it doesn't have a quantitative assessment of high or low this risk. (63)

3.6.3 Penalized logistic regression

Penalized logistic regression (PLR) is a parametric approach using a L2 regularization to detect gene-gene interaction developed by Park and Hastie (2008).(62) L1 and L2 regularization are used to reduce model overfitting. The goal of L1 and l2 regularization is to reduce overfitting by preventing the model weights from becoming too small or too large. (67,68) L1 and L2 penalization are different with the L1 penalty resulting in regression coefficients shrunk toward zero and set some of them to zero, and the L2 penalty resulting in small but non-zero regression coefficients. (67,68)

Their method includes a variable selection done by a forward stepwise procedure: a forward selection followed by backward deletion. (62,69) The final model is the one with the smallest score C. (62,69) This score is C = deviance + cp x *df*. Cp is the complexity parameter; it is by default 2. (62,69) *Df* is the effective degrees of freedom. (62,69)

The advantages of PLR are that it can handle the problems that traditional logistic regression usually struggles with (overfitting and zero cells), and, in contrast to MDR, is easier to interpret. (62,69) However, as noted by Hue et al. (2009), PLR does not seem to perform well when the interaction patterns among the SNPs are complex, contrary to MDR. (69)

3.6.4 False Discovery Rate

False discovery rate (FDR) was used to control for multiple comparisons with the logistic regression models. FDR can be defined as "the expected proportion of false positives among all significant hypotheses". (70,71) Methods that account for FDR control the expected proportion of discoveries that are false (or false positives, type I error). (70,71)

FDR can be defined as: (70)

$$\mathrm{FDR} = \mathrm{E}\left[\frac{F}{F+T}\right] = \mathrm{E}\left[\frac{F}{S}\right]$$

where F is the number of false discoveries, T the number of true discoveries, and S the total number of discoveries. (70) A result is considered as significant when its p-value is less than or equal to a certain threshold, $t \in [0,1]$, which can be fixed or data-dependent. (70,71) Quantifying a desired error rate is needed in order to determine this threshold. (70,71) A popular approach is to fix the FDR level anteriorly, and then find a data-dependent thresholding rule. (70,71) The following algorithm was proposed by Benjamini and Hochberg (1995) to find a data based p-value threshold to control the FDR at level α when the p-values are independent and are distributed in a uniform (0,1) distribution (70–72):

1. Let $p_{(1)} \leq \ldots \leq p_{(m)}$ be the ordered, observed p-values.

2. Calculate $\hat{k} = \max\{1 \leq k \leq m : p_{(k)} \leq \alpha \cdot k/m\}$.
3. If $\hat{k}$ exists, then reject null hypotheses corresponding to $p_{(1)} \leq \ldots \leq p_{(\hat{k})}$. Otherwise, reject nothing.

The q-value is the FDR based measure of significance, which could be considered as the adjusted p-values. (71,73) The q-values are a set of values distributed between 0 and 1. (71,73) The q-value has been defined by Storey (2003) to be the minimum FDR at which the test is called significant (73):

$$\text{q-value}(p_i) = \min_{t \geq p_i} \text{FDR}(t)$$

3.6.5 Statistical analysis software

Exploratory analysis, and logistic regression models were performed using SAS statistical software (version 9.4, SAS Institute Inc, Cary, NC, USA). HWE and linkage disequilibrium were assessed using PLINK. (74,75) FDR analysis was performed using the R package "qvalue". (76) PLR models were performed using the R package "stepPlr". (77)

Chapter 4: Results

Subject characteristics based on their dichotomized BMI and WC are provided in Table 1. Using the high/low BMI as the outcome of interest, the high BMI group (overweight and obese participants) was composed of around 50% women and men. However, there was a significant difference with the low BMI group (underweight and normal), where 73% were women. Participants in the high BMI group were significantly older ($p = 0.018$), with a mean age of 23 years old. There was no difference between the two groups regarding the smoking status of the participants. Ethnicity proportions in BMI groups were different, where the high BMI group was composed of 56% of whites, 19% East Asians, 14% South Asians, and 11% others ($p < 0.001$). Most of the participants were college students or had received a college degree, but there was no difference between the high and low BMI groups with respect to education levels. No difference was observed in physical activity levels, with both groups performing around 6 METs; which is considered as moderate activity level. For macronutrients intakes, the high BMI group was significantly different from the low BMI group, with higher total calories ($p = 0.033$), fat ($p = 0.047$), protein ($p = 0.007$) and alcohol intakes ($p < 0.001$). Using the high/low WC as the outcome of interest, no statistically significant differences were observed for all the characteristics, except for the ethnocultural background ($p < 0.001$).

Table 2 shows the participants characteristics of high and low BMI groups, using alternative BMI cut-offs. Using these cut-offs adapted for Asian populations results in a larger high BMI group (n=444). Significant differences between the high and low alternative BMI groups were observed for sex ($p < 0.001$), ethnocultural background ($p < 0.001$), protein intakes ($p <0.001$), and alcohol intakes ($p < 0.001$). Thus, the alternative BMI cut-offs gave a larger sample for the

high BMI group, and fewer variables with statistically significant differences between the two groups than the standard BMI cut-offs.

The different allele frequencies in each ethnocultural group are shown in Table 3. Allele frequencies stratified by population and outcomes are shown in Table 4, Table 5 and Table 6 for BMI, WC and alternative BMI respectively.

4.1 Results: Logistic regression models

Odds ratios (ORs) from the logistic regression models of the genetic main effects are shown in Table 7 for high/low BMI, Table 8 for high/low WC, and Table 9 for high/low alternative BMI. For BMI and alternative BMI outcomes adjusted for covariates, no statistically significant main effect was observed. As for WC after adjustment for covariates, significant main effects were found with *NFKB1* rs3774932 (OR: 0.83 [0.70-0.99], p = 0.042), and with *NFKB1* rs3774968 (OR: 0.81 [0.68-0.96], p = 0.020). However, none was statistically significant after multiple testing correction using FDR. Because the results in Table 7 were vastly different between the adjusted and unadjusted models, a subsequent analysis was done by only adjusting for age and sex (Table 10). This was done to determine if the shift to non-significant nominal p-values in the adjusted models was due to the different allele frequencies or because of interaction between race and genetic effect. Results of this subsequent analysis (Table 10) show that all logistic regression models that were significant when unadjusted were still significant when adjusted for age and sex (but not ethnocultural group). However, even in this subsequent analysis, no model was statistically significant after multiple testing correction.

ORs and p-values of the logistic regression models of the macronutrients main effects are shown for each different outcome in Table 11 for high/low BMI, Table 12 for high/low WC, and Table 13 for high/low alternative BMI. Main effects adjusted for covariates were statistically significant for carbohydrate and protein intakes with BMI (respectively, OR: 0.97 [0.99-1.00], p = 0.040, and OR: 1.01 [1.00-1.02], p = 0.023), and with WC (respectively, OR: 0.99 [0.99-1.00], p = 0.041, and OR: 1.01 [1.00-1.02], p = 0.023). With the alternative BMI cut-offs, only protein intakes were statistically significant (OR: 1.01 [1.00-1.02], p = 0.001).

P-values and FDR q-values of gene-gene interaction models with BMI as the outcome are provided in Table 14. Significant interactions ($p < 0.05$) were observed between 14 SNPs pairs of *SOCS3* and *NFKB1*. Interaction models with WC as the outcome (Table 15) showed 8 SNPs pairs that were significant between *SOCS3* and *NFKB1*. Using the alternative BMI cut-offs, only one gene-gene interaction between *SOCS3* and *NFKB1* was statistically significant (Table 16). However, the significant gene-gene interactions found were no longer significant ($q > 0.05$) after correction for multiple testing with FDR. Additional analyses were done by repeating all interaction logistic regression models stratified by ethnicity to evaluate possible effect modification by race (Tables 17 to 25). In all the stratified analyses, we observed more interactions in whites and South Asians. For the white participants, this is most probably due to the large sample size enabling us to detect more interactions. Although results are different across the different strata, no interaction was significant after correction for multiple testing with FDR.

P-values and FDR q-values of gene-environment interaction models with BMI as the outcome are listed in Table 26. One statistically significant interaction was found between *SOCS3* rs7221341 and protein intake (p = 0.026). Gene-environment models with WC as the outcome (Table 27) found significant interactions between *SOCS3* rs12944581 and fat intake (p = 0.008),

IKBKB rs10958713 and fat intake (p = 0.034), and *SOCS3* rs7221341 and protein intake (p = 0.014). Gene-environment models with alternative BMI cut-offs as the outcome (Table 28) showed significant interactions between *SOCS3* rs7221341 and protein intake (p = 0.008), and *SOCS3* rs10958713 and alcohol intake (p = 0.029). After correction for multiple testing using FDR, none of these interactions were still significant.

The ORs of the most statistically significant gene-gene interactions before multiple testing adjustment are shown in Table 29. For the BMI outcome, each rare allele of rs1609798 (*NFKB1*) added in combination with a change of 1 in rs6501199 (*SOCS3*) decreases the odds of being in the high BMI group. For the WC outcome, the same SNPs were involved in the most significant interaction, where a change of 1 in rs6501199 (*SOCS3*) creates a protective effect against high WC for the homozygous of the rare allele of rs1609798 (*NFKB1*). For the alternative BMI outcome, a change of 1 in rs3774956 (*NFKB1*) creates an increase of 1.78 in the odds of being in the high alternative BMI category for the homozygous of the rare allele of rs9914220 (*SOCS3*).

The ORs of the most statistically significant gene-environment interactions before multiple testing adjustment are shown in Table 30. For the BMI outcome, for a change of 20 units in protein intakes, each addition of a rare allele of rs7221341 (*SOCS3*) increases the odds of high BMI, with an odds ratio of 1.37 for heterozygous of rs7221341 (*SOCS3*), and an odds ratio of 1.78 for homozygous for the rare allele of rs7221341 (*SOCS3*). A similar association can be seen for the same variables with the alternative BMI as the outcome, but with a higher ORs (1.45 for heterozygous, and 1.93 for homozygous for the rare allele). For the WC outcome, the most statistically significant interaction was composed of the same variables as the BMI and alternative BMI interactions. The same effect can be seen with WC, where, for a change of 20 units in protein

intakes, the addition of a rare allele of rs7221341 (*SOCS3*) increases the odds of being in the high WC group (1.34 for the heterozygous, and 1.78 for the homozygous for the rare allele).

4.2 Results: MDR models

We used the MDR software first to analyze gene-gene interactions only, and then we included the macronutrients to analyze gene-environment interactions. However, because the MDR algorithm searches through all the given variables to find the model best fitting the data, there is no guarantee that an environmental factor will be selected (e.g. MDR could select only genetic variables, despite the presence of environmental factors). For both gene-gene and gene-environment models, we looked at the best 2-fold and 3-fold interactions models for each outcome of interest (BMI, WC, alternative BMI) including all the participants. Then, we did a stratified analysis based on the ethnocultural background: whites only, East Asians only, South Asians only. We used the quartiles of the macronutrients residuals, based on ethnicity and sex, to evaluate the gene-environment interactions with MDR.

4.2.1 Gene-gene interactions MDR models

Table 31 shows the results for 2-fold and 3-fold gene-gene interaction MDR models considering all participants for each outcome. The 2-fold interaction model assessing BMI was composed of rs7221341 (*SOCS3*), and rs3747811 (*IKBKB*) with an average testing accuracy of 57% and CV consistency of 7/10. For models assessing WC, the 2-fold interaction model was composed of rs7221341 (*SOCS3*), and rs5029748 (*IKBKB*) with an average testing accuracy of 56% and a CV consistency of 8/10. The 3-fold interaction model with WC as the outcome was

composed of rs7221341 (*SOCS3*), rs3774968 (*NFKB1*), and rs5029748 (*IKBKB*) with an average testing accuracy of 58% and a CV consistency of 9/10. Other MDR models for gene-gene interaction considering all participants did not meet the required thresholds for average testing accuracy and CV consistency. Therefore, for models considering all participants, the best models based on average testing accuracy (≥ 55%) and CV consistency (≥ 6/10) are the 2-fold model for BMI (rs7221341, rs3747811), and the 3-fold models for WC (rs7221341, rs3774968, rs5029748). None of the models assessing the alternative BMI definition had an average testing accuracy > 55%. However, because the MDR models stratified by population presented in the next paragraphs showed evidence of population stratification, none of the gene-gene interaction MDR best models considering all participants was retained for analysis.

The 2-fold and 3-fold gene-gene interaction MDR models stratified for whites are listed in Table 32. The 3-fold interaction model for BMI was composed of the same first two SNPs with the addition of rs4969172 (*SOCS3*), and higher average testing accuracy (60%) and CV consistency (10/10). The 2-fold model for the WC outcome was rs6501199 (*SOCS3*), and rs160978 (*NFKB1*) with an average testing accuracy of 55% and a CV consistency of 7/10. The other models for the BMI and WC outcomes in the white population did not meet the required thresholds for average testing accuracy or CV consistency. Thus, for models considering only of whites, the best models were the 3-fold interaction model for BMI (rs6501199, rs4969172, rs3747811) and the 2-fold interaction model for WC (rs6501199, rs160978). Figure 2 shows the contingency table of the 3-fold interaction model for BMI stratified for whites, and Figure 3 shows the contingency table of the 2-fold interaction model for WC stratified for whites.

For gene-gene interaction models considering only East Asian participants, none of the models reached the average testing accuracy threshold of 55%, and all models had low CV

consistency (≤5). See Table 33 for all the results. Therefore, no best gene-gene interaction MDR model was selected among the East Asian population.

MDR models for gene-gene interactions considering only South Asians participants are listed in Table 34. The 2-fold interaction model with WC was the same as its BMI counterpart, but had a better average testing accuracy (55%) and CV consistency (8/10). The other MDR models for the South Asian participants did not meet the required thresholds for average testing accuracy CV consistency. Thus, for gene-gene interaction MDR models considering only South Asian participants, the only best model selected is the 2-fold interaction model with WC. Figure 4 shows the contingency table of the 2-fold interaction model for WC stratified for South Asians. It is worth noting that all the models were relatively the same in terms of selected factors. However, this is possibly due to the small sample size with the South Asian population (n=149). This small sample size creates nearly empty or empty cells in the MDR contingency table, and has an important negative effect on the possibility of a biological interpretation.

Logistic regression models (before adjustment for multiple testing) and MDR models detected similar gene-gene interactions. They both detected a 2-fold interaction between rs6501199 (*SOCS3*) and rs7674640 (*NFKB1*) (only in the East Asian population for MDR) influencing BMI, and a 2-fold interaction between rs6501199 (*SOCS3*) and rs1609798 (*NFKB1*) (only in the white population for MDR) influencing WC. The latter is the only one that was selected as a best MDR model.

4.2.2 Gene-environment interaction MDR models

Table 35 shows the results for 2-fold and 3-fold gene-environment MDR models. The 2-fold interaction model with BMI as the outcome was composed of rs7221341 (*SOCS3*), and protein intake with an average testing accuracy of 57% and a CV consistency of 10/10. The 3-fold interaction model with BMI was rs7221341 (*SOCS3*), carbohydrates, and fat intakes, and had an average testing accuracy of 57% and a CV consistency of 9/10. The 2-fold gene-environment interaction model with WC was rs7221341 (*SOCS3*), rs5029748 (*IKBKB*) with an average testing accuracy of 55% and a CV consistency of 6/10. This is the same model as the gene-gene interaction model with WC considering all participants seen in section 4.2.1 (Table 31), meaning that the addition of the environment data didn't influence the selection of the MDR algorithm for the 2-fold interaction model. The other gene-environment MDR models considering all participants did not meet the required thresholds for average testing accuracy and CV consistency required threshold. Thus, for gene-environment interaction MDR models, the best models are the 2-fold BMI model (rs7221341 and protein), and the two-fold WC model (rs7221341 and rs5029748). However, as for the gene-gene interaction counterpart, the gene-environment interaction MDR models stratified by population presented next showed evidence of population stratification. Hence, none of the gene-environment interaction MDR best models considering all participants was retained for analysis.

None of the gene-environment interaction MDR models stratified by ethnocultural group met the required thresholds for average testing accuracy and CV consistency. See Tables 36, 37 and 38 for all the results for whites, East Asians and South Asians respectively. The only model considered valid was the 2-fold MDR model with the alternative BMI in the South Asian population, since it had an average testing accuracy >55%. However, this model is not composed

of an environmental factor, and is in fact composed of the same variables as its gene-gene interaction counterpart (Table 34.), meaning that the added environmental factors did not explain the high/low alternative BMI pattern better than the genetic factors. Additionally, the difference in average testing accuracy (54% vs. 56%), and in CV consistency (7/10 vs. 5/10) between these two identical models can be explained by a small difference in the sample size of both models. The gene-gene interaction MDR model was evaluated with 149 participants, and the gene-environment MDR model with 144 participants (5 of the participants were not included in the latter model because of missing data in their diet assessment). This is an example of how sensitive is the MDR algorithm to a small change of sample size when the sample is already small. For these reasons, none of the gene-environment interaction MDR model was selected as a best model for analysis.

Logistic regression models (before adjustment for multiple testing) and MDR models detected similar gene-environment interactions. They both detected a 2-fold interaction between rs7221341 (*SOCS3*) and protein intakes (only in the MDR model considering all participants) influencing BMI and the alternative BMI. However, as stated before, we did not consider the MDR model considering all participants as valid, because of evidence of population stratification.

4.3 Results: PLR models

Following the method proposed by Park and Hastie, PLR models including all ethnicities were done for each three outcomes of interest, first to assess gene-gene interactions, and then for gene-environment interactions. (62) These six PLR models did not identify any gene-gene nor gene-environment interaction and, for each model, the only variable selected by the forward stepwise selection procedure was the ethnicity. Therefore, as for the MDR method, we decided to explore gene-gene and gene-environment interaction for BMI, WC, and alternative BMI with PLR

models stratified by ethnicity. However, most of the PLR models stratified by ethnicity did not detect interactions. Furthermore, all models selected the null model, except for the South Asians population, where gene-gene and the gene-environment interaction models for the alternative BMI both selected rs12944581 (*SOCS3*). Individuals with the common genotype for rs12944581 (*SOCS3*) have higher odds of having a high alternative BMI ($p<0.001$), while heterozygous ($p=0.322$) and homozygous ($p=0.088$) for rs12944581 (*SOCS3*) rare allele seems to reduce the odds of high alternative BMI.

Chapter 5: Discussion

In this study, we investigated gene-gene and gene-environment interactions in the association between variants of 3 genes (*NFKB1*, *SOCS3*, *IKBKB*), macronutrient intakes, and obesity-related phenotypes. These three genes are part of the hypothalamic IKKβ/NF-κB signaling pathway, which has been shown to play a role in obesity pathogenesis with overnutrition in mice. (32) The objective of this study was to investigate this phenomenon in humans using logistic regression (a traditional statistical method) and alternative statistical methods, such as PLR and MDR. In the following discussion, we compare the results of the different methods, we discuss their possible biological meaning, and we compare them to previous results in the literature.

MDR and PLR are both alternative methods to better detect high level gene-gene and gene-environment interactions. Nevertheless, both have limitations to consider. On the one hand, MDR is a non-parametric machine learning approach that doesn't specify a mode of inheritance. Hence, this method is advantageous for complex diseases, such as obesity. On the other hand, MDR suffers from some disadvantages. For instance, cells in high-dimensional tables could be empty or nearly empty (which was often the case with gene-environment models), making it impossible to categorize these cells into high risk or low-risk group. (69) This can occur more often if the sample size is too small for high order interactions, as more tables have to be created to evaluate the implication of each factor. Also, He et al. (2009) have observed that such issues with high-dimensional table could cause MDR to only identify a subset of the factors associated with the disease. Finally, as stated before, MDR models are difficult to interpret; they do not give a quantitative assessment of the effect, such as an odds ratio with logistic regression. (69) PLR models are easier to interpret, since they can be interpreted as a logistic regression model. However, because of the penalty, the real magnitude of the effect might be modified. Also, PLR

can give unstable estimates for parameters when investigating high-dimensional interactions, hence it suffers from a loss of power. (69)

Because of the non-parametric nature of the MDR method and that it cannot adjust for covariates, we were aware that the comparison with PLR would be difficult and their results possibly highly different. Plus, we investigated different levels of interaction: only 2-way interactions with logistic regression (because of overfitting problems), 2-way and 3-way interactions with MDR, and up to multiple 3-way interactions with PLR (in which effects were selected based on a forward stepwise procedure). Also, results from the MDR models showed evidence of population stratification, and we had to create multiple population specific MDR models since it is not possible to adjust for ethnicity directly in the MDR model selection. For both gene-gene and gene-environment interactions, and for both outcomes (BMI and WC), the best MDR models considering all ethnicities selected rs7221341 (*SOCS3*) as the primary factor for 2-fold and 3-fold interactions. *SOCS3* rs7221341 has been previously identified to be associated with multiple obesity-related phenotypes, such as BMI, WC, waist to hip ratio, and visceral adipose tissue. (48) However, rs7221341 was not selected by MDR when we stratified by ethnicity, except for the WC 3-fold gene-environment interactions considering whites only, but it had a low CV consistency (3/10), which suggests that it may not be a valid model. This finding of population stratification was not surprising. MDR's authors have issued warnings about possible spurious findings due to population stratification, and suggested analyzing separately in different ethnic groups. (66) Therefore, our interpretation of the MDR method and our comparison with the PLR method will focus on the best MDR models stratified by population. We also had to stratify PLR models by ethnicity, since the forward stepwise selection procedure for the models considering all ethnicities gave only PLR models with the ethnicity variable. Additionally, some of the MDR

models in each population were not considered as valid, based on two reasons. First, most of them did not reach the average testing accuracy threshold of 55%. Second, we considered some models as invalid since their MDR contingency table had multiple empty or nearly empty cells. This is mostly the case for all the gene-gene and gene-environment MDR models with the South Asian population. The best gene-gene interaction MDR models based on our criteria stated previously are the 2-fold model with WC, the 3-fold model with BMI for whites, and the 2-fold model with WC for South Asians. None of the gene-environment interaction MDR models were selected as best models, since they all had low average testing accuracy (<55%) and CV consistency (<6/10).

Although our goal was not to test for effect modification of gene-gene/environment interaction effects by ethnocultural group but rather to adjust for potential confounding by ethnocultural group, MDR and PLR analyses could only be adjusted using stratification by ethnocultural group. We detected differences in the interaction effects detected across ethnocultural groups. Hence, although our logistic regression models were originally adjusted for ethnocultural group we performed additional logistic regression analyses stratified by ethnicity in order to better compare the logistic regression results to the MDR and PLR results. Although results before correction for multiple testing suggest the existence of effect modification by ethnicity like with MDR, none were significant after FDR. Before correction for multiple testing, one logistic regression model including only white participants showed a significant interaction between SOCS3 rs6501199 and NFKB1 rs1609798, matching the result of one of the MDR models.

5.1 Gene-gene interaction models

None of the gene-gene interaction models with logistic regression were significant after correction for multiple comparisons with FDR. However, some of the logistic regression 2-fold gene-gene interactions statistically significant before adjustment for multiple testing were also detected with certain MDR models. Among them, only one was considered a best MDR model based on our criteria: the 2-fold gene-gene interaction MDR model assessing WC in the white population composed of rs6501199 (SOCS3) and rs1609798 (NFKB1). However, the logistic regression model and the MDR models do not have the same interpretation. For example, for rs6501199 heterozygous who have the common genotype for rs1609798, the logistic regression model suggests that these individuals have higher odds of being in the high WC group, while the MDR model suggests the opposite. Hence, we cannot confirm that MDR supports the logistic regression model.

For the gene-gene interaction models with logistic regression, the most statistically significant results with BMI (before multiple testing adjustment with FDR) was a protective effect of the presence of rare alleles in rs6501199 (*SOCS3*) in the homozygous for rs1609798 (*NFKB1*), suggesting that rare allele in both SNPs would make the NF-κB complex more difficult to activate, and the SOCS3 protein less efficient in its effect on insulin and leptin. For the WC outcome, the same model suggests a similar protective effect from the presence of a rare allele of rs1609798 (*NFKB1*) in the presence of the rare allele of rs6501199 (*SOCS3*) against high WC. Hence, the same biological effect on the NF- κB complex, and on SOCS3 protein efficiency to cause insulin/leptin resistance could be hypothesized. Finally, for the alternative BMI outcome, the model suggests that heterozygous for the rare allele of rs9914220 (*SOCS3*) in the presence of the rare allele of rs3774956 have higher alternative BMI, suggesting that the rare allele of rs3774956

makes the NF- κB complex more efficient to activate *SOCS3* gene expression. Hence, in that case both rare allele of rs9914220 and rs3774956 contribute to higher odds of having a high BMI, based on the alternative definition for East Asians and South Asians.

The first best MDR model was a 3-fold gene-gene interaction model assessing BMI in the white population composed of rs6501199 (*SOCS3*), rs4969172 (*SOCS3*), and rs3747811 (*IKBKB*). Only rs6501199 (*SOCS3*) has previously been found to be weakly associated with visceral adipose tissue. (48) In the same study, rs4969172 (*SOCS3*) was also investigated for association with multiple obesity-relate traits phenotypes (including BMI, and WC), but none was found. As for rs3747811 (*IKBKB*), it has not been yet investigated in previous studies for its involvement in the development of obesity-related phenotypes, and was only found to decrease the risk of colorectal cancer combined with rs4648110 (*NFKB1*). (78) A possible biological interpretation is that the rare allele of rs3747811 (*IKBKB*) triggers the activation of the NF- κB complex, and increases the expression of the NF- κB complex, thus also inducing *SOCS3* expression, resulting in insulin/leptin resistance. The two other SNPs in this 3-way interaction (rs6501199 and rs4969172) are part of the same gene, *SOCS3*. By looking at the MDR model contingency table their interpretation is less clear, but these two *SOCS3* polymorphisms or other unmeasured polymorphisms in high LD might modify the coded protein that contributes to insulin/leptin resistance.

The other best MDR model considering (only white participants) was the 2-fold gene-gene interaction model for WC composed of rs6501199 (*SOCS3*), and rs160978 (*NFKB1*). There is no study that has investigated the involvement of rs160978 (*NFKB1*), but this MDR suggests that the rare allele of rs160978 (*NFKB1*) may increase the activation of the NF-κB complex, which may contribute to an increased risk of obesity-related phenotypes in the presence of the wild type genotype (i.e., two common alleles) for rs6501199 (*SOCS3*). However, the rare allele of rs6501199

(*SOCS3*) seems to interact by generally cancelling the deleterious effect of the rs160978 (*NFKB1*) rare allele. Hence, the SOCS3 protein, which is downstream of the hypothalamic IKKβ/NF-κB pathway, of an individual heterozygous or homozygous for the rare allele would be harder to activate.

The WC 2-fold gene-gene interaction MDR model considering only South Asians suggests that the common alleles of rs4436839 (*SOCS3*) and rs3747811 (*IKBKB*) contribute to higher risk of high WC, potentially through a better activation of the NF-κB complex activity by the IKBKB protein and increased insulin/leptin resistance by the SOCS3 protein. However, this MDR model is less reliable on its biological interpretation, since several cells have low frequencies (particularly cells for the homozygous of the rare allele of rs3747811).

The only PLR model selected through the forward stepwise selection procedure proposed by Park and Hastie (2008) was composed of rs12944581 (*SOCS3*) main effect in the South Asian population, and suggested that individuals with the common genotype had higher odds of being in the high alternative BMI group. (62) This SNP has been investigated by Talbert et al. (2009) in a Hispanic cohort, but no association with obesity-related traits (including BMI and WC) was found. (48) This main effect of rs12944581 (*SOCS3*) in the PLR model was not detected by the logistic regression adjusted for covariates before correction for multiple testing.

5.2 Gene-environment interaction models

The most statistically significant gene-environment interaction with logistic regression (before multiple testing adjustment with FDR) suggested that for a change of 20 units in protein intakes, heterozygous and homozygous for the rare allele of rs7221341 (*SOCS3*) have higher ORs

of high BMI. Therefore, it suggests that the rare genotype for rs7221341 (*SOCS3*) somehow makes the SOCS3 protein more efficient, or easier to activate, while in interaction with overnutrition of protein, and results in higher risk of high BMI, WC, or high alternative BMI.

With both alternative statistical methods (MDR and PLR), no model involving the environmental factors was found, based on our MDR criteria or on PLR's forward stepwise selection procedure with MDR, none of the gene-environment interaction models stratified by ethnicity had high enough average testing accuracy and CV consistency to be considered as valid. Only the 2-fold gene-environment interaction MDR models for BMI and WC, and the 3-fold gene-environment interaction MDR models had average testing accuracy ≥55% and CV consistency 6/10. However, as for the gene-gene interaction MDR models, these models were not replicated in the analysis stratified by ethnicity. Also, with MDR, the addition of environmental factors did not influence the variable selection of the MDR algorithm in some gene-environment models, resulting in the same model as their gene-gene interaction model counterpart. Similarly, the only gene-environment PLR model identified was the same as its gene-gene PLR model counterpart: a main effect of rs12944581 (*SOCS3*) in the South Asian population.

In our study, MDR and PLR have identified very different gene-gene interaction models involving *SOCS3*, *NFKB1*, and *IKBKB* influencing obesity-related phenotypes. Also, both alternative methods did not detect any gene-environment interaction model. However, all the best MDR models involved at least one SNP of *SOCS3* (rs6501199 or rs4969172), and this gene was also involved in the only PLR model (rs12944581). In addition, with logistic regression, the majority of the statistically significant main effects, gene-gene interactions, and gene-environment interactions involved *SOCS3*, before adjustment for multiple comparisons with FDR. It might suggest that polymorphism in or near *SOCS3* has a more important role in the variation of obesity-

related phenotypes in humans than *NFKB1* or *IKBKB*. This supports previous studies that found evidence of the involvement of *SOCS3* in the association with obesity-related phenotypes in humans. (48,49,79) *SOCS3's* participation in various models be explained because it is the gene downstream of the hypothalamic NF-κB signaling pathway, and it codes for a protein that is well-known to induce insulin and leptin resistance. Hence, it may be that the real biological effect of *SOCS3* polymorphism on obesity pathogenesis is easier to detect by both MDR and PLR than polymorphism in upstream genes (*NFKB1* and *IKBKB*), which effects may be blurred by other molecular factors. For example, polymorphism in genes coding for other subparts of the NF-κB complex, other activators like *IKBKB*'s protein, or even inhibitors of the NF-κB complex could influence NF-κB's efficiency to bind upstream of the *SOCS3* gene. More importantly, *SOCS3* is not solely activated by the IKKβ/NF-κB pathway; it can also be activated by the leptin-JAK-STAT pathway. (80) This suggests that even though polymorphism in *NFKB1* and *IKBKB* might have, to some degree, an impact on the effect of insulin/leptin resistance and obesity pathogenesis through the activation of SOCS3, the latter is not entirely controlled by them, hence polymorphisms in other activators might also contribute to the effect SOCS3 on insulin/leptin resistance. Also, we did not consider the other genes that could potentially have an impact on obesity-related phenotypes by modifying the control of hunger through other hormones than insulin and leptin (e.g. ghrelin). However, the overall results seem to indicate that *SOCS3*'s SNPs are the most likely of the three genes under study to have a large effect on obesity-related phenotypes. Hence, further research is needed since *SOCS3* is involved in other insulin resistance pathways, and interaction with other genetic factors is possible. The MDR model involving rs6501199 (SOCS3), rs4969172 (SOCS3), and rs3747811 (IKBKB) had the highest average testing accuracy and CV consistency of all the best MDR models selected, and it identified possible

interactions within *SOCS3*'s SNPs, which is something that we did not investigate with the standard logistic regression method. Thus, future research should also consider investigating interactions between SNPs within the *SOCS3* genes.

5.3 Strengths and limitations

A major strength of this study is its relatively large sample size, which is necessary as one tries to investigate high level interactions. Other strengths are the use of alternative statistical methods to overcome the limitations of traditional approaches such as logistic regression. On the one hand, MDR is a non-parametric, machine learning approach. (69) On the other hand, PLR is a parametric approach using a variant of logistic regression with L2 regularization. (69) Hence, the combination of the two methods might give important leads for future research. Lastly, the present study is one of the first to investigate gene-gene interactions, and gene-environment interactions, between *NFKB1*, *SOCS3*, *IKBKB*, macronutrients on humans and their effect on the pathogenesis of obesity. Therefore, this study provides new results on the involvement of the hypothalamic NF-kB signaling pathway in obesity pathogenesis and will help to guide future research on this phenomenon.

Several limitations of the present study need to be acknowledged. The recruitment of the participants was done near the University of Toronto campus. Hence, most of the participants are highly educated, which has been identified as a factor reducing obesity prevalence. (81) The young age of the participants (20-29 years) was one of the inclusion/exclusion criteria of the Toronto Nutrigenomics and Health study, which was done to avoid possible environmental health consequences occurring with time. Both the education level, and the age of the participants explain why few participants were obese. In addition, it is possible that a selection bias occurred during

the enrollment of the participants, since obese participants might not be attracted to participate in a nutrition study. This is also why the high BMI category included overweight individuals: few were obese among the young participants, and perhaps obesity triggered by the gene-gene, and gene-environment interactions of interest was not yet developed at their age.

In addition, the multi-ethnic nature of the participants introduced problems of population heterogeneity: it drastically reduced the numbers of participants in the MDR and PLR stratified analyses, and logistic regression and PLR models (considering all ethnicities) may not have been perfectly adjusted for this stratification. Population stratification can bias inferences in genotype-disease association studies, and in gene-gene or gene-environment interaction studies. (82,83) It occurs when the sample is composed of cases and controls from multiple subpopulations. If the disease and the allele frequencies are different across these subpopulation, it creates false positive results. To adjust for population stratification, we used the ethnicity categorization from previous studies using data from the Toronto Nutrigenomics and Health study (whites, East Asians, South Asians, and others). This definition of ethnic groups is an important drawback of the study, since it doesn't accurately represent the ethno-cultural background of the participants. It is based on a subjective view of ethnicity that doesn't consider possible population stratification of sub-ethnicity within one category. For example, the East Asian population includes Chinese participants, and one of the few studies on *SOCS3* and obesity-related phenotypes have been conducted on three nationalities of the Xin-jiang region of China (Kazakh, Uygur and Han), and the results were different depending on their nationality. (49) In our study, we did not account for this, thus the participants were all classified as East Asians, and it might have blurred the true association. Nevertheless, we used the same classification as other studies using data from the Toronto Nutrigenomics and Health study, allowing future comparisons.

The measurement of physical activity is also susceptible to subjectivity, since it was done solely through a questionnaire, and then converted into a MET score. However, it sill gave a relative idea of the physical activity level, which is considerable considering the large sample size of the study, and that most studies in the field of nutritional epidemiology assume sedentary lifestyle without any assessment of physical activity. In addition, there was no statistically significant difference in physical activity level between high/low BMI, and high/low WC groups.

Finally, an important limitation of this study is the utilization of the FFQ for the assessment of macronutrient intakes. FFQs have been found to be prone to important measurement errors, which has created a fair number of debates in the field of nutritional epidemiology. (84) Succinctly, the problem with the FFQs is that it highly revolves on long-term memory, thus letting the food frequency estimates at the mercy of recall bias. (84,85) For example, the Observing Protein and Energy Nutrition study observed that the FFQ would give estimates that are greatly reduced, or even null, when the true association is modest. (85) This means that true gene-environment interactions might have been missed in our study. It is also possible that the FFQ used was not reliable for certain subpopulations of this highly multiethnic cohort, thus failing to measure the real diet of these participants. However, we tried to minimize FFQ's measurement errors by excluding individuals with implausible daily energy intakes based on biological limits (<800 kcal/day, and >3500 kcal/day for women, >4000 kcal/day for men). In addition, we used the residuals of the macronutrients intake on total caloric intake to adjust for the total energy intake, since we were interested in the effect of overnutrition for each macronutrient. Even with these precautions, gene-environment interactions assessment might have been biased toward the null, and results must be interpreted with caution. It is indubitable that future researches should investigate macronutrients involvement with more expensive – but more reliable – methods.

5.6 Conclusion

In summary, in this investigation of gene-gene and gene-environment interaction in the association between overnutrition and obesity-related phenotypes, MDR and PLR identified very different models involving genes part of the hypothalamic IKKβ/NF-κB signaling pathway. Both alternative statistical methods have found no gene-environment interaction. Results from alternative methods should always be cautiously interpreted and replicated to determine whether any effects are real. However, because this study is one of the first to explore interaction between polymorphism in *NFKB1*, *SOCS3*, *IKBKB*, and diet, its results offer suggestions for future investigation of these factors' role in obesity pathogenesis. This study also contributes to the understanding of the role of insulin and leptin resistance in obesity pathogenesis, and thus might help to pinpoint the true evolutionary origin of the obesity epidemic.

Tables

Table 1. General characteristics of study participants by high/low BMI and high/low WC categories (n=1512)

	High BMI (n=323)	Low BMI (n=1189)	p-values	High WC (n=376)	Low WC (n=1136)	p-values
Female	163 (50.5)	870 (73.2)	**< 0.001**	257 (68.4)	776 (68.3)	1.000
Age (years)	23.1 (2.7)	22.6148 (2.4)	**0.018**	23.0 (2.6)	22.6 (2.5)	0.239
Smoke	29 (9.0)	69 (5.8)	0.054	24 (6.4)	74 (6.5)	1.000
Race			**< 0.001**			**< 0.001**
White	180 (55.7)	553 (46.5)		226 (60.1)	507 (44.6)	
East Asian	60 (18.6)	449 (37.8)		72 (19.2)	437 (38.5)	
South Asian	46 (14.2)	114 (9.6)		48 (12.8)	112 (9.9)	
Others	37 (11.5)	73 (6.1)		30 (8.0)	80 (7.0)	
Education			0.800			0.394
High school	4 (1.2)	24 (2.0)		5 (1.3)	23 (2.0)	
Some College or undergrad	187 (57.9)	693 (58.3)		208 (55.3)	672 (59.2)	
College/undergrad degree received	103 (31.9)	363 (30.5)		127 (33.8)	339 (29.8)	
Graduate degree received	29 (9.0)	109 (9.)		36 (9.6)	102 (9.0)	
METS	6.3 (2.3)	6.2 (2.5)	0.233	6.3 (2.4)	6.2 (2.5)	0.333
Total calories (kcal/day)	2003.6 (698.6)	1960.8 (637.1)	**0.033**	1956.7 (647.1)	1974.3 (652.1)	0.867
Carbohydrates (kcal/day)	259.1 (99.6)	259.9 (92.1)	0.073	253.7 (92.5)	261.7 (94.1)	0.707
Fats (kcal/day)	67.1 (28.4)	65.3 (26.1)	**0.047**	66.00 (27.9)	65.6 (26.1)	0.119
Proteins (kcal/day)	88.2 (35.8)	84.7 (31.8)	**0.007**	85.6 (32.3)	85.3 (32.9)	0.697
Alcohol (kcal/day)	7.2 (11.6)	5.3 (8.5)	**< 0.001**	6.5 (9.3)	5.4 (9.3)	0.896

Data are n (%) or mean (standard deviation).

Table 2. General characteristics of study participants using alternate BMI cut-offs (n=1512)

	High BMI (n=444)	**Low BMI (n=1068)**	**p-values**
Female	236 (53.2)	797 (74.6)	**< 0.001**
Age (years)	22.8 (2.6)	22.7 (2.5)	0.060
Smoke	33 (7.4)	65 (6.1)	0.358
Race			**< 0.001**
White	180 (40.5)	553 (51.8)	
East Asian	152 (34.2)	357 (33.4)	
South Asian	75 (16.9)	85 (8.0)	
Other	37 (8.3)	73 (6.8)	
Education			0.664
High school	6 (1.4)	22 (2.1)	
Some College or undergrad	267 (60.1)	613 (57.4)	
College/undergrad degree received	132 (29.7)	334 (31.3)	
Graduate degree received	39 (8.8)	99 (9.3)	
METS	6.2 (2.4)	6.3 (2.5)	0.578
Total calories (kcal/day)	1995.7 (685.8)	1959.2 (635.6)	0.053
Carbohydrates (kcal/day)	261.0 (97.9)	259.2 (92.0)	0.116
Fats (kcal/day)	65.9 (27.3)	65.6 (26.3)	0.327
Proteins (kcal/day)	89.0 (35.9)	83.9 (31.2)	**< 0.001**
Alcohol (kcal/day)	5.8 (10.3)	5.63 (8.9)	**< 0.001**

Data are n (%) or mean (standard deviation).

Table 3. Allele frequencies stratified by population

SNP	Whites	East Asians	South Asians	Others
rs4436839				
C	0.51	0.37	0.51	0.57
A	0.49	0.63	0.49	0.43
rs7221341				
C	0.63	0.96	0.73	0.68
T	0.37	0.05	0.27	0.32
rs6501199				
C	0.67	0.73	0.72	0.58
G	0.33	0.27	0.28	0.42
rs12944581				
C	0.52	0.74	0.73	0.70
G	0.48	0.26	0.27	0.30
rs4969168				
G	0.73	0.56	0.81	0.65
A	0.27	0.44	0.19	0.35
rs11868378				
A	0.78	0.42	0.75	0.67
G	0.22	0.58	0.25	0.33
rs9914220				
C	0.92	0.63	0.88	0.76
T	0.08	0.37	0.12	0.19
rs4969172				
C	0.64	0.11	0.59	0.42

SNP	Whites	East Asians	South Asians	Others
T	0.36	0.89	0.41	0.58
rs3774932				
G	0.54	0.48	0.50	0.62
A	0.46	0.52	0.50	0.38
rs3774934				
G	0.91	0.62	0.73	0.87
A	0.09	0.38	0.27	0.13
rs1599961				
G	0.62	0.59	0.69	0.58
A	0.38	0.41	0.31	0.42
rs3774956				
C	0.60	0.53	0.69	0.54
T	0.40	0.47	0.31	0.46
rs11722146				
G	0.69	0.59	0.75	0.72
A	0.31	0.41	0.25	0.28
rs3774968				
G	0.56	0.54	0.50	0.66
A	0.44	0.46	0.50	0.34
rs7674640				
T	0.52	0.49	0.47	0.56
C	0.48	0.51	0.53	0.44
rs4698863				
C	0.68	0.60	0.74	0.66

SNP	Whites	East Asians	South Asians	Others
T	0.32	0.40	0.26	0.34
rs1609798				
C	0.69	0.61	0.72	0.73
T	0.31	0.39	0.28	0.27
rs10958713				
C	0.64	0.44	0.64	0.71
T	0.36	0.56	0.36	0.29
rs3747811				
T	0.54	0.41	0.62	0.62
A	0.46	0.59	0.38	0.38
rs5029748				
C	0.72	0.44	0.68	0.75
A	0.28	0.56	0.32	0.25

Table 4. Allele frequencies stratified by population and BMI

SNP	Whites		East Asians		South Asians		Others	
	High BMI	Low BMI	High BMI	Low BMI	High BMI	Low BMI	High BMI	Low BMI
rs4436839								
C	0.13	0.38	0.05	0.32	0.13	0.38	0.20	0.37
A	0.12	0.37	0.07	0.56	0.16	0.33	0.14	0.29
rs7221341								
C	0.15	0.48	0.10	0.86	0.19	0.54	0.23	0.45
T	0.10	0.27	0.02	0.03	0.10	0.17	0.10	0.22
rs6501199								
C	0.16	0.51	0.09	0.64	0.21	0.51	0.21	0.37
G	0.08	0.25	0.03	0.24	0.08	0.20	0.12	0.30
rs12944581								
C	0.18	0.55	0.09	0.65	0.24	0.49	0.23	0.47
G	0.07	0.20	0.03	0.23	0.05	0.22	0.10	0.20
rs4969168								
G	0.21	0.65	0.07	0.49	0.23	0.58	0.23	0.42
A	0.04	0.10	0.05	0.39	0.06	0.13	0.10	0.25
rs11868378								
A	0.19	0.59	0.06	0.36	0.23	0.52	0.21	0.46
G	0.06	0.16	0.06	0.52	0.06	0.19	0.12	0.21
rs9914220								
C	0.23	0.70	0.07	0.56	0.25	0.63	0.26	0.55
T	0.02	0.05	0.05	0.32	0.04	0.08	0.07	0.12
rs4969172								

SNP	Whites		East Asians		South Asians		Others	
	High BMI	Low BMI	High BMI	Low BMI	High BMI	Low BMI	High BMI	Low BMI
C	0.15	0.49	0.02	0.09	0.17	0.42	0.15	0.27
T	0.09	0.27	0.10	0.79	0.12	0.29	0.19	0.39
rs3774932								
G	0.13	0.40	0.06	0.42	0.14	0.36	0.21	0.41
A	0.12	0.35	0.06	0.46	0.15	0.35	0.13	0.25
rs3774934								
G	0.23	0.68	0.07	0.55	0.22	0.51	0.31	0.56
A	0.02	0.07	0.05	0.33	0.07	0.20	0.03	0.10
rs1599961								
G	0.16	0.46	0.07	0.52	0.20	0.49	0.20	0.38
A	0.09	0.29	0.05	0.36	0.09	0.22	0.14	0.28
rs3774956								
C	0.15	0.45	0.06	0.47	0.19	0.50	0.17	0.37
T	0.09	0.31	0.06	0.41	0.09	0.22	0.17	0.29
rs11722146								
G	0.17	0.52	0.07	0.52	0.22	0.53	0.25	0.47
A	0.08	0.23	0.05	0.36	0.07	0.18	0.09	0.19
rs3774968								
G	0.14	0.42	0.07	0.47	0.14	0.36	0.23	0.43
A	0.11	0.33	0.05	0.41	0.15	0.35	0.10	0.24
rs7674640								
T	0.13	0.39	0.06	0.43	0.12	0.35	0.20	0.36

SNP	Whites		East Asians		South Asians		Others	
	High BMI	Low BMI	High BMI	Low BMI	High BMI	Low BMI	High BMI	Low BMI
C	0.12	0.36	0.06	0.45	0.17	0.36	0.13	0.31
rs4698863								
C	0.17	0.51	0.07	0.53	0.24	0.50	0.21	0.45
T	0.08	0.24	0.04	0.36	0.05	0.21	0.12	0.22
rs1609798								
C	0.17	0.52	0.08	0.53	0.23	0.49	0.25	0.48
T	0.08	0.23	0.04	0.35	0.07	0.21	0.08	0.19
rs10958713								
C	0.15	0.49	0.05	0.39	0.19	0.45	0.23	0.48
T	0.10	0.26	0.07	0.49	0.10	0.26	0.11	0.18
rs3747811								
T	0.12	0.42	0.04	0.37	0.18	0.44	0.20	0.42
A	0.13	0.33	0.08	0.51	0.10	0.28	0.14	0.24
rs5029748								
C	0.17	0.55	0.05	0.39	0.20	0.48	0.25	0.5
A	0.07	0.21	0.07	0.49	0.09	0.23	0.08	0.17

Table 5. Allele frequencies stratified by population and WC

SNP	Whites		East Asians		South Asians		Others	
	High WC	Low WC	High WC	Low WC	High WC	Low WC	High WC	Low WC
rs4436839								
C	0.16	0.35	0.06	0.32	0.12	0.39	0.18	0.40
A	0.16	0.33	0.08	0.54	0.17	0.32	0.10	0.33
rs7221341								
C	0.20	0.44	0.12	0.83	0.21	0.53	0.20	0.48
T	0.11	0.25	0.02	0.03	0.09	0.17	0.08	0.24
rs6501199								
C	0.21	0.46	0.11	0.63	0.22	0.50	0.15	0.42
G	0.10	0.23	0.04	0.22	0.08	0.20	0.12	0.31
rs12944581								
C	0.22	0.50	0.10	0.64	0.25	0.47	0.18	0.52
G	0.09	0.19	0.04	0.22	0.06	0.22	0.09	0.21
rs4969168								
G	0.27	0.59	0.08	0.48	0.25	0.56	0.18	0.48
A	0.04	0.10	0.06	0.38	0.05	0.14	0.10	0.24
rs11868378								
A	0.24	0.55	0.07	0.35	0.24	0.51	0.18	0.50
G	0.07	0.14	0.08	0.50	0.06	0.19	0.09	0.23
rs9914220								
C	0.28	0.64	0.09	0.55	0.27	0.62	0.21	0.61
T	0.03	0.05	0.05	0.31	0.03	0.08	0.06	0.12
rs4969172								

SNP	Whites		East Asians		South Asians		Others	
	High WC	Low WC	High WC	Low WC	High WC	Low WC	High WC	Low WC
C	0.19	0.45	0.02	0.09	0.19	0.40	0.11	0.31
T	0.12	0.24	0.12	0.77	0.11	0.30	0.16	0.42
rs3774932								
G	0.18	0.35	0.08	0.40	0.16	0.35	0.17	0.45
A	0.14	0.33	0.07	0.45	0.13	0.36	0.11	0.27
rs3774934								
G	0.29	0.62	0.09	0.53	0.22	0.50	0.24	0.63
A	0.02	0.07	0.05	0.33	0.08	0.20	0.03	0.10
rs1599961								
G	0.19	0.43	0.08	0.51	0.20	0.49	0.16	0.42
A	0.12	0.26	0.06	0.35	0.10	0.21	0.12	0.30
rs3774956								
C	0.18	0.42	0.07	0.46	0.19	0.50	0.14	0.39
T	0.13	0.27	0.07	0.40	0.10	0.21	0.13	0.34
rs11722146								
G	0.21	0.48	0.08	0.51	0.22	0.52	0.21	0.51
A	0.10	0.21	0.06	0.35	0.07	0.19	0.06	0.22
rs3774968								
G	0.18	0.38	0.08	0.46	0.16	0.34	0.19	0.48
A	0.13	0.31	0.05	0.41	0.14	0.36	0.09	0.24
rs7674640								
T	0.16	0.36	0.08	0.42	0.14	0.33	0.16	0.41

SNP	Whites		East Asians		South Asians		Others	
	High WC	Low WC	High WC	Low WC	High WC	Low WC	High WC	Low WC
C	0.15	0.33	0.07	0.43	0.16	0.37	0.11	0.32
rs4698863								
C	0.20	0.47	0.08	0.51	0.23	0.50	0.17	0.50
T	0.11	0.22	0.06	0.35	0.07	0.20	0.10	0.23
rs1609798								
C	0.21	0.49	0.08	0.53	0.23	0.49	0.20	0.54
T	0.10	0.20	0.05	0.34	0.08	0.20	0.06	0.20
rs10958713								
C	0.19	0.45	0.06	0.38	0.20	0.44	0.20	0.51
T	0.12	0.24	0.08	0.48	0.10	0.26	0.07	0.22
rs3747811								
T	0.16	0.38	0.05	0.36	0.18	0.43	0.16	0.46
A	0.15	0.31	0.09	0.50	0.11	0.28	0.11	0.27
rs5029748								
C	0.22	0.50	0.06	0.38	0.22	0.47	0.20	0.55
A	0.09	0.19	0.08	0.48	0.08	0.23	0.06	0.19

Table 6. Allele frequencies stratified by population and alternative BMI

SNP	Whites		East Asians		South Asians		Others	
	High WC	Low WC	High WC	Low WC	High WC	Low WC	High WC	Low WC
rs4436839								
C	0.13	0.38	0.11	0.26	0.19	0.32	0.20	0.38
A	0.12	0.37	0.19	0.44	0.27	0.22	0.13	0.29
rs7221341								
C	0.15	0.48	0.27	0.67	0.34	0.40	0.23	0.45
T	0.10	0.27	0.03	0.03	0.13	0.13	0.10	0.22
rs6501199								
C	0.17	0.51	0.23	0.51	0.35	0.36	0.20	0.37
G	0.08	0.24	0.07	0.19	0.13	0.16	0.13	0.30
rs12944581								
C	0.18	0.55	0.23	0.51	0.39	0.33	0.23	0.46
G	0.07	0.20	0.07	0.19	0.08	0.20	0.11	0.20
rs4969168								
G	0.21	0.65	0.17	0.40	0.38	0.43	0.23	0.42
A	0.04	0.10	0.13	0.31	0.09	0.10	0.10	0.25
rs11868378								
A	0.19	0.59	0.13	0.28	0.36	0.39	0.21	0.46
G	0.06	0.16	0.17	0.42	0.11	0.14	0.12	0.21
rs9914220								
C	0.22	0.70	0.19	0.45	0.42	0.47	0.27	0.55
T	0.03	0.05	0.11	0.25	0.05	0.06	0.07	0.11
rs4969172								

SNP	Whites		East Asians		South Asians		Others	
	High WC	Low WC	High WC	Low WC	High WC	Low WC	High WC	Low WC
C	0.15	0.49	0.04	0.07	0.28	0.31	0.15	0.28
T	0.09	0.27	0.26	0.63	0.18	0.22	0.19	0.38
rs3774932								
G	0.13	0.40	0.15	0.33	0.23	0.27	0.21	0.41
A	0.11	0.36	0.15	0.37	0.24	0.26	0.13	0.25
rs3774934								
G	0.23	0.68	0.19	0.43	0.35	0.38	0.31	0.56
A	0.02	0.07	0.11	0.27	0.13	0.15	0.03	0.10
rs1599961								
G	0.16	0.46	0.16	0.43	0.34	0.36	0.20	0.38
A	0.09	0.29	0.13	0.28	0.13	0.17	0.14	0.28
rs3774956								
C	0.15	0.45	0.15	0.38	0.33	0.36	0.17	0.37
T	0.10	0.30	0.15	0.32	0.13	0.18	0.17	0.29
rs11722146								
G	0.17	0.50	0.17	0.42	0.36	0.38	0.25	0.48
A	0.08	0.23	0.13	0.28	0.10	0.15	0.09	0.18
rs3774968								
G	0.14	0.42	0.17	0.37	0.23	0.27	0.21	0.43
A	0.11	0.33	0.13	0.33	0.24	0.26	0.10	0.26
rs7674640								
T	0.13	0.39	0.15	0.34	0.21	0.26	0.20	0.36

SNP	Whites		East Asians		South Asians		Others	
	High WC	Low WC	High WC	Low WC	High WC	Low WC	High WC	Low WC
C	0.12	0.36	0.15	0.36	0.26	0.27	0.13	0.31
rs4698863								
C	0.17	0.51	0.17	0.42	0.37	0.36	0.21	0.45
T	0.08	0.24	0.12	0.29	0.09	0.18	0.12	0.22
rs1609798								
C	0.17	0.53	0.18	0.43	0.37	0.35	0.25	0.48
T	0.08	0.22	0.12	0.27	0.10	0.18	0.09	0.18
rs10958713								
C	0.15	0.49	0.13	0.31	0.32	0.33	0.23	0.48
T	0.10	0.26	0.17	0.39	0.15	0.20	0.18	0.18
rs3747811								
T	0.12	0.42	0.12	0.29	0.30	0.31	0.20	0.42
A	0.13	0.33	0.18	0.41	0.17	0.22	0.14	0.24
rs5029748								
C	0.17	0.55	0.13	0.31	0.33	0.35	0.25	0.50
A	0.07	0.21	0.17	0.39	0.13	0.19	0.08	0.17

Table 7. Odds ratios from logistic regression models of dichotomized BMI unadjusted and adjusted for covariates

		Unadjusted for covariates		Adjusted for covariates [a]		
Gene	SNP	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value	q-value
SOCS3	rs4436839	1.13 (0.95 - 1.35)	0.159	1.02 (0.85 - 1.22)	0.849	0.955
	rs7221341	**1.51 (1.26 - 1.81)**	**< 0.001**	1.16 (0.94 - 1.43)	0.172	0.786
	rs6501199	0.98 (0.81 - 1.19)	0.854	0.91 (0.75 - 1.11)	0.355	0.887
	rs12944581	0.97 (0.80 - 1.18)	0.742	0.99 (0.81 - 1.21)	0.912	0.955
	rs4969168	0.84 (0.69 - 1.02)	0.073	1.03 (0.83 - 1.28)	0.791	0.955
	rs11868378	**0.78 (0.65 - 0.93)**	**0.005**	0.97 (0.79 - 1.18)	0.742	0.955
	rs9914220	0.83 (0.67 - 1.04)	0.108	1.19 (0.92 - 1.54)	0.196	0.786
	rs4969172	**1.34 (1.15 - 1.57)**	**< 0.001**	1.01 (0.82 - 1.23)	0.955	0.955
NFKB1	rs3774932	0.91 (0.76 - 1.09)	0.288	0.90 (0.75 - 1.09)	0.277	0.793
	rs3774934	**0.71 (0.57 - 0.89)**	**0.002**	0.87 (0.68 - 1.11)	0.250	0.793
	rs1599961	0.94 (0.79 - 1.13)	0.519	1.02 (0.84 - 1.22)	0.867	0.955
	rs3774956	0.94 (0.79 - 1.12)	0.479	1.05 (0.88 - 1.26)	0.582	0.955
	rs11722146	0.87 (0.72 - 1.05)	0.134	1.02 (0.83 - 1.24)	0.880	0.955
	rs3774968	0.91 (0.76 - 1.09)	0.312	0.88 (0.73 - 1.06)	0.171	0.786
	rs7674640	1.00 (0.84 - 1.19)	0.978	0.97 (0.80 - 1.17)	0.740	0.955
	rs4698863	0.90 (0.74 - 1.08)	0.239	0.99 (0.81 - 1.20)	0.896	0.955
	rs1609798	0.85 (0.71 - 1.03)	0.097	0.97 (0.80 - 1.18)	0.738	0.955
IKBKB	rs10958713	0.98 (0.82 - 1.15)	0.769	1.13 (0.94 - 1.35)	0.196	0.786
	rs3747811	1.06 (0.90 - 1.25)	0.504	1.18 (0.98 - 1.41)	0.074	0.786
	rs5029748	0.87 (0.73 - 1.03)	0.108	1.05 (0.87 - 1.27)	0.628	0.955

[a] Adjusted for age, race and sex.

Table 8. Odds ratios from logistic regression models of dichotomized WC unadjusted and adjusted for covariates

		Unadjusted for covariates		Adjusted for covariates [a]		
Gene	SNP	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value	q-value
SOCS3	rs4436839	1.07 (0.91 - 1.26)	0.397	0.97 (0.82 - 1.15)	0.702	0.257
	rs7221341	**1.40 (1.17 - 1.67)**	**< 0.001**	1.05 (0.86 - 1.28)	0.623	0.254
	rs6501199	1.01 (0.84 - 1.20)	0.940	0.96 (0.80 - 1.15)	0.627	0.254
	rs12944581	0.94 (0.78 - 1.13)	0.479	0.92 (0.76 - 1.11)	0.371	0.254
	rs4969168	**0.75 (0.62 - 0.90)**	**0.002**	0.95 (0.78 - 1.17)	0.653	0.254
	rs11868378	**0.76 (0.64 - 0.90)**	**0.001**	0.99 (0.82 - 1.19)	0.884	0.289
	rs9914220	**0.75 (0.61 - 0.93)**	**0.009**	1.08 (0.85 - 1.38)	0.536	0.254
	rs4969172	**1.41 (1.21 - 1.64)**	**< 0.001**	1.01 (0.83 - 1.22)	0.936	0.291
NFKB1	rs3774932	**0.81 (0.68 - 0.96)**	**0.014**	**0.84 (0.70 - 0.99)**	**0.042**	0.130
	rs3774934	**0.67 (0.54 - 0.82)**	**< 0.001**	0.86 (0.68 - 1.08)	0.188	0.201
	rs1599961	1.08 (0.92 - 1.28)	0.351	1.12 (0.94 - 1.33)	0.194	0.201
	rs3774956	1.07 (0.91 - 1.27)	0.399	1.15 (0.97 - 1.36)	0.104	0.201
	rs11722146	0.98 (0.83 - 1.17)	0.858	1.09 (0.91 - 1.31)	0.333	0.254
	rs3774968	**0.81 (0.69 - 0.96)**	**0.017**	**0.81 (0.68 - 0.97)**	**0.020**	0.127
	rs7674640	0.95 (0.80 - 1.12)	0.518	0.96 (0.81 - 1.14)	0.618	0.254
	rs4698863	1.00 (0.84 - 1.19)	0.987	1.08 (0.91 - 1.29)	0.390	0.254
	rs1609798	0.97 (0.81 - 1.15)	0.695	1.05 (0.88 - 1.26)	0.581	0.254
IKBKB	rs10958713	0.90 (0.76 - 1.05)	0.184	1.05 (0.89 - 1.24)	0.568	0.254
	rs3747811	1.01 (0.86 - 1.19)	0.889	1.13 (0.96 - 1.33)	0.147	0.201
	rs5029748	**0.83 (0.70 - 0.98)**	**0.024**	1.03 (0.86 - 1.23)	0.764	0.264

[a] Adjusted for age, race and sex.

Table 9. Odds ratios of logistic regression models of alternate dichotomized BMI unadjusted and adjusted for covariates

		Unadjusted for covariates		Adjusted for covariates [a]		
Gene	SNP	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value	q-value
SOCS3	rs4436839	0.94 (0.81 - 1.10)	0.437	0.95 (0.80 - 1.11)	0.507	0.812
	rs7221341	1.05 (0.89 - 1.25)	0.556	1.12 (0.91 - 1.37)	0.296	0.764
	rs6501199	0.88 (0.74 - 1.05)	0.155	0.90 (0.75 - 1.07)	0.226	0.764
	rs12944581	0.87 (0.73 - 1.04)	0.131	0.91 (0.75 - 1.09)	0.296	0.764
	rs4969168	1.09 (0.93 - 1.29)	0.293	1.04 (0.86 - 1.26)	0.656	0.842
	rs11868378	1.04 (0.89 - 1.21)	0.655	0.98 (0.83 - 1.17)	0.860	0.892
	rs9914220	1.12 (0.92 - 1.35)	0.258	1.10 (0.88 - 1.37)	0.402	0.782
	rs4969172	0.96 (0.84 - 1.11)	0.613	0.99 (0.82 - 1.19)	0.883	0.892
NFKB1	rs3774932	0.95 (0.81 - 1.11)	0.507	0.89 (0.75 - 1.05)	0.156	0.764
	rs3774934	1.03 (0.86 - 1.24)	0.714	0.89 (0.72 - 1.09)	0.257	0.764
	rs1599961	1.00 (0.85 - 1.17)	0.963	1.07 (0.91 - 1.27)	0.407	0.782
	rs3774956	1.00 (0.85 - 1.17)	0.992	1.09 (0.92 - 1.28)	0.318	0.764
	rs11722146	0.97 (0.82 - 1.14)	0.702	1.04 (0.87 - 1.24)	0.658	0.842
	rs3774968	0.94 (0.80 - 1.10)	0.409	0.86 (0.73 - 1.02)	0.085	0.764
	rs7674640	1.00 (0.86 - 1.18)	0.970	0.94 (0.80 - 1.11)	0.465	0.812
	rs4698863	0.98 (0.83 - 1.15)	0.771	1.02 (0.86 - 1.21)	0.819	0.892
	rs1609798	0.95 (0.80 - 1.12)	0.541	1.00 (0.84 - 1.19)	0.960	0.922
IKBKB	rs10958713	1.07 (0.92 - 1.24)	0.387	1.05 (0.89 - 1.23)	0.568	0.839
	rs3747811	1.08 (0.93 - 1.26)	0.318	1.09 (0.93 - 1.28)	0.282	0.764
	rs5029748	1.03 (0.89 - 1.20)	0.687	0.99 (0.83 - 1.17)	0.857	0.892

[a] Adjusted for age, race and sex.

Table 10. Odds ratios from logistic regression models of dichotomized BMI unadjusted and adjusted for age and sex only

		Unadjusted for covariates		Adjusted for covariates [a]		
Gene	SNP	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value	q-value
SOCS3	rs4436839	1.13 (0.95 - 1.35)	0.159	1.14 (0.95 - 1.35)	0.157	0.955
	rs7221341	**1.51 (1.26 - 1.81)**	**< 0.001**	**1.45 (1.20 - 1.75)**	**< 0.001**	0.955
	rs6501199	0.98 (0.81 - 1.19)	0.854	0.98 (0.81 - 1.19)	0.865	0.955
	rs12944581	0.97 (0.80 - 1.18)	0.742	1.01 (0.83 - 1.24)	0.904	0.955
	rs4969168	0.84 (0.69 - 1.02)	0.073	0.85 (0.70 - 1.04)	0.104	0.955
	rs11868378	**0.78 (0.65 - 0.93)**	**0.005**	**0.78 (0.65 - 0.94)**	**0.007**	0.955
	rs9914220	0.83 (0.67 - 1.04)	0.108	0.87 (0.70 - 1.10)	0.246	0.955
	rs4969172	**1.34 (1.15 - 1.57)**	**< 0.001**	**1.31 (1.11 - 1.54)**	**0.001**	0.955
NFKB1	rs3774932	0.91 (0.76 - 1.09)	0.288	0.85 (0.71 - 1.03)	0.090	0.955
	rs3774934	**0.71 (0.57 - 0.89)**	**0.002**	**0.71 (0.56 - 0.88)**	**0.002**	0.955
	rs1599961	0.94 (0.79 - 1.13)	0.519	0.99 (0.83 - 1.20)	0.985	0.955
	rs3774956	0.94 (0.79 - 1.12)	0.479	1.00 (0.84 - 1.21)	0.935	0.955
	rs11722146	0.87 (0.72 - 1.05)	0.134	0.92 (0.76 - 1.12)	0.423	0.955
	rs3774968	0.91 (0.76 - 1.09)	0.312	0.85 (0.71 - 1.03)	0.089	0.955
	rs7674640	1.00 (0.84 - 1.19)	0.978	0.95 (0.79 - 1.14)	0.549	0.955
	rs4698863	0.90 (0.74 - 1.08)	0.239	0.93 (0.77 - 1.12)	0.447	0.955
	rs1609798	0.85 (0.71 - 1.03)	0.097	0.90 (0.74 - 1.09)	0.282	0.955
IKBKB	rs10958713	0.98 (0.82 - 1.15)	0.769	0.97 (0.82 - 1.16)	0.736	0.955
	rs3747811	1.06 (0.90 - 1.25)	0.504	1.05 (0.89 - 1.25)	0.568	0.955
	rs5029748	0.87 (0.73 - 1.03)	0.108	0.87 (0.73 - 1.04)	0.114	0.955

[a] Adjusted for age and sex

Table 11. Main effect logistic regression models of dichotomized BMI

Nutrient	Unadjusted for covariates		Adjusted for covariates [a]	
	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value
Carbohydrate	**0.996 (0.993 - 0.999)**	**0.014**	**0.997 (0.994 - 1.000)**	**0.040**
Fat	1.00 (0.99 - 1.01)	0.700	1.00 (0.99 - 1.01)	0.821
Protein	1.00 (0.99 - 1.01)	0.123	**1.01 (1.00 - 1.02)**	**0.006**
Alcohol	**1.02 (1.01 - 1.03)**	**0.002**	1.01 (1.00 - 1.02)	0.222

[a] Adjusted for age, sex, METS and race.

Table 12. Main effect logistic regression models of dichotomized WC

Nutrient	Unadjusted for covariates		Adjusted for covariates [a]	
	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value
Carbohydrate	**0.997 (0.994 - 0.999)**	**0.020**	**0.997 (0.994 - 1.000)**	**0.041**
Fat	1.00 (0.99 - 1.01)	0.216	1.00 (0.99 - 1.01)	0.559
Protein	1.00 (0.99 - 1.01)	0.324	**1.01 (1.00 - 1.02)**	**0.023**
Alcohol	**1.01 (1.00 - 1.03)**	**0.039**	1.00 (0.99 - 1.02)	0.516

[a] Adjusted for age, sex, METS and race.

Table 13. Main effect logistic regression models of alternate dichotomized BMI

Nutrient	Unadjusted for covariates		Adjusted for covariates [a]	
	OR (95% C.I.)	p-value	OR (95% C.I.)	p-value
Carbohydrate	0.998 (0.996 - 1.001)	0.219	0.998 (0.995 - 1.001)	0.131
Fat	0.99 (0.98 - 1.00)	0.264	1.00 (0.99 - 1.01)	0.680
Protein	**1.01 (1.00 - 1.02)**	**< 0.001**	**1.01 (1.00 - 1.01)**	**0.001**
Alcohol	1.00 (0.99 - 1.01)	0.875	1.00 (0.99 - 1.01)	0.495

[a] Adjusted for age, sex, METS and race.

Table 14. Gene-gene interaction logistic regression models of dichotomized BMI

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	**rs4436839-rs3774932**	**0.037**	0.332
	rs4436839-rs3774934	0.532	0.921
	rs4436839-rs1599961	**0.013**	0.291
	rs4436839-rs3774956	**0.022**	0.291
	rs4436839-rs11722146	**0.005**	0.291
	rs4436839-rs3774968	0.069	0.480
	rs4436839-rs7674640	0.193	0.875
	rs4436839-rs4698863	**0.040**	0.338
	rs4436839-rs1609798	**0.007**	0.291
	rs7221341-rs3774932	0.434	0.921
	rs7221341-rs3774934	0.837	0.921
	rs7221341-rs1599961	0.920	0.921
	rs7221341-rs3774956	0.415	0.921
	rs7221341-rs11722146	0.495	0.921
	rs7221341-rs3774968	0.284	0.921
	rs7221341-rs7674640	0.216	0.877
	rs7221341-rs4698863	0.165	0.811
	rs7221341-rs1609798	0.382	0.921
	rs6501199-rs3774932	**0.022**	0.291
	rs6501199-rs3774934	0.360	0.921
	rs6501199-rs1599961	0.076	0.496
	rs6501199-rs3774956	0.066	0.480
	rs6501199-rs11722146	**0.011**	0.291

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199 rs3774968	**0.035**	0.332
	rs6501199-rs7674640	**0.030**	0.332
	rs6501199-rs4698863	**0.022**	0.291
	rs6501199-rs1609798	**0.004**	0.291
	rs12944581-rs3774932	**0.037**	0.332
	rs12944581-rs3774934	0.144	0.746
	rs12944581-rs1599961	**0.017**	0.291
	rs12944581-rs3774956	0.081	0.504
	rs12944581-rs11722146	0.107	0.625
	rs12944581-rs3774968	0.111	0.625
	rs12944581-rs7674640	0.534	0.921
	rs12944581-rs4698863	0.214	0.877
	rs12944581-rs1609798	0.058	0.456
	rs4969168-rs3774932	0.414	0.921
	rs4969168- rs3774934	0.477	0.921
	rs4969168-rs1599961	0.848	0.921
	rs4969168-rs3774956	0.812	0.921
	rs4969168-rs11722146	0.776	0.921
	rs4969168-rs3774968	0.814	0.921
	rs4969168-rs7674640	0.769	0.921
	rs4969168-rs4698863	0.576	0.921
	rs4969168-rs1609798	0.248	0.921
	rs11868378-rs3774932	0.260	0.921

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774934	0.609	0.921
	rs11868378-rs1599961	0.885	0.921
	rs11868378-rs3774956	0.716	0.921
	rs11868378-rs11722146	0.396	0.921
	rs11868378-rs3774968	0.507	0.921
	rs11868378-rs7674640	0.276	0.921
	rs11868378-rs4698863	0.853	0.921
	rs11868378-rs1609798	0.871	0.921
	rs9914220-rs3774932	0.882	0.921
	rs9914220-rs3774934	0.213	0.877
	rs9914220-rs1599961	0.369	0.921
	rs9914220-rs3774956	0.146	0.746
	rs9914220-rs11722146	0.600	0.921
	rs9914220-rs3774968	0.588	0.921
	rs9914220-rs7674640	0.725	0.921
	rs9914220-rs4698863	0.467	0.921
	rs9914220-rs1609798	0.730	0.921
	rs4969172-rs3774932	0.395	0.921
	rs4969172-rs3774934	0.920	0.921
	rs4969172-rs1599961	0.545	0.921
	rs4969172-rs3774956	0.562	0.921
	rs4969172-rs11722146	0.933	0.921
	rs4969172-rs3774968	0.439	0.921

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs7674640	0.632	0.921
	rs4969172-rs4698863	0.601	0.921
	rs4969172-rs1609798	0.750	0.921
SOCS3-IKBKB	rs4436839-rs10958713	0.328	0.921
	rs4436839-rs3747811	0.459	0.921
	rs4436839-rs5029748	0.502	0.921
	rs7221341-rs10958713	0.492	0.921
	rs7221341-rs3747811	0.886	0.921
	rs7221341-rs5029748	0.782	0.921
	rs6501199-rs10958713	0.681	0.921
	rs6501199-rs3747811	0.647	0.921
	rs6501199-rs5029748	0.374	0.921
	rs12944581-rs10958713	0.725	0.921
	rs12944581-rs3747811	0.943	0.921
	rs12944581-rs5029748	0.912	0.921
	rs4969168-rs10958713	0.414	0.921
	rs4969168-rs3747811	0.227	0.921
	rs4969168-rs5029748	0.440	0.921
	rs11868378-rs10958713	0.633	0.921
	rs11868378-rs3747811	0.810	0.921
	rs11868378-rs5029748	0.660	0.921
	rs9914220-rs10958713	0.599	0.921
	rs9914220-rs3747811	0.953	0.921

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs5029748	0.912	0.921
	rs4969172-rs10958713	0.952	0.921
	rs4969172-rs3747811	0.473	0.921
	rs4969172-rs5029748	0.815	0.921
IKBKB-NFKB1	rs10958713-rs3774932	0.708	0.921
	rs10958713-rs3774934	0.304	0.921
	rs10958713-rs1599961	0.656	0.921
	rs10958713-rs3774956	0.923	0.921
	rs10958713-rs11722146	0.880	0.921
	rs10958713-rs3774968	0.810	0.921
	rs10958713-rs7674640	0.833	0.921
	rs10958713-rs4698863	0.869	0.921
	rs10958713-rs1609798	0.831	0.921
	rs3747811-rs3774932	0.705	0.921
	rs3747811- rs3774934	0.186	0.874
	rs3747811-rs1599961	0.646	0.920
	rs3747811-rs3774956	0.999	0.957
	rs3747811-rs11722146	0.813	0.920
	rs3747811-rs3774968	0.944	0.920
	rs3747811-rs7674640	0.824	0.920
	rs3747811-rs4698863	0.649	0.920
	rs3747811-rs1609798	0.489	0.920
	rs5029748-rs3774932	0.824	0.920

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774934	0.802	0.920
	rs5029748-rs1599961	0.746	0.920
	rs5029748-rs3774956	0.841	0.920
	rs5029748-rs11722146	0.926	0.920
	rs5029748-rs3774968	0.792	0.920
	rs5029748-rs7674640	0.549	0.920
	rs5029748-rs4698863	0.834	0.920
	rs5029748-rs1609798	0.934	0.920

Adjusted for age, sex and ethnocultural background.

Table 15. Gene-gene interaction logistic regression models of dichotomized WC

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.350	0.849
	rs4436839-rs3774934	0.783	0.887
	rs4436839-rs1599961	0.284	0.849
	rs4436839-rs3774956	0.253	0.849
	rs4436839-rs11722146	**0.041**	0.597
	rs4436839-rs3774968	0.374	0.849
	rs4436839-rs7674640	0.354	0.849
	rs4436839-rs4698863	0.080	0.707
	rs4436839-rs1609798	**0.032**	0.597
	rs7221341-rs3774932	0.573	0.849
	rs7221341-rs3774934	0.967	0.926
	rs7221341-rs1599961	0.860	0.887
	rs7221341-rs3774956	0.640	0.849
	rs7221341-rs11722146	0.636	0.849
	rs7221341-rs3774968	0.390	0.849
	rs7221341-rs7674640	0.247	0.849
	rs7221341-rs4698863	0.115	0.849
	rs7221341-rs1609798	0.301	0.849
	rs6501199-rs3774932	**0.023**	0.597
	rs6501199-rs3774934	0.325	0.849
	rs6501199-rs1599961	0.134	0.849
	rs6501199-rs3774956	0.121	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	**0.019**	0.597
	rs6501199 rs3774968	**0.034**	0.597
	rs6501199-rs7674640	**0.038**	0.597
	rs6501199-rs4698863	**0.018**	0.597
	rs6501199-rs1609798	**0.006**	0.597
	rs12944581-rs3774932	0.442	0.849
	rs12944581-rs3774934	0.304	0.849
	rs12944581-rs1599961	0.297	0.849
	rs12944581-rs3774956	0.582	0.849
	rs12944581-rs11722146	0.085	0.707
	rs12944581-rs3774968	0.741	0.887
	rs12944581-rs7674640	0.970	0.926
	rs12944581-rs4698863	0.182	0.849
	rs12944581-rs1609798	0.080	0.707
	rs4969168-rs3774932	0.891	0.895
	rs4969168- rs3774934	0.384	0.849
	rs4969168-rs1599961	0.814	0.887
	rs4969168-rs3774956	0.926	0.923
	rs4969168-rs11722146	0.612	0.849
	rs4969168-rs3774968	0.498	0.849
	rs4969168-rs7674640	0.554	0.849
	rs4969168-rs4698863	0.999	0.931
	rs4969168-rs1609798	0.167	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.625	0.849
	rs11868378-rs3774934	0.653	0.850
	rs11868378-rs1599961	0.587	0.849
	rs11868378-rs3774956	0.568	0.849
	rs11868378-rs11722146	0.265	0.849
	rs11868378-rs3774968	0.875	0.887
	rs11868378-rs7674640	0.999	0.931
	rs11868378-rs4698863	0.956	0.926
	rs11868378-rs1609798	0.559	0.849
	rs9914220-rs3774932	0.734	0.887
	rs9914220-rs3774934	0.338	0.849
	rs9914220-rs1599961	0.823	0.887
	rs9914220-rs3774956	0.421	0.849
	rs9914220-rs11722146	0.626	0.849
	rs9914220-rs3774968	0.410	0.849
	rs9914220-rs7674640	0.484	0.849
	rs9914220-rs4698863	0.540	0.849
	rs9914220-rs1609798	0.624	0.849
	rs4969172-rs3774932	0.864	0.887
	rs4969172-rs3774934	0.818	0.887
	rs4969172-rs1599961	0.842	0.887
	rs4969172-rs3774956	0.951	0.926
	rs4969172-rs11722146	0.840	0.887

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.589	0.849
	rs4969172-rs7674640	0.444	0.849
	rs4969172-rs4698863	0.645	0.849
	rs4969172-rs1609798	0.623	0.849
SOCS3-IKBKB	rs4436839-rs10958713	0.086	0.707
	rs4436839-rs3747811	0.083	0.707
	rs4436839-rs5029748	0.127	0.849
	rs7221341-rs10958713	0.084	0.707
	rs7221341-rs3747811	0.184	0.849
	rs7221341-rs5029748	0.185	0.849
	rs6501199-rs10958713	0.410	0.849
	rs6501199-rs3747811	0.307	0.849
	rs6501199-rs5029748	0.667	0.850
	rs12944581-rs10958713	0.839	0.887
	rs12944581-rs3747811	0.525	0.849
	rs12944581-rs5029748	0.869	0.887
	rs4969168-rs10958713	0.802	0.887
	rs4969168-rs3747811	0.834	0.887
	rs4969168-rs5029748	0.935	0.924
	rs11868378-rs10958713	0.561	0.849
	rs11868378-rs3747811	0.743	0.887
	rs11868378-rs5029748	0.457	0.849
	rs9914220-rs10958713	0.354	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.614	0.849
	rs9914220-rs5029748	0.870	0.887
	rs4969172-rs10958713	0.621	0.849
	rs4969172-rs3747811	0.989	0.931
	rs4969172-rs5029748	0.858	0.887
IKBKB-NFKB1	rs10958713-rs3774932	0.788	0.887
	rs10958713-rs3774934	0.640	0.849
	rs10958713-rs1599961	0.456	0.849
	rs10958713-rs3774956	0.388	0.849
	rs10958713-rs11722146	0.287	0.849
	rs10958713-rs3774968	0.668	0.850
	rs10958713-rs7674640	0.849	0.887
	rs10958713-rs4698863	0.565	0.849
	rs10958713-rs1609798	0.258	0.849
	rs3747811-rs3774932	0.316	0.849
	rs3747811- rs3774934	0.543	0.849
	rs3747811-rs1599961	0.213	0.849
	rs3747811-rs3774956	0.255	0.849
	rs3747811-rs11722146	0.310	0.849
	rs3747811-rs3774968	0.369	0.849
	rs3747811-rs7674640	0.351	0.849
	rs3747811-rs4698863	0.283	0.849
	rs3747811-rs1609798	0.144	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.803	0.887
	rs5029748-rs3774934	0.689	0.867
	rs5029748-rs1599961	0.555	0.849
	rs5029748-rs3774956	0.335	0.849
	rs5029748-rs11722146	0.365	0.849
	rs5029748-rs3774968	0.556	0.849
	rs5029748-rs7674640	0.726	0.887
	rs5029748-rs4698863	0.514	0.849
	rs5029748-rs1609798	0.414	0.849

Adjusted for age, sex and ethnocultural background.

Table 16. Gene-gene interaction logistic regression models of alternate dichotomized BMI

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.475	0.469
	rs4436839-rs3774934	0.111	0.469
	rs4436839-rs1599961	0.226	0.469
	rs4436839-rs3774956	0.246	0.469
	rs4436839-rs11722146	0.104	0.469
	rs4436839-rs3774968	0.673	0.477
	rs4436839-rs7674640	0.881	0.505
	rs4436839-rs4698863	0.248	0.469
	rs4436839-rs1609798	0.105	0.469
	rs7221341-rs3774932	0.783	0.495
	rs7221341-rs3774934	0.646	0.476
	rs7221341-rs1599961	0.929	0.514
	rs7221341-rs3774956	0.602	0.476
	rs7221341-rs11722146	0.926	0.514
	rs7221341-rs3774968	0.780	0.495
	rs7221341-rs7674640	0.725	0.483
	rs7221341-rs4698863	0.350	0.469
	rs7221341-rs1609798	0.664	0.476
	rs6501199-rs3774932	0.190	0.469
	rs6501199-rs3774934	0.832	0.498
	rs6501199-rs1599961	0.384	0.469
	rs6501199-rs3774956	0.301	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	0.108	0.469
	rs6501199 rs3774968	0.222	0.469
	rs6501199-rs7674640	0.354	0.469
	rs6501199-rs4698863	0.218	0.469
	rs6501199-rs1609798	0.095	0.469
	rs12944581-rs3774932	0.570	0.469
	rs12944581-rs3774934	0.361	0.469
	rs12944581-rs1599961	0.296	0.469
	rs12944581-rs3774956	0.472	0.469
	rs12944581-rs11722146	0.377	0.469
	rs12944581-rs3774968	0.896	0.509
	rs12944581-rs7674640	0.958	0.521
	rs12944581-rs4698863	0.413	0.469
	rs12944581-rs1609798	0.145	0.469
	rs4969168-rs3774932	0.492	0.469
	rs4969168- rs3774934	0.551	0.469
	rs4969168-rs1599961	0.534	0.469
	rs4969168-rs3774956	0.660	0.476
	rs4969168-rs11722146	0.817	0.495
	rs4969168-rs3774968	0.458	0.469
	rs4969168-rs7674640	0.681	0.477
	rs4969168-rs4698863	0.800	0.495
	rs4969168-rs1609798	0.312	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.525	0.469
	rs11868378-rs3774934	0.987	0.529
	rs11868378-rs1599961	0.515	0.469
	rs11868378-rs3774956	0.869	0.502
	rs11868378-rs11722146	0.772	0.495
	rs11868378-rs3774968	0.566	0.469
	rs11868378-rs7674640	0.406	0.469
	rs11868378-rs4698863	0.230	0.469
	rs11868378-rs1609798	0.216	0.469
	rs9914220-rs3774932	0.480	0.469
	rs9914220-rs3774934	0.427	0.469
	rs9914220-rs1599961	0.066	0.469
	rs9914220-rs3774956	**0.032**	0.469
	rs9914220-rs11722146	0.570	0.469
	rs9914220-rs3774968	0.510	0.469
	rs9914220-rs7674640	0.967	0.522
	rs9914220-rs4698863	0.426	0.469
	rs9914220-rs1609798	0.792	0.495
	rs4969172-rs3774932	0.551	0.469
	rs4969172-rs3774934	0.842	0.500
	rs4969172-rs1599961	0.135	0.469
	rs4969172-rs3774956	0.162	0.469
	rs4969172-rs11722146	0.388	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.609	0.476
	rs4969172-rs7674640	0.632	0.476
	rs4969172-rs4698863	0.177	0.469
	rs4969172-rs1609798	0.478	0.469
SOCS3-IKBKB	rs4436839-rs10958713	0.274	0.469
	rs4436839-rs3747811	0.499	0.469
	rs4436839-rs5029748	0.577	0.469
	rs7221341-rs10958713	0.404	0.469
	rs7221341-rs3747811	0.636	0.476
	rs7221341-rs5029748	0.819	0.495
	rs6501199-rs10958713	0.391	0.469
	rs6501199-rs3747811	0.327	0.469
	rs6501199-rs5029748	0.155	0.469
	rs12944581-rs10958713	0.726	0.483
	rs12944581-rs3747811	0.616	0.476
	rs12944581-rs5029748	0.926	0.514
	rs4969168-rs10958713	0.504	0.469
	rs4969168-rs3747811	0.332	0.469
	rs4969168-rs5029748	0.394	0.469
	rs11868378-rs10958713	0.473	0.469
	rs11868378-rs3747811	0.497	0.469
	rs11868378-rs5029748	0.486	0.469
	rs9914220-rs10958713	0.219	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.471	0.469
	rs9914220-rs5029748	0.563	0.469
	rs4969172-rs10958713	0.857	0.502
	rs4969172-rs3747811	0.699	0.480
	rs4969172-rs5029748	0.862	0.502
IKBKB-NFKB1	rs10958713-rs3774932	0.317	0.469
	rs10958713-rs3774934	0.407	0.469
	rs10958713-rs1599961	0.266	0.469
	rs10958713-rs3774956	0.473	0.469
	rs10958713-rs11722146	0.664	0.476
	rs10958713-rs3774968	0.403	0.469
	rs10958713-rs7674640	0.949	0.521
	rs10958713-rs4698863	0.743	0.489
	rs10958713-rs1609798	0.484	0.469
	rs3747811-rs3774932	0.319	0.469
	rs3747811- rs3774934	0.217	0.469
	rs3747811-rs1599961	0.351	0.469
	rs3747811-rs3774956	0.554	0.469
	rs3747811-rs11722146	0.634	0.476
	rs3747811-rs3774968	0.440	0.469
	rs3747811-rs7674640	0.690	0.478
	rs3747811-rs4698863	0.399	0.469
	rs3747811-rs1609798	0.275	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.649	0.476
	rs5029748-rs3774934	0.817	0.495
	rs5029748-rs1599961	0.211	0.469
	rs5029748-rs3774956	0.294	0.469
	rs5029748-rs11722146	0.461	0.469
	rs5029748-rs3774968	0.716	0.483
	rs5029748-rs7674640	0.778	0.495
	rs5029748-rs4698863	0.535	0.469
	rs5029748-rs1609798	0.425	0.469

Adjusted for age, sex and ethnocultural background.

Table 17. Gene-gene interaction logistic regression models of dichotomized BMI considering only whites

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.207	0.849
	rs4436839-rs3774934	**0.038**	0.887
	rs4436839-rs1599961	**0.035**	0.849
	rs4436839-rs3774956	**0.011**	0.849
	rs4436839-rs11722146	**0.028**	0.597
	rs4436839-rs3774968	0.144	0.849
	rs4436839-rs7674640	0.327	0.849
	rs4436839-rs4698863	**0.046**	0.707
	rs4436839-rs1609798	0.095	0.597
	rs7221341-rs3774932	0.753	0.849
	rs7221341-rs3774934	0.884	0.926
	rs7221341-rs1599961	0.852	0.887
	rs7221341-rs3774956	0.343	0.849
	rs7221341-rs11722146	0.377	0.849
	rs7221341-rs3774968	0.383	0.849
	rs7221341-rs7674640	0.328	0.849
	rs7221341-rs4698863	0.120	0.849
	rs7221341-rs1609798	0.497	0.849
	rs6501199-rs3774932	**0.013**	0.597
	rs6501199-rs3774934	0.284	0.849
	rs6501199-rs1599961	0.147	0.849
	rs6501199-rs3774956	0.093	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	**0.030**	0.597
	rs6501199 rs3774968	**0.010**	0.597
	rs6501199-rs7674640	**0.006**	0.597
	rs6501199-rs4698863	**0.031**	0.597
	rs6501199-rs1609798	**0.023**	0.597
	rs12944581-rs3774932	**0.009**	0.849
	rs12944581-rs3774934	0.116	0.849
	rs12944581-rs1599961	**0.029**	0.849
	rs12944581-rs3774956	**0.048**	0.849
	rs12944581-rs11722146	0.069	0.707
	rs12944581-rs3774968	**0.012**	0.887
	rs12944581-rs7674640	**0.026**	0.926
	rs12944581-rs4698863	0.113	0.849
	rs12944581-rs1609798	0.072	0.707
	rs4969168-rs3774932	0.067	0.895
	rs4969168- rs3774934	0.218	0.849
	rs4969168-rs1599961	0.631	0.887
	rs4969168-rs3774956	0.512	0.923
	rs4969168-rs11722146	0.701	0.849
	rs4969168-rs3774968	0.078	0.849
	rs4969168-rs7674640	**0.041**	0.849
	rs4969168-rs4698863	0.433	0.931
	rs4969168-rs1609798	0.726	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.935	0.849
	rs11868378-rs3774934	0.661	0.850
	rs11868378-rs1599961	0.953	0.849
	rs11868378-rs3774956	0.809	0.849
	rs11868378-rs11722146	0.617	0.849
	rs11868378-rs3774968	0.644	0.887
	rs11868378-rs7674640	0.894	0.931
	rs11868378-rs4698863	0.595	0.926
	rs11868378-rs1609798	0.599	0.849
	rs9914220-rs3774932	0.626	0.887
	rs9914220-rs3774934	0.359	0.849
	rs9914220-rs1599961	0.510	0.887
	rs9914220-rs3774956	0.442	0.849
	rs9914220-rs11722146	0.648	0.849
	rs9914220-rs3774968	0.727	0.849
	rs9914220-rs7674640	0.334	0.849
	rs9914220-rs4698863	0.816	0.849
	rs9914220-rs1609798	0.999	0.849
	rs4969172-rs3774932	0.958	0.887
	rs4969172-rs3774934	0.906	0.887
	rs4969172-rs1599961	0.647	0.887
	rs4969172-rs3774956	0.413	0.926
	rs4969172-rs11722146	0.963	0.887

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.834	0.849
	rs4969172-rs7674640	0.976	0.849
	rs4969172-rs4698863	0.752	0.849
	rs4969172-rs1609798	0.606	0.849
SOCS3-IKBKB	rs4436839-rs10958713	0.387	0.707
	rs4436839-rs3747811	0.542	0.707
	rs4436839-rs5029748	0.585	0.849
	rs7221341-rs10958713	0.678	0.707
	rs7221341-rs3747811	0.781	0.849
	rs7221341-rs5029748	0.899	0.849
	rs6501199-rs10958713	0.911	0.849
	rs6501199-rs3747811	0.848	0.849
	rs6501199-rs5029748	0.816	0.850
	rs12944581-rs10958713	0.773	0.887
	rs12944581-rs3747811	0.595	0.849
	rs12944581-rs5029748	0.540	0.887
	rs4969168-rs10958713	**0.035**	0.887
	rs4969168-rs3747811	**0.012**	0.887
	rs4969168-rs5029748	0.890	0.924
	rs11868378-rs10958713	0.676	0.849
	rs11868378-rs3747811	0.106	0.887
	rs11868378-rs5029748	0.876	0.849
	rs9914220-rs10958713	0.543	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.230	0.849
	rs9914220-rs5029748	0.327	0.887
	rs4969172-rs10958713	0.173	0.849
	rs4969172-rs3747811	0.683	0.931
	rs4969172-rs5029748	0.689	0.887
IKBKB-NFKB1	rs10958713-rs3774932	0.608	0.887
	rs10958713-rs3774934	0.603	0.849
	rs10958713-rs1599961	0.634	0.849
	rs10958713-rs3774956	0.813	0.849
	rs10958713-rs11722146	0.740	0.849
	rs10958713-rs3774968	0.560	0.850
	rs10958713-rs7674640	0.863	0.887
	rs10958713-rs4698863	0.897	0.849
	rs10958713-rs1609798	0.812	0.849
	rs3747811-rs3774932	0.756	0.849
	rs3747811- rs3774934	0.243	0.849
	rs3747811-rs1599961	0.678	0.849
	rs3747811-rs3774956	0.980	0.849
	rs3747811-rs11722146	0.812	0.849
	rs3747811-rs3774968	0.945	0.849
	rs3747811-rs7674640	0.883	0.849
	rs3747811-rs4698863	0.612	0.849
	rs3747811-rs1609798	0.508	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.850	0.887
	rs5029748-rs3774934	0.834	0.867
	rs5029748-rs1599961	0.854	0.849
	rs5029748-rs3774956	0.832	0.849
	rs5029748-rs11722146	0.920	0.849
	rs5029748-rs3774968	0.712	0.849
	rs5029748-rs7674640	0.549	0.887
	rs5029748-rs4698863	0.849	0.849
	rs5029748-rs1609798	0.943	0.849

Adjusted for age, sex.

Table 18. Gene-gene interaction logistic regression models of dichotomized BMI considering only East Asians

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.172	0.849
	rs4436839-rs3774934	0.152	0.887
	rs4436839-rs1599961	0.035	0.849
	rs4436839-rs3774956	0.433	0.849
	rs4436839-rs11722146	0.011	0.597
	rs4436839-rs3774968	0.434	0.849
	rs4436839-rs7674640	0.128	0.849
	rs4436839-rs4698863	0.214	0.707
	rs4436839-rs1609798	0.119	0.597
	rs7221341-rs3774932	0.133	0.849
	rs7221341-rs3774934	0.247	0.926
	rs7221341-rs1599961	0.132	0.887
	rs7221341-rs3774956	0.208	0.849
	rs7221341-rs11722146	0.690	0.849
	rs7221341-rs3774968	0.081	0.849
	rs7221341-rs7674640	**0.048**	0.849
	rs7221341-rs4698863	0.943	0.849
	rs7221341-rs1609798	0.724	0.849
	rs6501199-rs3774932	0.389	0.597
	rs6501199-rs3774934	0.495	0.849
	rs6501199-rs1599961	0.678	0.849
	rs6501199-rs3774956	0.686	0.849
	rs6501199-rs11722146	0.407	0.597

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199 rs3774968	0.427	0.597
	rs6501199-rs7674640	0.151	0.597
	rs6501199-rs4698863	0.273	0.597
	rs6501199-rs1609798	0.144	0.597
	rs12944581-rs3774932	0.420	0.849
	rs12944581-rs3774934	0.333	0.849
	rs12944581-rs1599961	0.284	0.849
	rs12944581-rs3774956	0.428	0.849
	rs12944581-rs11722146	0.380	0.707
	rs12944581-rs3774968	0.530	0.887
	rs12944581-rs7674640	0.859	0.926
	rs12944581-rs4698863	0.379	0.849
	rs12944581-rs1609798	0.226	0.707
	rs4969168-rs3774932	0.651	0.895
	rs4969168- rs3774934	0.538	0.849
	rs4969168-rs1599961	0.583	0.887
	rs4969168-rs3774956	0.792	0.923
	rs4969168-rs11722146	0.993	0.849
	rs4969168-rs3774968	0.765	0.849
	rs4969168-rs7674640	0.839	0.849
	rs4969168-rs4698863	0.884	0.931
	rs4969168-rs1609798	0.504	0.849
	rs11868378-rs3774932	0.110	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774934	0.667	0.850
	rs11868378-rs1599961	0.617	0.849
	rs11868378-rs3774956	0.286	0.849
	rs11868378-rs11722146	0.228	0.849
	rs11868378-rs3774968	0.281	0.887
	rs11868378-rs7674640	0.246	0.931
	rs11868378-rs4698863	0.378	0.926
	rs11868378-rs1609798	0.447	0.849
	rs9914220-rs3774932	0.733	0.887
	rs9914220-rs3774934	0.332	0.849
	rs9914220-rs1599961	0.497	0.887
	rs9914220-rs3774956	0.514	0.849
	rs9914220-rs11722146	0.520	0.849
	rs9914220-rs3774968	0.651	0.849
	rs9914220-rs7674640	0.989	0.849
	rs9914220-rs4698863	0.631	0.849
	rs9914220-rs1609798	0.976	0.849
	rs4969172-rs3774932	0.066	0.887
	rs4969172-rs3774934	0.088	0.887
	rs4969172-rs1599961	0.062	0.887
	rs4969172-rs3774956	**0.048**	0.926
	rs4969172-rs11722146	0.137	0.887
	rs4969172-rs3774968	0.114	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs7674640	0.055	0.849
	rs4969172-rs4698863	0.480	0.849
	rs4969172-rs1609798	0.259	0.849
SOCS3-IKBKB	rs4436839-rs10958713	0.365	0.707
	rs4436839-rs3747811	0.398	0.707
	rs4436839-rs5029748	0.329	0.849
	rs7221341-rs10958713	0.114	0.707
	rs7221341-rs3747811	0.128	0.849
	rs7221341-rs5029748	0.114	0.849
	rs6501199-rs10958713	0.825	0.849
	rs6501199-rs3747811	0.826	0.849
	rs6501199-rs5029748	0.880	0.850
	rs12944581-rs10958713	0.811	0.887
	rs12944581-rs3747811	0.901	0.849
	rs12944581-rs5029748	0.925	0.887
	rs4969168-rs10958713	0.751	0.887
	rs4969168-rs3747811	0.610	0.887
	rs4969168-rs5029748	0.678	0.924
	rs11868378-rs10958713	0.256	0.849
	rs11868378-rs3747811	0.802	0.887
	rs11868378-rs5029748	0.620	0.849
	rs9914220-rs10958713	0.645	0.849
	rs9914220-rs3747811	0.978	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs5029748	0.934	0.887
	rs4969172-rs10958713	0.967	0.849
	rs4969172-rs3747811	0.489	0.931
	rs4969172-rs5029748	0.834	0.887
IKBKB-NFKB1	rs10958713-rs3774932	0.767	0.887
	rs10958713-rs3774934	0.364	0.849
	rs10958713-rs1599961	0.664	0.849
	rs10958713-rs3774956	0.968	0.849
	rs10958713-rs11722146	0.895	0.849
	rs10958713-rs3774968	0.880	0.850
	rs10958713-rs7674640	0.803	0.887
	rs10958713-rs4698863	0.860	0.849
	rs10958713-rs1609798	0.808	0.849
	rs3747811-rs3774932	0.795	0.849
	rs3747811- rs3774934	0.128	0.849
	rs3747811-rs1599961	0.679	0.849
	rs3747811-rs3774956	0.923	0.849
	rs3747811-rs11722146	0.856	0.849
	rs3747811-rs3774968	0.979	0.849
	rs3747811-rs7674640	0.843	0.849
	rs3747811-rs4698863	0.666	0.849
	rs3747811-rs1609798	0.423	0.849
	rs5029748-rs3774932	0.838	0.887

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774934	0.781	0.867
	rs5029748-rs1599961	0.650	0.849
	rs5029748-rs3774956	0.579	0.849
	rs5029748-rs11722146	0.359	0.849
	rs5029748-rs3774968	0.593	0.849
	rs5029748-rs7674640	0.558	0.887
	rs5029748-rs4698863	0.829	0.849
	rs5029748-rs1609798	0.939	0.849

Adjusted for age, sex.

Table 19. Gene-gene interaction logistic regression models of alternative dichotomized BMI considering only South Asians

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.673	0.849
	rs4436839-rs3774934	0.787	0.887
	rs4436839-rs1599961	0.060	0.849
	rs4436839-rs3774956	0.051	0.849
	rs4436839-rs11722146	0.056	0.597
	rs4436839-rs3774968	0.438	0.849
	rs4436839-rs7674640	0.527	0.849
	rs4436839-rs4698863	**0.010**	0.707
	rs4436839-rs1609798	**0.025**	0.597
	rs7221341-rs3774932	0.289	0.849
	rs7221341-rs3774934	0.593	0.926
	rs7221341-rs1599961	0.228	0.887
	rs7221341-rs3774956	0.266	0.849
	rs7221341-rs11722146	0.893	0.849
	rs7221341-rs3774968	0.173	0.849
	rs7221341-rs7674640	**0.022**	0.849
	rs7221341-rs4698863	0.125	0.849
	rs7221341-rs1609798	0.321	0.849
	rs6501199-rs3774932	0.148	0.597
	rs6501199-rs3774934	0.074	0.849
	rs6501199-rs1599961	0.487	0.849
	rs6501199-rs3774956	0.135	0.849
	rs6501199-rs11722146	0.056	0.597

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199 rs3774968	0.112	0.597
	rs6501199-rs7674640	0.094	0.597
	rs6501199-rs4698863	**0.030**	0.597
	rs6501199-rs1609798	0.056	0.597
	rs12944581-rs3774932	0.771	0.849
	rs12944581-rs3774934	0.730	0.849
	rs12944581-rs1599961	0.062	0.849
	rs12944581-rs3774956	0.098	0.849
	rs12944581-rs11722146	0.114	0.707
	rs12944581-rs3774968	0.765	0.887
	rs12944581-rs7674640	0.511	0.926
	rs12944581-rs4698863	0.103	0.849
	rs12944581-rs1609798	0.107	0.707
	rs4969168-rs3774932	0.373	0.895
	rs4969168- rs3774934	0.851	0.849
	rs4969168-rs1599961	0.380	0.887
	rs4969168-rs3774956	0.568	0.923
	rs4969168-rs11722146	0.512	0.849
	rs4969168-rs3774968	0.335	0.849
	rs4969168-rs7674640	0.185	0.849
	rs4969168-rs4698863	0.158	0.931
	rs4969168-rs1609798	0.115	0.849
	rs11868378-rs3774932	0.797	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774934	0.644	0.850
	rs11868378-rs1599961	0.138	0.849
	rs11868378-rs3774956	0.213	0.849
	rs11868378-rs11722146	0.104	0.849
	rs11868378-rs3774968	0.959	0.887
	rs11868378-rs7674640	0.915	0.931
	rs11868378-rs4698863	0.094	0.926
	rs11868378-rs1609798	0.157	0.849
	rs9914220-rs3774932	0.712	0.887
	rs9914220-rs3774934	0.614	0.849
	rs9914220-rs1599961	0.559	0.887
	rs9914220-rs3774956	0.798	0.849
	rs9914220-rs11722146	0.362	0.849
	rs9914220-rs3774968	0.631	0.849
	rs9914220-rs7674640	0.298	0.849
	rs9914220-rs4698863	0.309	0.849
	rs9914220-rs1609798	0.220	0.849
	rs4969172-rs3774932	0.866	0.887
	rs4969172-rs3774934	0.643	0.887
	rs4969172-rs1599961	0.763	0.887
	rs4969172-rs3774956	0.990	0.926
	rs4969172-rs11722146	0.813	0.887
	rs4969172-rs3774968	0.735	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs7674640	0.501	0.849
	rs4969172-rs4698863	0.109	0.849
	rs4969172-rs1609798	0.624	0.849
SOCS3-IKBKB	rs4436839-rs10958713	0.568	0.707
	rs4436839-rs3747811	0.403	0.707
	rs4436839-rs5029748	0.606	0.849
	rs7221341-rs10958713	0.876	0.707
	rs7221341-rs3747811	0.568	0.849
	rs7221341-rs5029748	0.743	0.849
	rs6501199-rs10958713	0.173	0.849
	rs6501199-rs3747811	0.125	0.849
	rs6501199-rs5029748	0.171	0.850
	rs12944581-rs10958713	0.129	0.887
	rs12944581-rs3747811	0.127	0.849
	rs12944581-rs5029748	0.314	0.887
	rs4969168-rs10958713	0.431	0.887
	rs4969168-rs3747811	0.348	0.887
	rs4969168-rs5029748	0.560	0.924
	rs11868378-rs10958713	0.233	0.849
	rs11868378-rs3747811	0.857	0.887
	rs11868378-rs5029748	0.623	0.849
	rs9914220-rs10958713	0.654	0.849
	rs9914220-rs3747811	0.934	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs5029748	0.910	0.887
	rs4969172-rs10958713	0.932	0.849
	rs4969172-rs3747811	0.480	0.931
	rs4969172-rs5029748	0.803	0.887
IKBKB-NFKB1	rs10958713-rs3774932	0.768	0.887
	rs10958713-rs3774934	0.339	0.849
	rs10958713-rs1599961	0.659	0.849
	rs10958713-rs3774956	0.939	0.849
	rs10958713-rs11722146	0.845	0.849
	rs10958713-rs3774968	0.853	0.850
	rs10958713-rs7674640	0.834	0.887
	rs10958713-rs4698863	0.870	0.849
	rs10958713-rs1609798	0.865	0.849
	rs3747811-rs3774932	0.706	0.849
	rs3747811- rs3774934	0.148	0.849
	rs3747811-rs1599961	0.639	0.849
	rs3747811-rs3774956	0.999	0.849
	rs3747811-rs11722146	0.843	0.849
	rs3747811-rs3774968	0.969	0.849
	rs3747811-rs7674640	0.859	0.849
	rs3747811-rs4698863	0.659	0.849
	rs3747811-rs1609798	0.457	0.849
	rs5029748-rs3774932	0.830	0.887

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774934	0.898	0.867
	rs5029748-rs1599961	0.843	0.849
	rs5029748-rs3774956	0.783	0.849
	rs5029748-rs11722146	0.851	0.849
	rs5029748-rs3774968	0.776	0.849
	rs5029748-rs7674640	0.539	0.887
	rs5029748-rs4698863	0.860	0.849
	rs5029748-rs1609798	0.956	0.849

Adjusted for age, sex.

Table 20. Gene-gene interaction logistic regression models of dichotomized WC considering only whites

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.439	0.849
	rs4436839-rs3774934	0.749	0.887
	rs4436839-rs1599961	0.305	0.849
	rs4436839-rs3774956	0.240	0.849
	rs4436839-rs11722146	**0.038**	0.597
	rs4436839-rs3774968	0.320	0.849
	rs4436839-rs7674640	0.389	0.849
	rs4436839-rs4698863	0.087	0.707
	rs4436839-rs1609798	**0.028**	0.597
	rs7221341-rs3774932	0.532	0.849
	rs7221341-rs3774934	0.984	0.926
	rs7221341-rs1599961	0.879	0.887
	rs7221341-rs3774956	0.628	0.849
	rs7221341-rs11722146	0.694	0.849
	rs7221341-rs3774968	0.373	0.849
	rs7221341-rs7674640	0.238	0.849
	rs7221341-rs4698863	0.197	0.849
	rs7221341-rs1609798	0.357	0.849
	rs6501199-rs3774932	**0.030**	0.597
	rs6501199-rs3774934	0.332	0.849
	rs6501199-rs1599961	0.154	0.849
	rs6501199-rs3774956	0.134	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	**0.023**	0.597
	rs6501199 rs3774968	**0.044**	0.597
	rs6501199-rs7674640	0.053	0.597
	rs6501199-rs4698863	**0.015**	0.597
	rs6501199-rs1609798	**0.008**	0.597
	rs12944581-rs3774932	0.443	0.849
	rs12944581-rs3774934	0.364	0.849
	rs12944581-rs1599961	0.279	0.849
	rs12944581-rs3774956	0.538	0.849
	rs12944581-rs11722146	0.096	0.707
	rs12944581-rs3774968	0.723	0.887
	rs12944581-rs7674640	0.954	0.926
	rs12944581-rs4698863	0.168	0.849
	rs12944581-rs1609798	0.078	0.707
	rs4969168-rs3774932	0.832	0.895
	rs4969168- rs3774934	0.328	0.849
	rs4969168-rs1599961	0.846	0.887
	rs4969168-rs3774956	0.972	0.923
	rs4969168-rs11722146	0.649	0.849
	rs4969168-rs3774968	0.440	0.849
	rs4969168-rs7674640	0.540	0.849
	rs4969168-rs4698863	0.989	0.931
	rs4969168-rs1609798	0.124	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.637	0.849
	rs11868378-rs3774934	0.639	0.850
	rs11868378-rs1599961	0.557	0.849
	rs11868378-rs3774956	0.568	0.849
	rs11868378-rs11722146	0.267	0.849
	rs11868378-rs3774968	0.865	0.887
	rs11868378-rs7674640	0.958	0.931
	rs11868378-rs4698863	0.946	0.926
	rs11868378-rs1609798	0.587	0.849
	rs9914220-rs3774932	0.861	0.887
	rs9914220-rs3774934	0.378	0.849
	rs9914220-rs1599961	0.830	0.887
	rs9914220-rs3774956	0.450	0.849
	rs9914220-rs11722146	0.607	0.849
	rs9914220-rs3774968	0.463	0.849
	rs9914220-rs7674640	0.450	0.849
	rs9914220-rs4698863	0.586	0.849
	rs9914220-rs1609798	0.697	0.849
	rs4969172-rs3774932	0.856	0.887
	rs4969172-rs3774934	0.834	0.887
	rs4969172-rs1599961	0.875	0.887
	rs4969172-rs3774956	0.978	0.926
	rs4969172-rs11722146	0.912	0.887

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.621	0.849
	rs4969172-rs7674640	0.501	0.849
	rs4969172-rs4698863	0.644	0.849
	rs4969172-rs1609798	0.634	0.849
SOCS3-IKBKB	rs4436839-rs10958713	0.065	0.707
	rs4436839-rs3747811	0.078	0.707
	rs4436839-rs5029748	0.168	0.849
	rs7221341-rs10958713	0.079	0.707
	rs7221341-rs3747811	0.134	0.849
	rs7221341-rs5029748	0.157	0.849
	rs6501199-rs10958713	0.444	0.849
	rs6501199-rs3747811	0.368	0.849
	rs6501199-rs5029748	0.721	0.850
	rs12944581-rs10958713	0.837	0.887
	rs12944581-rs3747811	0.568	0.849
	rs12944581-rs5029748	0.879	0.887
	rs4969168-rs10958713	0.854	0.887
	rs4969168-rs3747811	0.867	0.887
	rs4969168-rs5029748	0.945	0.924
	rs11868378-rs10958713	0.578	0.849
	rs11868378-rs3747811	0.786	0.887
	rs11868378-rs5029748	0.458	0.849
	rs9914220-rs10958713	0.389	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.656	0.849
	rs9914220-rs5029748	0.872	0.887
	rs4969172-rs10958713	0.635	0.849
	rs4969172-rs3747811	0.999	0.931
	rs4969172-rs5029748	0.843	0.887
IKBKB-NFKB1	rs10958713-rs3774932	0.643	0.887
	rs10958713-rs3774934	0.651	0.849
	rs10958713-rs1599961	0.445	0.849
	rs10958713-rs3774956	0.357	0.849
	rs10958713-rs11722146	0.286	0.849
	rs10958713-rs3774968	0.734	0.850
	rs10958713-rs7674640	0.860	0.887
	rs10958713-rs4698863	0.545	0.849
	rs10958713-rs1609798	0.257	0.849
	rs3747811-rs3774932	0.354	0.849
	rs3747811- rs3774934	0.576	0.849
	rs3747811-rs1599961	0.202	0.849
	rs3747811-rs3774956	0.246	0.849
	rs3747811-rs11722146	0.356	0.849
	rs3747811-rs3774968	0.378	0.849
	rs3747811-rs7674640	0.360	0.849
	rs3747811-rs4698863	0.292	0.849
	rs3747811-rs1609798	0.167	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.812	0.887
	rs5029748-rs3774934	0.732	0.867
	rs5029748-rs1599961	0.623	0.849
	rs5029748-rs3774956	0.345	0.849
	rs5029748-rs11722146	0.367	0.849
	rs5029748-rs3774968	0.538	0.849
	rs5029748-rs7674640	0.757	0.887
	rs5029748-rs4698863	0.534	0.849
	rs5029748-rs1609798	0.468	0.849

Adjusted for age, sex.

Table 21. Gene-gene interaction logistic regression models of dichotomized WC considering only East Asians

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.346	0.849
	rs4436839-rs3774934	0.768	0.887
	rs4436839-rs1599961	0.345	0.849
	rs4436839-rs3774956	0.234	0.849
	rs4436839-rs11722146	**0.032**	0.597
	rs4436839-rs3774968	0.334	0.849
	rs4436839-rs7674640	0.357	0.849
	rs4436839-rs4698863	0.079	0.707
	rs4436839-rs1609798	**0.025**	0.597
	rs7221341-rs3774932	0.545	0.849
	rs7221341-rs3774934	0.964	0.926
	rs7221341-rs1599961	0.823	0.887
	rs7221341-rs3774956	0.626	0.849
	rs7221341-rs11722146	0.665	0.849
	rs7221341-rs3774968	0.346	0.849
	rs7221341-rs7674640	0.296	0.849
	rs7221341-rs4698863	0.192	0.849
	rs7221341-rs1609798	0.336	0.849
	rs6501199-rs3774932	**0.048**	0.597
	rs6501199-rs3774934	0.345	0.849
	rs6501199-rs1599961	0.132	0.849
	rs6501199-rs3774956	0.157	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	**0.014**	0.597
	rs6501199 rs3774968	0.057	0.597
	rs6501199-rs7674640	0.078	0.597
	rs6501199-rs4698863	0.069	0.597
	rs6501199-rs1609798	**0.012**	0.597
	rs12944581-rs3774932	0.445	0.849
	rs12944581-rs3774934	0.379	0.849
	rs12944581-rs1599961	0.256	0.849
	rs12944581-rs3774956	0.538	0.849
	rs12944581-rs11722146	0.023	0.707
	rs12944581-rs3774968	0.705	0.887
	rs12944581-rs7674640	0.904	0.926
	rs12944581-rs4698863	0.179	0.849
	rs12944581-rs1609798	0.075	0.707
	rs4969168-rs3774932	0.846	0.895
	rs4969168- rs3774934	0.345	0.849
	rs4969168-rs1599961	0.865	0.887
	rs4969168-rs3774956	0.976	0.923
	rs4969168-rs11722146	0.679	0.849
	rs4969168-rs3774968	0.480	0.849
	rs4969168-rs7674640	0.597	0.849
	rs4969168-rs4698863	0.968	0.931
	rs4969168-rs1609798	0.167	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.653	0.849
	rs11868378-rs3774934	0.678	0.850
	rs11868378-rs1599961	0.587	0.849
	rs11868378-rs3774956	0.558	0.849
	rs11868378-rs11722146	0.254	0.849
	rs11868378-rs3774968	0.903	0.887
	rs11868378-rs7674640	0.956	0.931
	rs11868378-rs4698863	0.968	0.926
	rs11868378-rs1609798	0.543	0.849
	rs9914220-rs3774932	0.845	0.887
	rs9914220-rs3774934	0.367	0.849
	rs9914220-rs1599961	0.887	0.887
	rs9914220-rs3774956	0.454	0.849
	rs9914220-rs11722146	0.634	0.849
	rs9914220-rs3774968	0.502	0.849
	rs9914220-rs7674640	0.457	0.849
	rs9914220-rs4698863	0.543	0.849
	rs9914220-rs1609798	0.657	0.849
	rs4969172-rs3774932	0.880	0.887
	rs4969172-rs3774934	0.934	0.887
	rs4969172-rs1599961	0.854	0.887
	rs4969172-rs3774956	0.967	0.926
	rs4969172-rs11722146	0.938	0.887

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.656	0.849
	rs4969172-rs7674640	0.592	0.849
	rs4969172-rs4698863	0.657	0.849
	rs4969172-rs1609798	0.633	0.849
SOCS3-IKBKB	rs4436839-rs10958713	0.079	0.707
	rs4436839-rs3747811	0.062	0.707
	rs4436839-rs5029748	0.134	0.849
	rs7221341-rs10958713	0.069	0.707
	rs7221341-rs3747811	0.132	0.849
	rs7221341-rs5029748	0.145	0.849
	rs6501199-rs10958713	0.446	0.849
	rs6501199-rs3747811	0.332	0.849
	rs6501199-rs5029748	0.756	0.850
	rs12944581-rs10958713	0.867	0.887
	rs12944581-rs3747811	0.553	0.849
	rs12944581-rs5029748	0.878	0.887
	rs4969168-rs10958713	0.845	0.887
	rs4969168-rs3747811	0.823	0.887
	rs4969168-rs5029748	0.956	0.924
	rs11868378-rs10958713	0.586	0.849
	rs11868378-rs3747811	0.746	0.887
	rs11868378-rs5029748	0.489	0.849
	rs9914220-rs10958713	0.354	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.634	0.849
	rs9914220-rs5029748	0.876	0.887
	rs4969172-rs10958713	0.645	0.849
	rs4969172-rs3747811	0.989	0.931
	rs4969172-rs5029748	0.897	0.887
IKBKB-NFKB1	rs10958713-rs3774932	0.665	0.887
	rs10958713-rs3774934	0.643	0.849
	rs10958713-rs1599961	0.467	0.849
	rs10958713-rs3774956	0.378	0.849
	rs10958713-rs11722146	0.223	0.849
	rs10958713-rs3774968	0.745	0.850
	rs10958713-rs7674640	0.878	0.887
	rs10958713-rs4698863	0.543	0.849
	rs10958713-rs1609798	0.345	0.849
	rs3747811-rs3774932	0.357	0.849
	rs3747811- rs3774934	0.567	0.849
	rs3747811-rs1599961	0.245	0.849
	rs3747811-rs3774956	0.276	0.849
	rs3747811-rs11722146	0.368	0.849
	rs3747811-rs3774968	0.397	0.849
	rs3747811-rs7674640	0.300	0.849
	rs3747811-rs4698863	0.256	0.849
	rs3747811-rs1609798	0.125	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.872	0.887
	rs5029748-rs3774934	0.729	0.867
	rs5029748-rs1599961	0.35	0.849
	rs5029748-rs3774956	0.367	0.849
	rs5029748-rs11722146	0.367	0.849
	rs5029748-rs3774968	0.554	0.849
	rs5029748-rs7674640	0.734	0.887
	rs5029748-rs4698863	0.567	0.849
	rs5029748-rs1609798	0.489	0.849

Adjusted for age, sex.

Table 22. Gene-gene interaction logistic regression models of dichotomized WC considering only South Asians

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.445	0.849
	rs4436839-rs3774934	0.743	0.887
	rs4436839-rs1599961	0.358	0.849
	rs4436839-rs3774956	0.298	0.849
	rs4436839-rs11722146	**0.040**	0.597
	rs4436839-rs3774968	0.356	0.849
	rs4436839-rs7674640	0.387	0.849
	rs4436839-rs4698863	0.076	0.707
	rs4436839-rs1609798	**0.025**	0.597
	rs7221341-rs3774932	0.554	0.849
	rs7221341-rs3774934	0.965	0.926
	rs7221341-rs1599961	0.865	0.887
	rs7221341-rs3774956	0.625	0.849
	rs7221341-rs11722146	0.645	0.849
	rs7221341-rs3774968	0.365	0.849
	rs7221341-rs7674640	0.276	0.849
	rs7221341-rs4698863	0.175	0.849
	rs7221341-rs1609798	0.345	0.849
	rs6501199-rs3774932	**0.027**	0.597
	rs6501199-rs3774934	0.345	0.849
	rs6501199-rs1599961	0.167	0.849
	rs6501199-rs3774956	0.145	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	**0.016**	0.597
	rs6501199 rs3774968	**0.050**	0.597
	rs6501199-rs7674640	0.067	0.597
	rs6501199-rs4698863	**0.015**	0.597
	rs6501199-rs1609798	**0.007**	0.597
	rs12944581-rs3774932	0.443	0.849
	rs12944581-rs3774934	0.366	0.849
	rs12944581-rs1599961	0.286	0.849
	rs12944581-rs3774956	0.590	0.849
	rs12944581-rs11722146	0.679	0.707
	rs12944581-rs3774968	0.764	0.887
	rs12944581-rs7674640	0.946	0.926
	rs12944581-rs4698863	0.145	0.849
	rs12944581-rs1609798	0.084	0.707
	rs4969168-rs3774932	0.845	0.895
	rs4969168- rs3774934	0.365	0.849
	rs4969168-rs1599961	0.832	0.887
	rs4969168-rs3774956	0.946	0.923
	rs4969168-rs11722146	0.645	0.849
	rs4969168-rs3774968	0.440	0.849
	rs4969168-rs7674640	0.567	0.849
	rs4969168-rs4698863	0.989	0.931
	rs4969168-rs1609798	0.176	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.678	0.849
	rs11868378-rs3774934	0.636	0.850
	rs11868378-rs1599961	0.521	0.849
	rs11868378-rs3774956	0.510	0.849
	rs11868378-rs11722146	0.294	0.849
	rs11868378-rs3774968	0.886	0.887
	rs11868378-rs7674640	0.959	0.931
	rs11868378-rs4698863	0.992	0.926
	rs11868378-rs1609798	0.530	0.849
	rs9914220-rs3774932	0.845	0.887
	rs9914220-rs3774934	0.365	0.849
	rs9914220-rs1599961	0.921	0.887
	rs9914220-rs3774956	0.445	0.849
	rs9914220-rs11722146	0.667	0.849
	rs9914220-rs3774968	0.531	0.849
	rs9914220-rs7674640	0.478	0.849
	rs9914220-rs4698863	0.545	0.849
	rs9914220-rs1609798	0.645	0.849
	rs4969172-rs3774932	0.896	0.887
	rs4969172-rs3774934	0.854	0.887
	rs4969172-rs1599961	0.834	0.887
	rs4969172-rs3774956	0.978	0.926
	rs4969172-rs11722146	0.943	0.887

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.656	0.849
	rs4969172-rs7674640	0.543	0.849
	rs4969172-rs4698863	0.665	0.849
	rs4969172-rs1609798	0.638	0.849
SOCS3-IKBKB	rs4436839-rs10958713	0.057	0.707
	rs4436839-rs3747811	0.098	0.707
	rs4436839-rs5029748	0.186	0.849
	rs7221341-rs10958713	0.097	0.707
	rs7221341-rs3747811	0.130	0.849
	rs7221341-rs5029748	0.167	0.849
	rs6501199-rs10958713	0.497	0.849
	rs6501199-rs3747811	0.388	0.849
	rs6501199-rs5029748	0.700	0.850
	rs12944581-rs10958713	0.896	0.887
	rs12944581-rs3747811	0.547	0.849
	rs12944581-rs5029748	0.818	0.887
	rs4969168-rs10958713	0.880	0.887
	rs4969168-rs3747811	0.811	0.887
	rs4969168-rs5029748	0.983	0.924
	rs11868378-rs10958713	0.539	0.849
	rs11868378-rs3747811	0.758	0.887
	rs11868378-rs5029748	0.485	0.849
	rs9914220-rs10958713	0.396	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.679	0.849
	rs9914220-rs5029748	0.935	0.887
	rs4969172-rs10958713	0.687	0.849
	rs4969172-rs3747811	0.943	0.931
	rs4969172-rs5029748	0.8457	0.887
IKBKB-NFKB1	rs10958713-rs3774932	0.676	0.887
	rs10958713-rs3774934	0.634	0.849
	rs10958713-rs1599961	0.447	0.849
	rs10958713-rs3774956	0.374	0.849
	rs10958713-rs11722146	0.246	0.849
	rs10958713-rs3774968	0.747	0.850
	rs10958713-rs7674640	0.849	0.887
	rs10958713-rs4698863	0.559	0.849
	rs10958713-rs1609798	0.285	0.849
	rs3747811-rs3774932	0.346	0.849
	rs3747811- rs3774934	0.558	0.849
	rs3747811-rs1599961	0.278	0.849
	rs3747811-rs3774956	0.248	0.849
	rs3747811-rs11722146	0.308	0.849
	rs3747811-rs3774968	0.357	0.849
	rs3747811-rs7674640	0.334	0.849
	rs3747811-rs4698863	0.257	0.849
	rs3747811-rs1609798	0.179	0.849

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.845	0.887
	rs5029748-rs3774934	0.758	0.867
	rs5029748-rs1599961	0.656	0.849
	rs5029748-rs3774956	0.379	0.849
	rs5029748-rs11722146	0.369	0.849
	rs5029748-rs3774968	0.594	0.849
	rs5029748-rs7674640	0.721	0.887
	rs5029748-rs4698863	0.522	0.849
	rs5029748-rs1609798	0.458	0.849

Adjusted for age, sex.

Table 23. Gene-gene interaction logistic regression models of alternate dichotomized BMI considering only whites

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.568	0.469
	rs4436839-rs3774934	0.354	0.469
	rs4436839-rs1599961	0.267	0.469
	rs4436839-rs3774956	0.435	0.469
	rs4436839-rs11722146	0.237	0.469
	rs4436839-rs3774968	0.668	0.477
	rs4436839-rs7674640	0.847	0.505
	rs4436839-rs4698863	0.239	0.469
	rs4436839-rs1609798	0.123	0.469
	rs7221341-rs3774932	0.769	0.495
	rs7221341-rs3774934	0.638	0.476
	rs7221341-rs1599961	0.969	0.514
	rs7221341-rs3774956	0.668	0.476
	rs7221341-rs11722146	0.968	0.514
	rs7221341-rs3774968	0.880	0.495
	rs7221341-rs7674640	0.723	0.483
	rs7221341-rs4698863	0.310	0.469
	rs7221341-rs1609798	0.649	0.476
	rs6501199-rs3774932	0.168	0.469
	rs6501199-rs3774934	0.834	0.498
	rs6501199-rs1599961	0.389	0.469
	rs6501199-rs3774956	0.322	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	0.147	0.469
	rs6501199 rs3774968	0.269	0.469
	rs6501199-rs7674640	0.358	0.469
	rs6501199-rs4698863	0.240	0.469
	rs6501199-rs1609798	0.083	0.469
	rs12944581-rs3774932	0.548	0.469
	rs12944581-rs3774934	0.335	0.469
	rs12944581-rs1599961	0.238	0.469
	rs12944581-rs3774956	0.469	0.469
	rs12944581-rs11722146	0.396	0.469
	rs12944581-rs3774968	0.856	0.509
	rs12944581-rs7674640	0.986	0.521
	rs12944581-rs4698863	0.446	0.469
	rs12944581-rs1609798	0.175	0.469
	rs4969168-rs3774932	0.521	0.469
	rs4969168- rs3774934	0.557	0.469
	rs4969168-rs1599961	0.546	0.469
	rs4969168-rs3774956	0.657	0.476
	rs4969168-rs11722146	0.875	0.495
	rs4969168-rs3774968	0.434	0.469
	rs4969168-rs7674640	0.732	0.477
	rs4969168-rs4698863	0.854	0.495
	rs4969168-rs1609798	0.334	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.524	0.469
	rs11868378-rs3774934	0.997	0.529
	rs11868378-rs1599961	0.511	0.469
	rs11868378-rs3774956	0.801	0.502
	rs11868378-rs11722146	0.773	0.495
	rs11868378-rs3774968	0.565	0.469
	rs11868378-rs7674640	0.445	0.469
	rs11868378-rs4698863	0.268	0.469
	rs11868378-rs1609798	0.200	0.469
	rs9914220-rs3774932	0.443	0.469
	rs9914220-rs3774934	0.465	0.469
	rs9914220-rs1599961	0.075	0.469
	rs9914220-rs3774956	**0.029**	0.469
	rs9914220-rs11722146	0.534	0.469
	rs9914220-rs3774968	0.554	0.469
	rs9914220-rs7674640	0.964	0.522
	rs9914220-rs4698863	0.423	0.469
	rs9914220-rs1609798	0.754	0.495
	rs4969172-rs3774932	0.565	0.469
	rs4969172-rs3774934	0.845	0.500
	rs4969172-rs1599961	0.132	0.469
	rs4969172-rs3774956	0.144	0.469
	rs4969172-rs11722146	0.365	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.679	0.476
	rs4969172-rs7674640	0.643	0.476
	rs4969172-rs4698863	0.134	0.469
	rs4969172-rs1609798	0.445	0.469
SOCS3-IKBKB	rs4436839-rs10958713	0.276	0.469
	rs4436839-rs3747811	0.445	0.469
	rs4436839-rs5029748	0.523	0.469
	rs7221341-rs10958713	0.476	0.469
	rs7221341-rs3747811	0.698	0.476
	rs7221341-rs5029748	0.813	0.495
	rs6501199-rs10958713	0.323	0.469
	rs6501199-rs3747811	0.325	0.469
	rs6501199-rs5029748	0.231	0.469
	rs12944581-rs10958713	0.711	0.483
	rs12944581-rs3747811	0.654	0.476
	rs12944581-rs5029748	0.968	0.514
	rs4969168-rs10958713	0.534	0.469
	rs4969168-rs3747811	0.356	0.469
	rs4969168-rs5029748	0.387	0.469
	rs11868378-rs10958713	0.447	0.469
	rs11868378-rs3747811	0.492	0.469
	rs11868378-rs5029748	0.458	0.469
	rs9914220-rs10958713	0.254	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.429	0.469
	rs9914220-rs5029748	0.559	0.469
	rs4969172-rs10958713	0.868	0.502
	rs4969172-rs3747811	0.643	0.480
	rs4969172-rs5029748	0.859	0.502
IKBKB-NFKB1	rs10958713-rs3774932	0.369	0.469
	rs10958713-rs3774934	0.443	0.469
	rs10958713-rs1599961	0.260	0.469
	rs10958713-rs3774956	0.478	0.469
	rs10958713-rs11722146	0.664	0.476
	rs10958713-rs3774968	0.467	0.469
	rs10958713-rs7674640	0.943	0.521
	rs10958713-rs4698863	0.745	0.489
	rs10958713-rs1609798	0.432	0.469
	rs3747811-rs3774932	0.356	0.469
	rs3747811- rs3774934	0.267	0.469
	rs3747811-rs1599961	0.335	0.469
	rs3747811-rs3774956	0.575	0.469
	rs3747811-rs11722146	0.677	0.476
	rs3747811-rs3774968	0.443	0.469
	rs3747811-rs7674640	0.667	0.478
	rs3747811-rs4698863	0.344	0.469
	rs3747811-rs1609798	0.298	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.660	0.476
	rs5029748-rs3774934	0.843	0.495
	rs5029748-rs1599961	0.267	0.469
	rs5029748-rs3774956	0.233	0.469
	rs5029748-rs11722146	0.479	0.469
	rs5029748-rs3774968	0.779	0.483
	rs5029748-rs7674640	0.707	0.495
	rs5029748-rs4698863	0.545	0.469
	rs5029748-rs1609798	0.473	0.469

Adjusted for age, sex.

Table 24. Gene-gene interaction logistic regression models of alternate dichotomized BMI considering only East Asians

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.545	0.469
	rs4436839-rs3774934	0.321	0.469
	rs4436839-rs1599961	0.211	0.469
	rs4436839-rs3774956	0.400	0.469
	rs4436839-rs11722146	0.238	0.469
	rs4436839-rs3774968	0.653	0.477
	rs4436839-rs7674640	0.857	0.505
	rs4436839-rs4698863	0.299	0.469
	rs4436839-rs1609798	0.135	0.469
	rs7221341-rs3774932	0.795	0.495
	rs7221341-rs3774934	0.629	0.476
	rs7221341-rs1599961	0.963	0.514
	rs7221341-rs3774956	0.634	0.476
	rs7221341-rs11722146	0.967	0.514
	rs7221341-rs3774968	0.839	0.495
	rs7221341-rs7674640	0.759	0.483
	rs7221341-rs4698863	0.329	0.469
	rs7221341-rs1609798	0.699	0.476
	rs6501199-rs3774932	0.137	0.469
	rs6501199-rs3774934	0.858	0.498
	rs6501199-rs1599961	0.383	0.469
	rs6501199-rs3774956	0.312	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	0.106	0.469
	rs6501199 rs3774968	0.250	0.469
	rs6501199-rs7674640	0.330	0.469
	rs6501199-rs4698863	0.248	0.469
	rs6501199-rs1609798	0.081	0.469
	rs12944581-rs3774932	0.568	0.469
	rs12944581-rs3774934	0.364	0.469
	rs12944581-rs1599961	0.234	0.469
	rs12944581-rs3774956	0.478	0.469
	rs12944581-rs11722146	0.343	0.469
	rs12944581-rs3774968	0.868	0.509
	rs12944581-rs7674640	0.980	0.521
	rs12944581-rs4698863	0.443	0.469
	rs12944581-rs1609798	0.168	0.469
	rs4969168-rs3774932	0.536	0.469
	rs4969168- rs3774934	0.543	0.469
	rs4969168-rs1599961	0.564	0.469
	rs4969168-rs3774956	0.633	0.476
	rs4969168-rs11722146	0.850	0.495
	rs4969168-rs3774968	0.449	0.469
	rs4969168-rs7674640	0.792	0.477
	rs4969168-rs4698863	0.858	0.495
	rs4969168-rs1609798	0.379	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.534	0.469
	rs11868378-rs3774934	0.976	0.529
	rs11868378-rs1599961	0.534	0.469
	rs11868378-rs3774956	0.887	0.502
	rs11868378-rs11722146	0.734	0.495
	rs11868378-rs3774968	0.587	0.469
	rs11868378-rs7674640	0.443	0.469
	rs11868378-rs4698863	0.268	0.469
	rs11868378-rs1609798	0.276	0.469
	rs9914220-rs3774932	0.434	0.469
	rs9914220-rs3774934	0.476	0.464
	rs9914220-rs1599961	0.057	0.468
	rs9914220-rs3774956	0.073	0.469
	rs9914220-rs11722146	0.674	0.469
	rs9914220-rs3774968	0.344	0.469
	rs9914220-rs7674640	0.684	0.522
	rs9914220-rs4698863	0.873	0.469
	rs9914220-rs1609798	0.344	0.495
	rs4969172-rs3774932	0.895	0.469
	rs4969172-rs3774934	0.355	0.500
	rs4969172-rs1599961	0.772	0.469
	rs4969172-rs3774956	0.124	0.469
	rs4969172-rs11722146	0.985	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.459	0.476
	rs4969172-rs7674640	0.873	0.476
	rs4969172-rs4698863	0.175	0.469
	rs4969172-rs1609798	0.434	0.469
SOCS3-IKBKB	rs4436839-rs10958713	0.234	0.469
	rs4436839-rs3747811	0.433	0.469
	rs4436839-rs5029748	0.574	0.469
	rs7221341-rs10958713	0.404	0.469
	rs7221341-rs3747811	0.683	0.476
	rs7221341-rs5029748	0.814	0.495
	rs6501199-rs10958713	0.334	0.469
	rs6501199-rs3747811	0.325	0.469
	rs6501199-rs5029748	0.264	0.469
	rs12944581-rs10958713	0.745	0.483
	rs12944581-rs3747811	0.677	0.476
	rs12944581-rs5029748	0.934	0.514
	rs4969168-rs10958713	0.598	0.469
	rs4969168-rs3747811	0.334	0.469
	rs4969168-rs5029748	0.378	0.469
	rs11868378-rs10958713	0.476	0.469
	rs11868378-rs3747811	0.434	0.469
	rs11868378-rs5029748	0.458	0.469
	rs9914220-rs10958713	0.253	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.429	0.469
	rs9914220-rs5029748	0.565	0.469
	rs4969172-rs10958713	0.834	0.502
	rs4969172-rs3747811	0.676	0.480
	rs4969172-rs5029748	0.845	0.502
IKBKB-NFKB1	rs10958713-rs3774932	0.359	0.469
	rs10958713-rs3774934	0.465	0.469
	rs10958713-rs1599961	0.234	0.469
	rs10958713-rs3774956	0.465	0.469
	rs10958713-rs11722146	0.679	0.476
	rs10958713-rs3774968	0.434	0.469
	rs10958713-rs7674640	0.965	0.521
	rs10958713-rs4698863	0.723	0.489
	rs10958713-rs1609798	0.438	0.469
	rs3747811-rs3774932	0.354	0.469
	rs3747811- rs3774934	0.246	0.469
	rs3747811-rs1599961	0.376	0.469
	rs3747811-rs3774956	0.576	0.469
	rs3747811-rs11722146	0.643	0.476
	rs3747811-rs3774968	0.430	0.469
	rs3747811-rs7674640	0.659	0.478
	rs3747811-rs4698863	0.349	0.469
	rs3747811-rs1609798	0.234	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.665	0.476
	rs5029748-rs3774934	0.834	0.495
	rs5029748-rs1599961	0.764	0.469
	rs5029748-rs3774956	0.233	0.469
	rs5029748-rs11722146	0.473	0.469
	rs5029748-rs3774968	0.740	0.483
	rs5029748-rs7674640	0.700	0.495
	rs5029748-rs4698863	0.544	0.469
	rs5029748-rs1609798	0.432	0.469

Adjusted for age, sex.

Table 25. Gene-gene interaction logistic regression models of alternate dichotomized BMI considering only South Asians

Gene-gene	SNP-SNP	Wald test p-value	q-values
SOCS3-NFKB1	rs4436839-rs3774932	0.679	0.469
	rs4436839-rs3774934	0.33	0.469
	rs4436839-rs1599961	0.234	0.469
	rs4436839-rs3774956	0.434	0.469
	rs4436839-rs11722146	0.223	0.469
	rs4436839-rs3774968	0.623	0.477
	rs4436839-rs7674640	0.868	0.505
	rs4436839-rs4698863	0.293	0.469
	rs4436839-rs1609798	0.111	0.469
	rs7221341-rs3774932	0.734	0.495
	rs7221341-rs3774934	0.665	0.476
	rs7221341-rs1599961	0.969	0.514
	rs7221341-rs3774956	0.634	0.476
	rs7221341-rs11722146	0.960	0.514
	rs7221341-rs3774968	0.843	0.495
	rs7221341-rs7674640	0.756	0.483
	rs7221341-rs4698863	0.387	0.469
	rs7221341-rs1609798	0.634	0.476
	rs6501199-rs3774932	0.168	0.469
	rs6501199-rs3774934	0.854	0.498
	rs6501199-rs1599961	0.334	0.469
	rs6501199-rs3774956	0.376	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs6501199-rs11722146	0.142	0.469
	rs6501199 rs3774968	0.295	0.469
	rs6501199-rs7674640	0.395	0.469
	rs6501199-rs4698863	0.239	0.469
	rs6501199-rs1609798	0.085	0.469
	rs12944581-rs3774932	0.534	0.469
	rs12944581-rs3774934	0.334	0.469
	rs12944581-rs1599961	0.262	0.469
	rs12944581-rs3774956	0.459	0.469
	rs12944581-rs11722146	0.369	0.469
	rs12944581-rs3774968	0.839	0.509
	rs12944581-rs7674640	0.959	0.521
	rs12944581-rs4698863	0.469	0.469
	rs12944581-rs1609798	0.139	0.469
	rs4969168-rs3774932	0.559	0.469
	rs4969168- rs3774934	0.550	0.469
	rs4969168-rs1599961	0.523	0.469
	rs4969168-rs3774956	0.656	0.476
	rs4969168-rs11722146	0.880	0.495
	rs4969168-rs3774968	0.400	0.469
	rs4969168-rs7674640	0.743	0.477
	rs4969168-rs4698863	0.877	0.495
	rs4969168-rs1609798	0.335	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs11868378-rs3774932	0.509	0.469
	rs11868378-rs3774934	0.989	0.529
	rs11868378-rs1599961	0.511	0.469
	rs11868378-rs3774956	0.802	0.502
	rs11868378-rs11722146	0.756	0.495
	rs11868378-rs3774968	0.567	0.469
	rs11868378-rs7674640	0.423	0.469
	rs11868378-rs4698863	0.246	0.469
	rs11868378-rs1609798	0.223	0.469
	rs9914220-rs3774932	0.453	0.469
	rs9914220-rs3774934	0.498	0.469
	rs9914220-rs1599961	0.075	0.469
	rs9914220-rs3774956	0.0602	0.469
	rs9914220-rs11722146	0.578	0.469
	rs9914220-rs3774968	0.534	0.469
	rs9914220-rs7674640	0.948	0.522
	rs9914220-rs4698863	0.433	0.469
	rs9914220-rs1609798	0.763	0.495
	rs4969172-rs3774932	0.556	0.469
	rs4969172-rs3774934	0.876	0.500
	rs4969172-rs1599961	0.130	0.469
	rs4969172-rs3774956	0.129	0.469
	rs4969172-rs11722146	0.398	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs4969172-rs3774968	0.643	0.476
	rs4969172-rs7674640	0.667	0.476
	rs4969172-rs4698863	0.129	0.469
	rs4969172-rs1609798	0.459	0.469
SOCS3-IKBKB	rs4436839-rs10958713	0.220	0.469
	rs4436839-rs3747811	0.469	0.469
	rs4436839-rs5029748	0.579	0.469
	rs7221341-rs10958713	0.423	0.469
	rs7221341-rs3747811	0.650	0.476
	rs7221341-rs5029748	0.830	0.495
	rs6501199-rs10958713	0.320	0.469
	rs6501199-rs3747811	0.325	0.469
	rs6501199-rs5029748	0.245	0.469
	rs12944581-rs10958713	0.765	0.483
	rs12944581-rs3747811	0.634	0.476
	rs12944581-rs5029748	0.967	0.514
	rs4969168-rs10958713	0.587	0.469
	rs4969168-rs3747811	0.334	0.469
	rs4969168-rs5029748	0.365	0.469
	rs11868378-rs10958713	0.434	0.469
	rs11868378-rs3747811	0.487	0.469
	rs11868378-rs5029748	0.453	0.469
	rs9914220-rs10958713	0.255	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs9914220-rs3747811	0.476	0.469
	rs9914220-rs5029748	0.678	0.469
	rs4969172-rs10958713	0.834	0.502
	rs4969172-rs3747811	0.644	0.480
	rs4969172-rs5029748	0.854	0.502
IKBKB-NFKB1	rs10958713-rs3774932	0.345	0.469
	rs10958713-rs3774934	0.465	0.469
	rs10958713-rs1599961	0.276	0.469
	rs10958713-rs3774956	0.434	0.469
	rs10958713-rs11722146	0.676	0.476
	rs10958713-rs3774968	0.423	0.469
	rs10958713-rs7674640	0.987	0.521
	rs10958713-rs4698863	0.742	0.489
	rs10958713-rs1609798	0.434	0.469
	rs3747811-rs3774932	0.355	0.469
	rs3747811- rs3774934	0.239	0.469
	rs3747811-rs1599961	0.364	0.469
	rs3747811-rs3774956	0.651	0.469
	rs3747811-rs11722146	0.634	0.476
	rs3747811-rs3774968	0.465	0.469
	rs3747811-rs7674640	0.693	0.478
	rs3747811-rs4698863	0.346	0.469
	rs3747811-rs1609798	0.298	0.469

Gene-gene	SNP-SNP	Wald test p-value	q-values
	rs5029748-rs3774932	0.634	0.476
	rs5029748-rs3774934	0.822	0.495
	rs5029748-rs1599961	0.205	0.469
	rs5029748-rs3774956	0.256	0.469
	rs5029748-rs11722146	0.432	0.469
	rs5029748-rs3774968	0.782	0.483
	rs5029748-rs7674640	0.745	0.495
	rs5029748-rs4698863	0.507	0.469
	rs5029748-rs1609798	0.424	0.469

Adjusted for age, sex.

Table 26. Gene-environment interaction logistic regression models of dichotomized BMI

Gene	SNP - Nutrient	Wald test p-value	q-values
SOCS3	rs4436839*carbohydrates	0.110	0.914
	rs7221341*carbohydrates	0.941	0.992
	rs6501199*carbohydrates	0.703	0.921
	rs12944581*carbohydrate	0.524	0.914
	rs4969168*carbohydrates	0.961	0.992
	rs11868378*carbohydrates	0.480	0.914
	rs9914220*carbohydrates	0.536	0.914
	rs4969172*carbohydrates	0.967	0.992
NFKB1	rs3774932*carbohydrates	0.651	0.921
	rs3774934*carbohydrates	0.383	0.914
	rs1599961*carbohydrates	0.525	0.914
	rs3774956*carbohydrates	0.664	0.921
	rs11722146*carbohydrates	0.536	0.914
	rs3774968*carbohydrates	0.997	0.998
	rs7674640*carbohydrates	0.783	0.950
	rs4698863*carbohydrates	0.319	0.914
	rs1609798*carbohydrates	0.295	0.914
IKBKB	rs10958713*carbohydrates	0.369	0.914
	rs3747811*carbohydrates	0.624	0.921
	rs5029748 *carbohydrates	0.204	0.914
SOCS3	rs4436839*fat	0.909	0.992
	rs7221341*fat	0.169	0.914

Gene	SNP - Nutrient	Wald test p-value	q-values
	rs6501199*fat	0.262	0.914
	rs12944581*fat	0.998	0.998
	rs4969168*fat	0.577	0.921
	rs11868378*fat	0.900	0.992
	rs9914220*fat	0.149	0.914
	rs4969172*fat	0.461	0.914
NFKB1	rs3774932*fat	0.382	0.914
	rs3774934*fat	0.149	0.914
	rs1599961*fat	0.748	0.921
	rs3774956*fat	0.6572	0.921
	rs11722146*fat	0.746	0.921
	rs3774968*fat	0.425	0.914
	rs7674640*fat	0.602	0.921
	rs4698863*fat	0.489	0.914
	rs1609798*fat	0.227	0.914
IKBKB	rs10958713*fat	0.693	0.921
	rs3747811*fat	0.459	0.914
	rs5029748 *fat	0.363	0.914
SOCS3	rs4436839*protein	0.063	0.914
	rs7221341*protein	**0.026**	0.914
	rs6501199*protein	0.193	0.914
	rs12944581*protein	0.394	0.914
	rs4969168*protein	0.704	0.921

Gene	SNP - Nutrient	Wald test p-value	q-values
	rs11868378*protein	0.078	0.914
	rs9914220*protein	0.473	0.914
	rs4969172*protein	0.537	0.914
NFKB1	rs3774932*protein	0.821	0.953
	rs3774934*protein	0.298	0.914
	rs1599961*protein	0.821	0.953
	rs3774956*protein	0.948	0.992
	rs11722146*protein	0.366	0.914
	rs3774968*protein	0.906	0.992
	rs7674640*protein	0.699	0.921
	rs4698863*protein	0.747	0.921
	rs1609798*protein	0.200	0.914
IKBKB	rs10958713*protein	0.196	0.914
	rs3747811*protein	0.215	0.914
	rs5029748 *protein	0.571	0.921
SOCS3	rs4436839*alcohol	0.270	0.914
	rs7221341*alcohol	0.930	0.992
	rs6501199*alcohol	0.214	0.914
	rs12944581*alcohol	0.475	0.914
	rs4969168*alcohol	0.495	0.914
	rs11868378*alcohol	0.822	0.953
	rs9914220*alcohol	0.739	0.921
	rs4969172*alcohol	0.245	0.914

Gene	SNP - Nutrient	Wald test p-value	q-values
SOCS3	rs3774932*alcohol	0.600	0.921
	rs3774934*alcohol	0.374	0.914
	rs1599961*alcohol	0.430	0.914
	rs3774956*alcohol	0.960	0.992
	rs11722146*alcohol	0.055	0.914
	rs3774968*alcohol	0.650	0.921
	rs7674640*alcohol	0.599	0.921
	rs4698863*alcohol	0.265	0.914
	rs1609798*alcohol	0.090	0.914
	rs10958713*alcohol	0.055	0.914
	rs3747811*alcohol	0.209	0.914
	rs5029748 *alcohol	0.104	0.914

Adjusted for age, physical activity, race and sex.

Table 27. Gene-environment interaction logistic regression models of dichotomized WC

Gene	SNP-Nutrient	Wald test p-value	q-values
SOCS3	rs4436839*carbohydrates	0.512	0.914
	rs7221341*carbohydrates	0.753	0.992
	rs6501199*carbohydrates	0.888	0.921
	rs12944581*carbohydrate	0.137	0.914
	rs4969168*carbohydrates	0.121	0.992
	rs11868378*carbohydrates	0.301	0.914
	rs9914220*carbohydrates	0.325	0.914
	rs4969172*carbohydrates	0.551	0.992
NFKB1	rs3774932*carbohydrates	0.109	0.921
	rs3774934*carbohydrates	0.589	0.914
	rs1599961*carbohydrates	0.538	0.914
	rs3774956*carbohydrates	0.462	0.921
	rs11722146*carbohydrates	0.372	0.914
	rs3774968*carbohydrates	0.091	0.998
	rs7674640*carbohydrates	0.121	0.950
	rs4698863*carbohydrates	0.751	0.914
	rs1609798*carbohydrates	0.346	0.914
IKBKB	rs10958713*carbohydrates	0.056	0.914
	rs3747811*carbohydrates	0.904	0.921
	rs5029748 *carbohydrates	0.117	0.914
SOCS3	rs4436839*fat	0.366	0.992
	rs7221341*fat	0.284	0.914

Gene	SNP-Nutrient	Wald test p-value	q-values
	rs6501199*fat	0.071	0.914
	rs12944581*fat	**0.009**	0.998
	rs4969168*fat	0.104	0.921
	rs11868378*fat	0.469	0.992
	rs9914220*fat	0.165	0.914
	rs4969172*fat	0.339	0.914
NFKB1	rs3774932*fat	0.368	0.914
	rs3774934*fat	0.982	0.914
	rs1599961*fat	0.934	0.921
	rs3774956*fat	0.859	0.921
	rs11722146*fat	0.649	0.921
	rs3774968*fat	0.357	0.914
	rs7674640*fat	0.702	0.921
	rs4698863*fat	0.931	0.914
	rs1609798*fat	0.334	0.914
IKBKB	**rs10958713*fat**	**0.034**	0.921
	rs3747811*fat	0.731	0.914
	rs5029748 *fat	0.086	0.914
SOCS3	rs4436839*protein	0.087	0.914
	rs7221341*protein	**0.010**	0.914
	rs6501199*protein	0.195	0.914
	rs12944581*protein	0.958	0.914
	rs4969168*protein	0.221	0.921

Gene	SNP-Nutrient	Wald test p-value	q-values
	rs11868378*protein	0.096	0.914
	rs9914220*protein	0.938	0.914
	rs4969172*protein	0.839	0.914
NFKB1	rs3774932*protein	0.431	0.953
	rs3774934*protein	0.207	0.914
	rs1599961*protein	0.927	0.953
	rs3774956*protein	0.446	0.992
	rs11722146*protein	0.846	0.914
	rs3774968*protein	0.112	0.992
	rs7674640*protein	0.183	0.921
	rs4698863*protein	0.763	0.921
	rs1609798*protein	0.338	0.914
IKBKB	rs10958713*protein	0.833	0.914
	rs3747811*protein	0.296	0.914
	rs5029748 *protein	0.997	0.921
SOCS3	rs4436839*alcohol	0.363	0.914
	rs7221341*alcohol	0.663	0.992
	rs6501199*alcohol	0.179	0.914
	rs12944581*alcohol	0.303	0.914
	rs4969168*alcohol	0.963	0.914
	rs11868378*alcohol	0.686	0.953
	rs9914220*alcohol	0.701	0.921
	rs4969172*alcohol	0.669	0.914

Gene	SNP-Nutrient	Wald test p-value	q-values
SOCS3	rs3774932*alcohol	0.518	0.921
	rs3774934*alcohol	0.730	0.914
	rs1599961*alcohol	0.509	0.914
	rs3774956*alcohol	0.824	0.992
	rs11722146*alcohol	0.307	0.914
	rs3774968*alcohol	0.690	0.921
	rs7674640*alcohol	0.473	0.921
	rs4698863*alcohol	0.689	0.914
	rs1609798*alcohol	0.279	0.914
	rs10958713*alcohol	0.697	0.914
	rs3747811*alcohol	0.894	0.914
	rs5029748 *alcohol	0.801	0.914

Adjusted for age, physical activity, race and sex.

Table 28. Gene-environment interaction logistic regression models of alternate dichotomized BMI

Gene	SNP-Nutrient	Wald test p-value	q-values
SOCS3	rs4436839*carbohydrates	0.327	0.864
	rs7221341*carbohydrates	0.334	0.864
	rs6501199*carbohydrates	0.665	0.980
	rs12944581*carbohydrate	0.773	0.980
	rs4969168*carbohydrates	0.261	0.864
	rs11868378*carbohydrates	0.313	0.864
	rs9914220*carbohydrates	0.194	0.864
	rs4969172*carbohydrates	0.344	0.864
NFKB1	rs3774932*carbohydrates	0.895	0.980
	rs3774934*carbohydrates	0.681	0.980
	rs1599961*carbohydrates	0.703	0.980
	rs3774956*carbohydrates	0.783	0.980
	rs11722146*carbohydrates	0.709	0.980
	rs3774968*carbohydrates	0.669	0.980
	rs7674640*carbohydrates	0.697	0.980
	rs4698863*carbohydrates	0.503	0.980
	rs1609798*carbohydrates	0.353	0.864
IKBKB	rs10958713*carbohydrates	0.908	0.980
	rs3747811*carbohydrates	0.214	0.864
	rs5029748 *carbohydrates	0.861	0.980
SOCS3	rs4436839*fat	0.786	0.980
	rs7221341*fat	0.518	0.980

Gene	SNP-Nutrient	Wald test p-value	q-values
	rs6501199*fat	0.340	0.864
	rs12944581*fat	0.649	0.980
	rs4969168*fat	0.143	0.864
	rs11868378*fat	0.744	0.980
	rs9914220*fat	0.065	0.863
	rs4969172*fat	0.245	0.864
NFKB1	rs3774932*fat	0.755	0.980
	rs3774934*fat	0.675	0.980
	rs1599961*fat	0.801	0.980
	rs3774956*fat	0.677	0.980
	rs11722146*fat	0.845	0.980
	rs3774968*fat	0.904	0.980
	rs7674640*fat	0.762	0.980
	rs4698863*fat	0.582	0.980
	rs1609798*fat	0.279	0.864
IKBKB	rs10958713*fat	0.831	0.980
	rs3747811*fat	0.179	0.864
	rs5029748 *fat	0.884	0.980
SOCS3	rs4436839*protein	0.362	0.864
	rs7221341*protein	**0.009**	0.712
	rs6501199*protein	0.243	0.864
	rs12944581*protein	0.614	0.980
	rs4969168*protein	0.253	0.864

Gene	SNP-Nutrient	Wald test p-value	q-values
	rs11868378*protein	0.218	0.864
	rs9914220*protein	0.980	0.980
	rs4969172*protein	0.162	0.864
NFKB1	rs3774932*protein	0.684	0.980
	rs3774934*protein	0.947	0.980
	rs1599961*protein	0.951	0.980
	rs3774956*protein	0.973	0.980
	rs11722146*protein	0.378	0.865
	rs3774968*protein	0.969	0.980
	rs7674640*protein	0.667	0.980
	rs4698863*protein	0.686	0.980
	rs1609798*protein	0.295	0.864
IKBKB	rs10958713*protein	0.071	0.863
	rs3747811*protein	0.063	0.863
	rs5029748 *protein	0.167	0.864
SOCS3	rs4436839*alcohol	0.097	0.863
	rs7221341*alcohol	0.649	0.980
	rs6501199*alcohol	0.241	0.864
	rs12944581*alcohol	0.294	0.864
	rs4969168*alcohol	0.919	0.980
	rs11868378*alcohol	0.850	0.980
	rs9914220*alcohol	0.503	0.980
	rs4969172*alcohol	0.355	0.864

Gene	SNP-Nutrient	Wald test p-value	q-values
SOCS3	rs3774932*alcohol	0.501	0.980
	rs3774934*alcohol	0.813	0.980
	rs1599961*alcohol	0.508	0.980
	rs3774956*alcohol	0.903	0.980
	rs11722146*alcohol	0.093	0.863
	rs3774968*alcohol	0.511	0.980
	rs7674640*alcohol	0.636	0.980
	rs4698863*alcohol	0.367	0.864
	rs1609798*alcohol	0.148	0.864
	rs10958713*alcohol	**0.029**	0.863
	rs3747811*alcohol	0.089	0.863
	rs5029748 *alcohol	0.076	0.863

Adjusted for age, physical activity, race and sex.

Table 29. ORs of the most significant gene-gene interaction with logistic regression

a)

rs1609798 = (*NFKB1*)	**rs6501199 (*SOCS3*)**
CC	1.18 (0.91 - 1.53)
CT	0.75 (0.58 - 0.95)
TT	0.47 (0.28 - 0.77)

b)

rs1609798 = (*NFKB1*)	**rs6501199 (*SOCS3*)**
CC	1.22 (0.95 - 1.56)
CT	0.82 (0.66 - 1.03)
TT	0.56 (0.36 - 0.87)

c)

rs9914220 = (*SOCS3*)	**rs3774956 (*NFKB1*)**
CC	0.97 (0.79 - 1.18)
CT	1.31 (1.03 - 1.67)
TT	1.78 (1.10 - 2.88)

ORs (confidence interval) of the most statistically significant gene-gene interactions with logistic regression before multiple testing adjustment with FDR. a) outcome: BMI ; b) outcome: WC ; c) outcome: alternative BMI.

Table 30. ORs of the most significant gene-environment interaction with logistic regression

a)

rs7221341 = (*SOCS3*)	**Protein intakes (change of 20 units)**
CC	1.06 (0.88 - 1.28)
CT	1.37 (1.15 - 1.65)
TT	1.78 (1.23 - 2.56)

b)

rs7221341 = (*SOCS3*)	**Protein intakes (change of 20 units)**
CC	1.01 (0.85- 1.21)
CT	1.34 (1.13 - 1.60)
TT	1.78 (1.25 - 2.53)

c)

rs7221341 = (*SOCS3*)	**Protein intakes (change of 20 unite)**
CC	1.09 (0.92 - 1.28)
CT	1.45 (1.21 – 1.74)
TT	1.93 (1.34 – 2.78)

ORs (confidence interval) of the most statistically significant gene-environment interactions with logistic regression before multiple testing adjustment with FDR. a) outcome: BMI ; b) outcome: WC ; c) outcome: alternative BMI.

Table 31. MDR models of two- and three-fold gene-gene interactions considering all ethnicities

Outcome	Model	Average testing accuracy	CV Consistency
BMI	rs7221341 (*SOCS3*), rs3747811 (*IKBKB*)	57%	7/10
BMI	rs7221341 (*SOCS3*), rs3774932 (*NFKB1*), rs1599961 (*NFKB1*)	54%	5/10
WC	rs7221341 (*SOCS3*), rs5029748 (*IKBKB*)	56%	8/10
WC	rs7221341 (*SOCS3*), rs3774968 (*NFKB1*), rs5029748 (*IKBKB*)	58%	9/10
Alternative BMI	rs650119 (*SOCS3*), rs3747811(*IKBKB*)	50%	4/10
Alternative BMI	rs6501199 (*SOCS3*), rs4969168 (*SOCS3*), rs3747811 (*IKBKB*)	49%	5/10

Table 32. MDR models of two- and three-fold gene-gene interactions considering only whites (n=665)

Outcome	Model	Average testing accuracy	CV Consistency
BMI	rs6501199 (*SOCS3*), rs3747811 (*IKBKB*)	55%	9/10
BMI	rs6501199 (*SOCS3*), rs4969172 (*SOCS3*), rs3747811 (*IKBKB*)	60%	10/10
WC	rs6501199 (*SOCS3*), rs1609798 (*NFKB1*)	55%	7/10
WC	rs6501199 (*SOCS3*), rs4698863 (*NFKB1*), rs3747811 (*IKBKB*)	52%	4/10

Table 33. MDR models of two- and three-fold gene-gene interactions considering only East Asians (n=450)

Outcome	Model	Average testing accuracy	CV Consistency
BMI	rs6501199 (*SOCS3*), rs7674640 (*NFKB1*)	38%	4/10
BMI	rs4436839 (*SOCS3*), rs3774968 (*NFKB1*), rs3747811 (*IKBKB*)	44%	3/10
WC	rs4436839 (*SOCS3*), rs9914220 (*SOCS3*)	47%	4/10
WC	rs4436839 (*SOCS3*), rs3774968 (*NFKB1*), rs3747811 (*IKBKB*)	43%	3/10
Alternative BMI	rs1599961 (*NFKB1*), rs7674640 (*NFKB1*)	46%	4/10
Alternative BMI	rs12944581 (*SOCS3*), rs1599961 (*NFKB1*), rs5029748 (*IKBKB*)	45%	310

Table 34. MDR models of two- and three-fold gene-gene interactions considering only South Asians (n=149)

Outcome	Model	Average testing accuracy	CV Consistency
BMI	rs4436839 (*SOCS3*), rs3747811 (*IKBKB*)	44%	4/10
BMI	rs4436839 (*SOCS3*), rs7674640 (*NFKB1*), rs3747811 (*IKBKB*)	52%	6/10
WC	rs4436839 (*SOCS3*), rs3747811 (*IKBKB*)	55%	8/10
WC	rs4436839 (*SOCS3*), rs7674640 (*NFKB1*), rs3747811 (*IKBKB*)	47%	4/10
Alternative BMI	rs4436839 (*SOCS3*), rs3747811 (*IKBKB*)	54%	6/10
Alternative BMI	rs4436839 (*SOCS3*), rs1609798 (*NFKB1*), rs3747811 (*IKBKB*)	57%	410

Table 35. MDR models of two- and three-fold gene-environment interactions considering all ethnicities

Outcome	Model	Average testing accuracy	CV Consistency
BMI	rs7221341 (*SOCS3*), proteins	58%	10/10
BMI	rs7221341 (*SOCS3*), carbohydrates, fat	57%	9/10
WC	rs7221341 (*SOCS3*), rs5029748 (*IKBKB*)	55%	6/10
WC	rs7221341 (*SOCS3*), rs5029748 (*IKBKB*), proteins	55%	4/10
Alternative BMI	rs7221341 (*SOCS3*), proteins	49%	4/10
Alternative BMI	Fat, proteins, alcohol	50%	6/10

Table 36. MDR models of two- and three-fold gene-environment interactions considering only whites (n=660)

Outcome	Model	Average testing accuracy	CV Consistency
BMI	rs3774932 (*NFKB1*), proteins	53%	7/10
BMI	rs3774932 (*NFKB1*), carbohydrates, alcohol	52%	4/10
WC	rs11722146 (*NFKB1*), proteins	49%	3/10
WC	rs7221341 (*SOCS3*), carbohydrates, proteins	50%	3/10

Table 37. MDR models of two- and three-fold gene-environment interactions considering only East Asians (n=448)

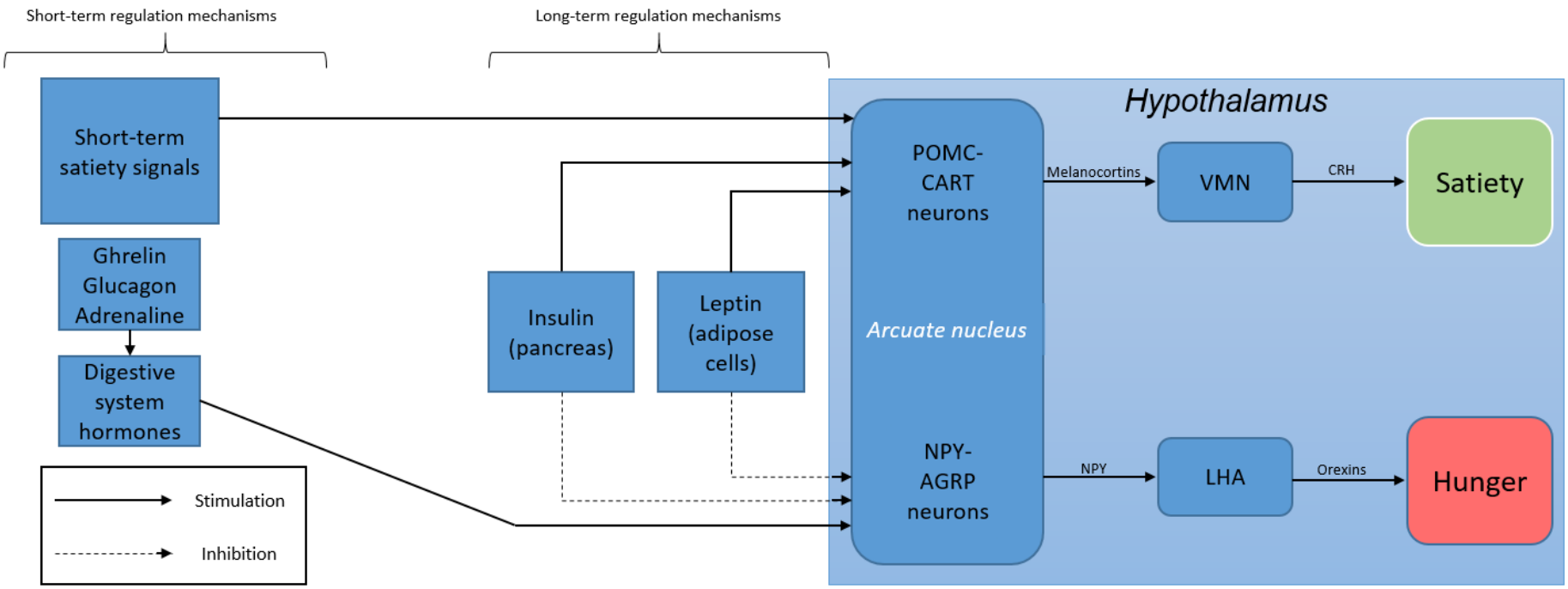
Outcome	Model	Average testing accuracy	CV Consistency
BMI	rs4969172 (*SOCS3*), alcohol	44%	6/10
BMI	rs11868378 (*SOCS3*), rs3774932 (*NFKB1*), proteins	47%	3/10
WC	rs4436839 (*SOCS3*), rs9914220 (*SOCS3*)	44%	2/10
WC	Fat, proteins, alcohol	53%	8/10
Alternative BMI	Carbohydrates, alcohol	51%	10/10
Alternative BMI	rs3747811 (*IKBKB*), carbohydrates, alcohol	53%	6/10

Table 38. MDR models of two- and three-fold gene-environment interactions considering only South Asians (n=144)

Outcome	Model	Average testing accuracy	CV Consistency
BMI	rs3774934 (*NFKB1*), alcohol	43%	3/10
BMI	Fat, proteins, alcohol	49%	9/10
WC	rs4436839 (*SOCS3*), rs3747811 (*IKBKB*)	49%	4/10
WC	Fat, proteins, alcohol	51%	9/10
Alternative BMI	rs4436839 (*SOCS3*), rs3747811 (*IKBKB*)	56%	5/10
Alternative BMI	rs4436839 (*SOCS3*), carbohydrates, alcohol	45%	3/10

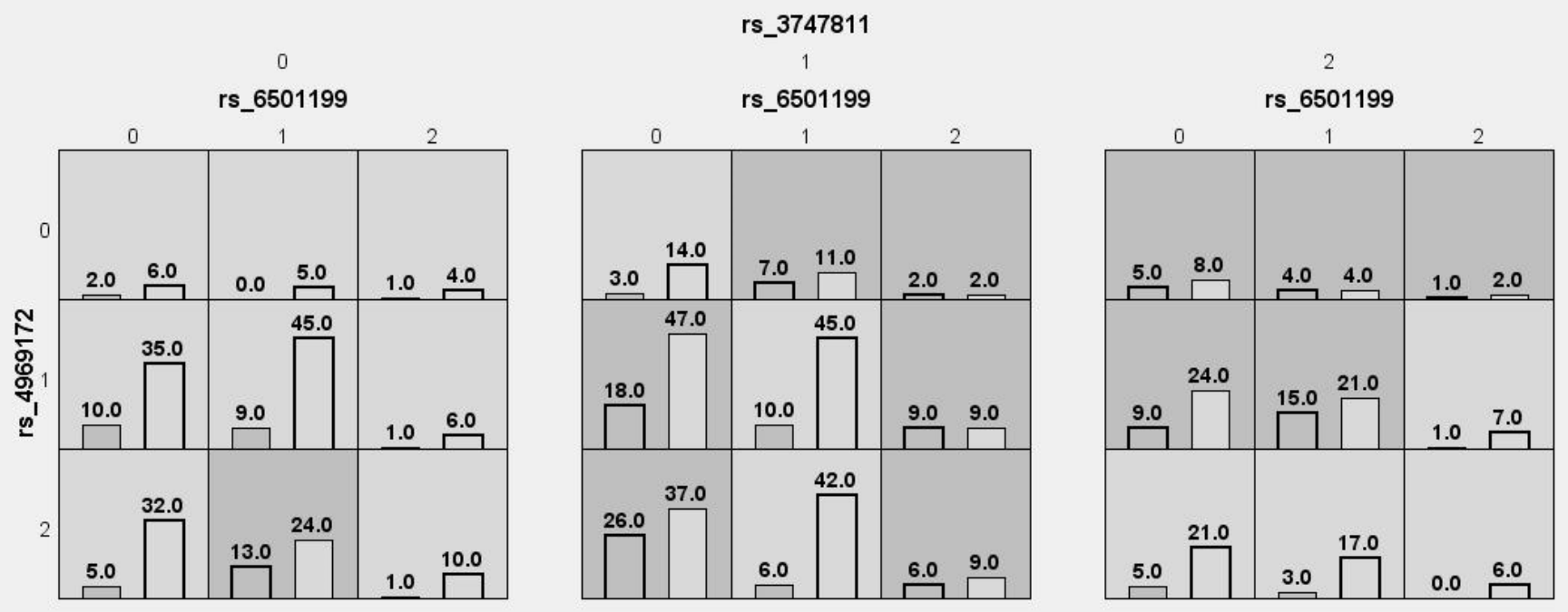
Figures

Figure 1. Diagram of the hypothalamic regulation of satiety and hunger



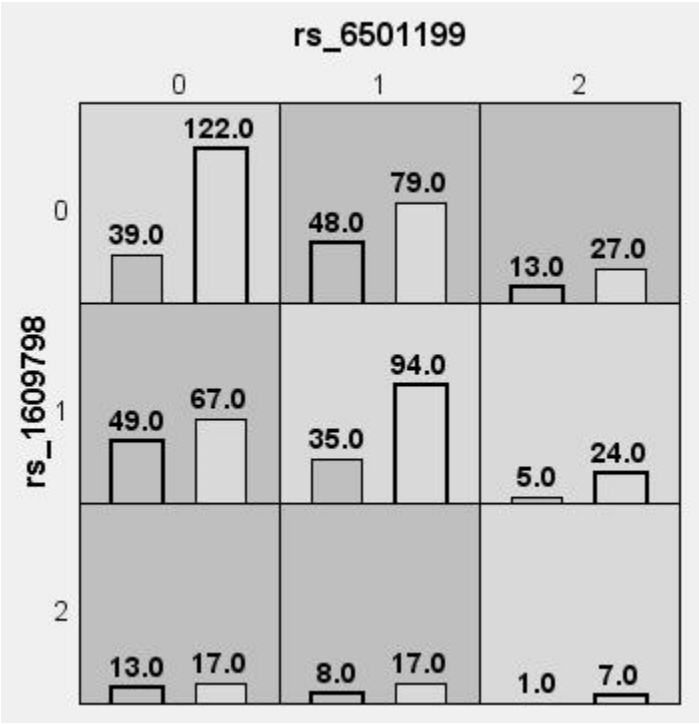
The arcuate nucleus, located in the mediobasal hypothalamus, contains two types of neurons with antagonist effects. Stimulation of NPY neurons and secretion of orexins stimulate appetite, while POMC and CART neurons stimulate satiety. Elevated levels of insulin and leptin contribute to the stimulation of satiety, and to the inhibition of the orexins secretion. When insulin/leptin resistance occurs, POMC and CART neurons are not stimulated, and NPY and AGRP neurons are not inhibited, resulting in hunger, and in increase in energy intake. Insulin/leptin resistance can be caused by overnutrition, creating a vicious circle by stimulating hunger. (AGRP: agouti-related protein; CART: cocaine and amphetamine-regulated transcript; CRH: corticotropin-releasing hormone; LHA: l ateral hypothalamus area; NPY: neuropeptide Y; POMC: proopiomelanocortin; VMN: ventromedial nucleus)

Figure 2. MDR contingency table of the 3-fold gene-gene interaction model of high/low BMI (whites only)



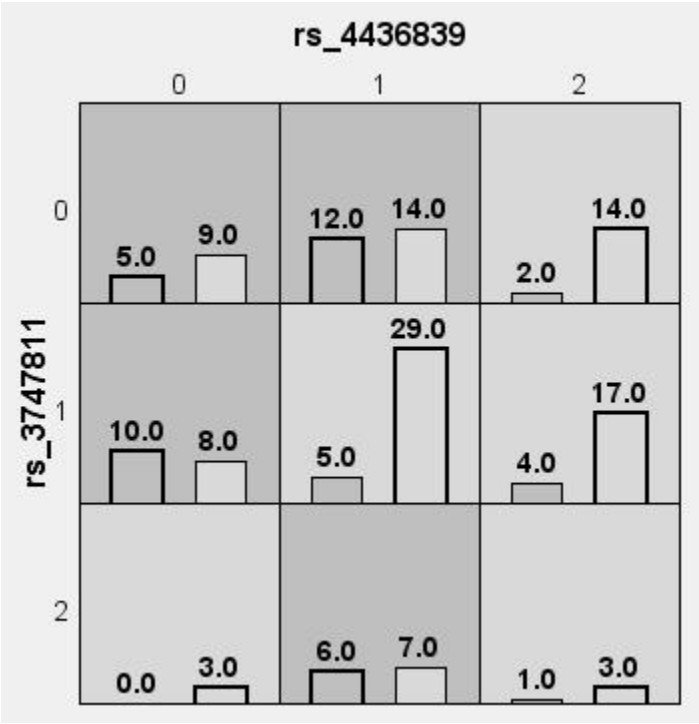
MDR contingency tables of the 3-fold gene-gene interaction model considering only whites. The SNPs involved are rs6501199 (*SOCS3*), rs4969172 (*SOCS3*), and rs3747811 (*IKBKB*). Each cell represents a specific combination of SNPs alleles, where "0" represents individuals homozygous for the common allele, "1" the heterozygous, and "2" the homozygous for the rare allele. The number of individuals fitting of a specific genotype is represented by bars within the cells. The left bar is the count of cases (high BMI), and the right bar is the count of controls (low BMI). Dark grey cells are cells that have been identified as "high risk" by MDR, and the others are identified as "low risk" cells.

Figure 3. MDR contingency table of the best 2-fold gene-gene interaction model of high/low WC (whites only)



MDR contingency tables of the 2-fold gene-gene interaction model for WC considering only whites. The interaction is composed of rs6501199 (*SOCS3*) and rs160978 (*NFKB1*). Each cell represents a specific combination of both factors, where "0" represents individuals homozygous for the common allele, "1" the heterozygous, and "2" the homozygous for the rare allele. The number of individuals fitting of a specific combination of factors is represented by bars within the cells. The left bar is the count of cases (high WC), and the right bar is the count of controls (low WC). Dark grey cells are cells that have been identified as "high risk" by MDR, and the others are identified as "low risk" cells.

Figure 4. MDR contingency table of the best 2-fold gene-gene interaction model of high/low WC (South Asians only)



MDR contingency tables of the 2-fold gene-gene interaction model for WC considering only South Asians. The interaction is composed of rs3747811 (*IKBKB*) and rs4436839 (*SOCS3*). Each cell represents a specific combination of both factors, where "0" represents individuals homozygous for the common allele, "1" the heterozygous, and "2" the homozygous for the rare allele. The number of individuals fitting of a specific combination of factors is represented by bars within the cells. The left bar is the count of cases (high WC), and the right bar is the count of controls (low WC). Dark grey cells are cells that have been identified as "high risk" by MDR, and the others are identified as "low risk" cells.

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Appendix 1: Ottawa Health Science Network Research Ethics Board approval letter

Université d'Ottawa University of Ottawa

Bureau d'éthique et d'intégrité de la recherche — Office of Research Ethics and Integrity

June 29, 2016

Marie-Hélène Roy Gagnon
Department of Epidemiology and Community Medicine
Faculty of Medecine

Co-Investigators: Kelly Burkett, University of Ottawa
François Tessier, University of Ottawa

Re: U of O Ethics file no. A06-16-05 – "Investigating gene-gene and gene-environment interactions in the association between overnutrition and obesity"

Dear Dr. Roy-Gagnon, Professor Burkett and Mr. Tessier

Thank you for the protocol documents and Certificate of Approval from the OHSN-REB (protocol # 20160098-01H) for your project named above.

This is to confirm that, in accordance with the agreement between the University of Ottawa and the OHSN-REB, the University of Ottawa has authorized this board to act as Board of Record for the review and oversight of research involving human subjects conducted at or through the hospital.

We remind you of your obligation to:

- Follow all procedures of the OHSN-REB including reporting and renewal procedures;
- Submit to the authority of the OHSN-REB and that you are subject to the OHSN-REB requirements, including, without limitation, the requirement to modify or stop the research on demand of the OHSN-REB.

If you have any questions, please contact our ethics office at 562-5387.

Sincerely yours,

Catherine Paquet
Director
Office of Research Ethics and Integrity

Appendix 2: Ethics approval from the University of Toronto

UNIVERSITY OF TORONTO

OFFICE OF THE VICE-PRESIDENT, RESEARCH AND INNOVATION

PROTOCOL REFERENCE # 24100

July 3, 2014

Dr. Ahmed El-Sohemy
DEPT OF NUTRITIONAL SCIENCES
FACULTY OF MEDICINE

Dear Dr. El-Sohemy,

Re: Your research protocol entitled, "Nutrigenomics and biomarkers of chronic disease"

ETHICS APPROVAL

Original Approval Date: June 3, 2009
Expiry Date: June 2, 2015
Continuing Review Level: 1
Renewal: Data Analysis Only

We are writing to advise you that you have been granted annual renewal of ethics approval to the above-referenced research protocol through the Research Ethics Board (REB) delegated process. Please note that all protocols involving ongoing data collection or interaction with human participants are subject to re-evaluation after 5 years. Ongoing research under this protocol must be renewed prior to the expiry date.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your protocol. Note that annual renewals for protocols cannot be accepted more than 30 days prior to the date of expiry as per our guidelines.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible. If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

Elizabeth Peter, Ph.D.
REB Chair

Daniel Gyewu
REB Manager

Appendix 3: General health and lifestyle questionnaire

ID # _____

General Health and Lifestyle Questionnaire

1. Gender
   - ❑ Male
   - ❑ Female

   Today's Date_____
   Day Month Year

2. Age _____

3. Date of Birth _____ Country of Birth _____
   Day Month Year

4. Highest level of education:
   - ❑ Elementary
   - ❑ High school
   - ❑ Some college or undergraduate training
   - ❑ College or Undergraduate degree received
   - ❑ Graduate degree received

5. Please describe your ethnicity (write as many as necessary).

   _____

6. Please indicate your blood type:
   - ❑ A
   - ❑ B
   - ❑ AB
   - ❑ O
   - ❑ don't know

   and Rh factor:
   - ❑ positive
   - ❑ negative
   - ❑ don't know

7. Do you currently, or have you ever, experienced headache attacks (including migraines, cluster headaches, etc.)?
   ❑ Yes ❑ No

   At what age did these attacks start? _____yrs old

   How long ago was your last headache attack? _____

   How many headache attacks have you had in the last year? _____

   How long do the attacks usually last? _____

8. Within the past **two weeks**, have you had

	Yes	No
a piercing, tattoo, acupuncture?		
medical or dental procedure?		
a vaccination or immunization?		
a flu?		
an infection?		
a fever?		

ID # _____

9. Please indicate if you have ever been diagnosed with any of the following conditions.

Condition	Tick if YES	Age or Date of Diagnosis
High cholesterol		
High blood pressure		
Depression		
Anxiety disorder		
Chest pain or shortness of breath		
Kidney problems		
Food allergies, specify_____		
Other allergies, specify_____		
Asthma		
Diabetes		
Cancer, specify_____		
Crohns		
Ulcerative Colitis		
Ulcer		
Thyroid conditions		
Celiac disease		
Diverticulitis		
Arthritis		
Osteoporosis		
Other condition, specify_____		

10. Has any family member ever been diagnosed with any of the above conditions?

Your....	Health conditions
Mother	
Father	
Brothers	
Sisters	

ID # _____

11. What medications have you taken within the **last month**?

Medication name	Reason	Amount	Duration

12. For **Females** only (Males skip to #13 on the next page)

Are you pregnant or nursing? ❑ Yes ❑ No

Are you using hormonal contraception (e.g., birth control pill or patch)?

❑ Yes ❑ No

If yes, what type? _____

how long? _____

Please indicate next to each of the following PMS (premenstrual syndrome) symptoms, the degree to which you experience them *within the 5 days before the onset of your period and ending by the 4th day of your period*:

Symptoms	None	Mild	Moderate	Severe
Acne, skin blemish				
Bloating, swelling, breast tenderness				
Cramping				
Mood swings, crying easily, irritability, angry outbursts				
Increased appetite, food cravings				
Fatigue				
Headaches				
Anxiety, tension, nervousness				
Clumsiness				
Confusion, difficulty concentrating, forgetfulness				
Sexual desire/activity change				
Insomnia				
Nausea				
Depression				
Desire to be alone				
Other (specify)_____				

ID # _____

13. What vitamins, minerals, herbal supplements or other nutritional supplements have you taken within the **last month** (i.e., multivitamin, protein powder, gingko)?

Name	Reason	Amount	Duration

14. Please list any food restrictions (e.g., salt, fat, carbohydrate, etc.) or special diets you are have been on in the **last month** (e.g., Atkins, South Beach, vegan) and the reason (e.g., health, religious or other reasons).

Food Restrictions/ Special Diet	Reason	How long ?

15. Do you **currently** smoke (at least 1 cigarette per day for 1 month or longer)?

❑ Yes ❑ No

If yes, how many years have you been smoking? _____

how many cigarettes do you smoke per day? _____

Are you a **past** smoker (have previously smoked at least 1 cigarette per day for 1 month or longer but have not smoked at least 1 cigarette per day in the last month)?

❑ Yes ❑ No

If yes, when did you quit (approximate date)? _____

how many years did you smoke? _____

how many cigarettes did you smoke per day? _____

ID # _____

16. Do you currently, or have you ever, consumed caffeine-containing beverages (e.g., coffee, tea, cola) *regularly?*

- ❑ Yes, I currently consume them *regularly*
- ❑ Yes, I used to consume them *regularly* but do not anymore
- ❑ No, I have never *regularly* consumed them (GO TO Q17)

If **yes**, please indicate next to each of the following **withdrawal** symptoms the degree to which you experience(d) them **up to 48 hours** after ceasing to consume caffeine-containing beverages.

SYMPTOM	**Don't know**	**None**	**Mild**	**Moderate**	**Severe**
Headache					
Tiredness/ Fatigue					
Decreased energy/activeness					
Decreased alertness/attentiveness					
Drowsiness/ Sleepiness					
Decreased contentedness/well-being					
Depressed mood					
Difficulty concentrating					
Irritability					
Foggy/ Not clearheaded					
"Flu-like" symptoms					
Nausea/ Vomiting/ Upset stomach					
Muscle pain/ Stiffness					
Anxiety/ Nervousness					
Other, please specify _____					

17. Do you experience any of the following effects **up to 12 hours** after consuming **one** caffeine-containing beverage (e.g., coffee, tea, cola)?

EFFECT	**Don't know**	**None**	**Mild**	**Moderate**	**Severe**
Headache					
Increased energy/activeness					
Increased alertness/attentiveness					
Elevated mood					
Increased heart rate					
Anxiety/ Nervousness					
Panic attacks					
Restlessness					
Agitation					
Tremors/ Jitters/ Shakiness					
Dizziness					
Insomnia/ Impaired sleep					
Upset stomach					
Laxative effect					
Other, please specify_____					

18. Do you try to avoid or limit your consumption of caffeine?

- ❑ No (GO TO Q19)
- ❑ Yes

If **yes**, please indicate the reason(s) below

REASON	YES	NO
Fear of dependence/addiction		
Fear of experiencing withdrawal symptoms		
Increased heart rate		
Increased blood pressure		
Anxiety/ Nervousness		
Panic attacks		
Restlessness		
Agitation		
Tremors/ Jitters/ Shakiness		
Dizziness		
Insomnia/ Impaired sleep		
Upset stomach		
Laxative effect		
General health		
Dislike taste of caffeine-containing beverages		
Other, please specify _____		

19. What other food(s), beverage(s) or ingredient(s) do you **avoid/dislike**?

Food, beverage, ingredient	Reason you avoid/dislike

ID # _____

20. On a usual weekday and weekend day in the **last month**, how much time did you spend on each of the following activities? *Total for each type of day should add up to 24 hours.*

Activity	**Effects**	Usual **week** day (hours/day)	Usual **weekend** day (hours/day)
Sleeping			
Sitting or reclining activity (studying, eating, reading, desk work, computer activity, watching TV, etc.)	• Minimal movement • Minimal exertion		
Light activity (office work, driving a car, strolling, standing, etc.)	• Some movement • Weak exertion		
Moderate activity (housework, light sports, regular walking, golf, yard work, lawn mowing, ballroom dancing, cycling, etc.)	• ↑ heart rate • Moderate exertion		
Vigorous activity (strenuous sports, jogging, aerobic dancing, swimming, brisk walking, rollerblading, cycling, etc.)	• ↑↑↑ heart rate • Strong exertion • Get out of breath • Sweating		
		= 24 hours	= 24 hours

Contact Information

Full Name: _____

Address _____

_____

_____

Phone number ( ) _____

e-mail address (please print **clearly**)

_____

Would you be interested in being contacted for a follow-up study?

❑ Yes ❑ No

Thank You!

Appendix 4: Food frequency questionnaire

CAJ-1 HARVARD UNIVERSITY

DIETARY ASSESSMENT

NAME (Please print)	_____ First _____ Last
DATE OF BIRTH	_____ / _____ / _____ Day Month Year
TODAY'S DATE	_____ / _____ / _____ Day Month Year

Please complete all three boxes above, using an HB (no. 2) pencil.

To ensure your confidentiality, this page will be removed after we receive it in our office.

DIETARY ASSESSMENT

For office use only

ID NUMBER: _____

DATE: _____

- **Darken one circle per question that corresponds to your answer**
- **Follow arrows**

VITAMINS

1. Have you ever regularly taken **multi-vitamins**?

- ○ **Never** have
- ○ Have in the **Past only** → **a) For how many years did you take them in the past?**
  ○ 1 year or less ○ 2–4 years ○ 5–9 years ○ 10 or more years
- ○ **Currently** take them →
  a) If you currently take multi-vitamins, how many do you take per week?
  ○ 2 or less ○ 3–5 ○ 6–9 ○ 10 or more
  b) If you are currently taking multi-vitamins, for how many years have you been taking them?
  ○ 1 year or less ○ 2–4 years ○ 5–9 years ○ 10 or more years
  c) If you currently take them, what brand do you usually use?
  (Specify exact brand and type)

2. **Not counting multi-vitamins,** have you ever taken any of the following specific vitamins or minerals?

Vitamin A	**Dose per day?**	**How long?**
○ **Never** taken	○ Less than 8,000 IU	○ 0–1 year
○ Taken in the **past only**	○ 8,000 to 12,000 IU	○ 2–4 years
○ Yes, **currently** take it	○ 13,000 to 22,000 IU	○ 5–9 years
	○ 23,000 IU or more	○ 10 years or more
	○ Don't know	

PLEASE DO NOT WRITE IN THIS AREA

05749

2. (Continued) **Not counting multi-vitamins,** have you ever taken any of the following specific vitamins or minerals?

Beta Carotene
- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?
- ○ Less than 8,000 IU
- ○ 8,000 to 12,000 IU
- ○ 13,000 to 22,000 IU
- ○ 23,000 IU or more
- ○ Don't know

How long?
- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

Vitamin B_6
- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?
- ○ Less than 10 mg
- ○ 10 to 39 mg
- ○ 40 to 79 mg
- ○ 80 mg or more
- ○ Don't know

How long?
- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

Vitamin C
- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?
- ○ Less than 400 mg
- ○ 400 to 700 mg
- ○ 750 to 1,250 mg
- ○ 1,300 mg or more
- ○ Don't know

How long?
- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

Vitamin E
- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?
- ○ Less than 100 IU
- ○ 100 to 250 IU
- ○ 300 to 500 IU
- ○ 600 IU or more
- ○ Don't know

How long?
- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

Selenium
- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?
- ○ Less than 80 mcg
- ○ 80 to 130 mcg
- ○ 140 to 250 mcg
- ○ 260 mcg or more
- ○ Don't know

How long?
- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

Iron
- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?

mg of elemental iron (325 mg Ferrous Sulfate = 65 mg elemental iron)
- ○ Less than 41 mg
- ○ 41 to 80 mg
- ○ 81 to 150 mg
- ○ 151 mg or more
- ○ Don't know

How long?
- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

Zinc
- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?
- ○ Less than 25 mg
- ○ 25 to 74 mg
- ○ 75 to 100 mg
- ○ 101 mg or more
- ○ Don't know

How long?
- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

2. (Continued) **Not counting multi-vitamins,** have you ever taken any of the following specific vitamins or minerals?

Calcium or Dolomite (Include Tums)

- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?

mg of elemental Calcium (1 Tums = 500 mg Calcium Carbonate = 200 mg elemental.)

- ○ Less than 400 mg
- ○ 400 to 900 mg
- ○ 901 to 1,300 mg
- ○ 1,301 mg or more
- ○ Don't know

How long?

- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

Fish Oil (Omega 3 fatty acids)

- ○ Never taken
- ○ Taken in the past only
- ○ Yes, currently take it

Dose per day?

- ○ Less than 2500 mg
- ○ 2500 to 4999 mg
- ○ 5000 to 9999 mg
- ○ 10,000 mg or more
- ○ Don't know

How long?

- ○ 0–1 year
- ○ 2–4 years
- ○ 5–9 years
- ○ 10 years or more

Which other supplements are you taking currently on a regular basis (at least once per week)?

- ○ None
- ○ Metamucil
- ○ Other fiber supplements (e.g., Citracil)
- ○ Cod liver oil
- ○ Brewer's yeast
- ○ Vitamin D
- ○ Folic acid or folate (B_9)
- ○ Potassium
- ○ Magnesium
- ○ Niacin
- ○ Other Supplements (specify) _____

DAIRY FOODS

In the following section, please describe how often on average you have used the amount specified in the past month. Please indicate your average total use, taking the portion size into account. For example, if you use 1/2 a glass of milk twice a week, mark 1 glass per week to represent your average total intake.

3. For each food listed, fill in the circle indicating your average total use of the amount specified during the past month. (Please include chocolate milk.)

Skim milk (8 oz. glass)

- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

1% or 2% milk (8 oz. glass)

- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

Whole milk (8 oz. glass)

- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

Soy milk (8 oz. glass)

- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4–5 glasses per day
- ○ 6+ glasses per day

3. (Continued) Please fill in your average total use, during the past month, of each specified food.

Cream, e.g., in coffee, whipped or sour cream (1 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2 or more tbs. per day

Non-dairy coffee whitener (tsp.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tsp. per month
- ○ 1 tsp. per week
- ○ 2–4 tsp. per week
- ○ 5–6 tsp. per week
- ○ 1 tsp. per day
- ○ 2 or more tsp. per day

Frozen yogurt, sherbet or non-fat ice cream (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Ice cream (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Flavored yogurt, without Nutrasweet (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 or more servings per day

Yogurt, plain or with Nutrasweet (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 or more servings per day

What type of yogurt do you usually eat?
- ○ None
- ○ Regular
- ○ Low fat
- ○ Nonfat

Cottage or ricotta cheese (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Cream cheese (1 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Other cheese, e.g., American, cheddar, etc., plain or as part of a dish (1 slice or 1 oz. serving)
- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ 1 slice per day
- ○ 2 or more slices per day

What type of cheese do you usually eat?
- ○ None
- ○ Regular
- ○ Low fat or lite
- ○ Nonfat

Butter (small pat or tsp.), added to food or bread; exclude use in cooking
- ○ Never
- ○ Less than once per month
- ○ 1–3 pats per month
- ○ 1 pat per week
- ○ 2–4 pats per week
- ○ 5–6 pats per week
- ○ 1 pat per day
- ○ 2–3 pats per day
- ○ 4 or more pats per day

3. (Continued) Please fill in your average total use, during the past month, of each specified food.

Margarine (small pat or tsp.), added to food or bread; exclude use in cooking

- ○ Never
- ○ Less than once per month
- ○ 1–3 pats per month
- ○ 1 pat per week
- ○ 2–4 pats per week
- ○ 5–6 pats per week
- ○ 1 pat per day
- ○ 2–3 pats per day
- ○ 4 or more pats per day

What form of margarine do you usually use? (Do not include "spray" type margarine)

- ○ None

Form?

- ○ Stick
- ○ Tub
- ○ Squeeze (liquid)

Type?

- ○ Regular
- ○ Light spread
- ○ Extra light spread
- ○ Nonfat

What specific **brand** and **type** (e.g., Land O' Lakes Country Morning Blend Light)?

FRUITS

4. Please fill in your average total use, during the past month, of each specified food.

Grapes (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Prunes (7 prunes or 1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Bananas (1)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

Cantaloupe (1/4 melon)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more servings per day

Honeydew (1/4 melon)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more servings per day

Watermelon (1 slice)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

Avocado (1/2 fruit or 1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Applesauce (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Fresh apples or pears (1)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

4. (Continued) Please fill in your average total use, during the past month, of each specified food.

100% apple juice or cider (small glass)
- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

Oranges, tangerines, clementines (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

100% orange juice (small glass)
- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

Grapefruit (1/2)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

100% grapefruit juice (small glass)
- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

Other 100% fruit juices (small glass)
- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

Strawberries, raspberries or blackberries, fresh or frozen (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 per times day
- ○ 4 or more per day

Blueberries, fresh or frozen (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 servings per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Peaches, apricots, plums or nectarines, fresh (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ Once per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ Once per day
- ○ 2–3 per day
- ○ 4 or more per day

Tropical fruit, not banana, - pineapple, kiwi, mango, papaya, guava, fresh figs, etc. (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Canned fruit, all kinds (1/2 cup) → **What type of canned fruit do you usually eat?**
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

What type of canned fruit do you usually eat?
- ○ Don't usually eat canned fruit
- ○ Canned in juice
- ○ Canned in light syrup
- ○ Canned in heavy syrup
- ○ Canned in water
- ○ Other
- ○ Don't know

4. (Continued) Please fill in your average total use, during the past month, of each specified food.

Dried apricots (1/4 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Raisins, dried figs or dried pears (1/4 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Dried dates (1/4 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Other fruit – gooseberries, black currants, red currants, cranberries, etc. (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

In summary, how many servings of fruit do you usually eat, not counting juices?
- ○ None
- ○ Less than one per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4–5 per day
- ○ 6+ per day

VEGETABLES

5. Please fill in your average total use, during the past month, of each specified food.

Tomatoes (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ Once per day
- ○ 2–3 per day
- ○ 4 or more per day

Tomato juice (small glass)
- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

Tomato sauce (1/2 cup) e.g., spaghetti sauce
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 servings per week
- ○ 1 serving per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Salsa, picante or taco sauce (1/4 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Tofu, soybeans, or vegetable protein (3–4 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

String beans (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 servings per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

5. (Continued) Please fill in your average total use, during the past month, of each specified food.

Broccoli (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Cabbage or cole slaw (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Cauliflower (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Brussels sprouts (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Carrots, raw (1/2 carrot or 2–4 sticks)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Carrots, cooked (1/2 cup) or carrot juice (2–3 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Corn (1 ear or 1/2 cup frozen or canned)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ Once per day
- ○ 2–3 per day
- ○ 4 or more per day

Peas or lima beans (1/2 cup fresh, frozen or canned)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Mixed vegetables (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4–6 times per day

5. (Continued) Please fill in your average total use, during the past month, of each specified food.

Dried lentils or beans (kidney, pinto, black-eyed, chick peas, etc.) baked, cooked or canned (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Dark orange (winter) squash (butternut, acorn etc.) (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Zucchini, marrow or other summer squash with thin, edible skin (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Eggplant (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Yams or sweet potatoes (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Spinach or Swiss chard, cooked (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Spinach, raw as in salad (1 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Kale, mustard, collard or turnip greens (1/2 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Iceberg or head lettuce (serving)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

5. (Continued) Please fill in your average total use, during the past month, of each specified food.

Romaine or leaf lettuce (serving)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Celery (4" stick)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ Once per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Green peppers (3 slices or 1/4 pepper)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Red peppers (3 slices or 1/4 pepper)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Onions as a garnish or in a salad (1 slice)
- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ One slice per day
- ○ 2–3 slices per day
- ○ 4 or more slices per day

Onions as a vegetable, rings or soup (1 onion)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Okra (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Cucumbers, raw (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Dill pickles (1 medium)
- ○ Never
- ○ Less than one per month
- ○ 1–3 per month
- ○ One per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ One per day
- ○ 2–3 per day
- ○ 4 or more per day

5. (Continued) Please fill in your average total use, during the past month, of each specified food.

Olives (1/4 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Beets (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Asparagus (1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

In summary, how many servings of vegetables do you usually eat, not counting salad or potatoes?
- ○ None
- ○ Less than one per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4–5 per day
- ○ 6+ per day

EGGS, MEAT & FISH

6. Please fill in your average total use, during the past month, of each specified food.

Egg Beaters or egg whites only (1/4 cup or 1 egg)
- ○ Never
- ○ Less than once per month
- ○ 1–3 eggs per month
- ○ 1 egg per week
- ○ 2–4 eggs per week
- ○ 5–6 eggs per week
- ○ 1 egg per day
- ○ 2 or more eggs per day

Eggs whole, with yolk (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 eggs per month
- ○ 1 egg per week
- ○ 2–4 eggs per week
- ○ 5–6 eggs per week
- ○ 1 egg per day
- ○ 2 or more eggs per day

Bacon (2 slices)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ 1 or more servings per day

Chicken or turkey sandwich
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5 or more per week

Other chicken or turkey, with skin (4–6 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Other chicken or turkey, without skin (4–6 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

6. (Continued) Please fill in your average total use, during the past month, of each specified food.

Beef or pork hot dogs (1)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2 or more per day

Chicken or turkey hot dogs (1)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2 or more per day

Salami, bologna, or other processed meat sandwiches

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5 or more per week

Processed meats, e.g., sausage, kielbasa, etc. (2 oz. or 2 small links)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Hamburger, lean or extra lean (1 patty)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 or more per day

Hamburger, regular (1 patty)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 or more per day

Beef, pork, or lamb as a sandwich or mixed dish, e.g., stew, casserole, lasagna, etc.

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ 1 or more times per day

Pork as a main dish, e.g., ham or chops (4–6 oz.)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ 1 or more times per day

Beef or lamb as a main dish, e.g., steak, roast (4–6 oz.)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ 1 or more times per day

Liver: beef, calf or pork (4 oz.)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2 or more servings per week

Liver: chicken or turkey (1 oz.)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2 or more servings per week

Other organ meats, e.g., chitterlings, gizzards, hog maws (3 oz.)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2 or more servings per week

6. (Continued) Please fill in your average total use, during the past month, of each specified food.

Canned tuna fish or salmon (3–4 oz.)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Breaded fish cakes, pieces, or fish sticks (1 serving, store bought)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ 1 or more per day

Shrimp, crabs, scallops, clams as a main dish (1 serving)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ 1 or more times per day

Dark meat fish, e.g., mackerel, salmon, sardines, bluefish, swordfish (3–5 oz.)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ 1 or more servings per day

Other fish, e.g., cod, haddock, catfish, whiting, perch (3–5 oz.)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ 1 or more servings per day

CEREALS, BREADS & STARCHES

7. Please fill in your average total use, during the past month, of each specified food.

Cold breakfast cereal (1 cup) →

- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

What brand and type of cold breakfast cereal do you usually eat?

Specify brand & type (e.g., "Ralston Rice Chex")

[ ]

○ Don't eat cold breakfast cereal

Cooked oatmeal (1 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

Cooked oat bran (1 cup)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

Other cooked breakfast cereal-include grits (1 cup) →

- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

What brand and type of other cooked breakfast cereal do you usually eat?

- ○ Don't eat cooked breakfast cereal
- ○ Red River Cereal
- ○ Cream of Wheat
- ○ Other – Specify brand & type

[ ]

7. (Continued) Please fill in your average total use, during the past month, of each specified food.

White bread (slice), including pita bread

- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ 1 slice per day
- ○ 2–3 slices per day
- ○ 4–5 slices per day
- ○ 6+ slices per day

Bagels, English muffins, or rolls made with white flour (1 whole)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more per day

Heavy bread packed with visible whole grains, e.g., pumpernickel rye (1 slice)

- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ 1 slice per day
- ○ 2–3 slices per day
- ○ 4–5 slices per day
- ○ 6+ slices per day

Other breads, including pita bread, made with whole grain or whole wheat flour (1 slice)

- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ 1 slice per day
- ○ 2–3 slices per day
- ○ 4–5 slices per day
- ○ 6+ slices per day

Are these breads usually made with stone ground flour?

- ○ Yes
- ○ No
- ○ Don't know

Bagels or rolls made with whole grain or whole wheat flour (1 whole)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more per day

Are these bagels or rolls usually made with stone ground flour?

- ○ Yes
- ○ No
- ○ Don't know

Cornbread (1 square), biscuits (1), or muffins (regular)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

Brown rice (1 cup) →

- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

What type of brown rice do you usually eat?

- ○ Don't usually eat brown rice
- ○ Regular
- ○ Converted or parboiled
- ○ Other – Specify type and brand

White rice (1 cup) →

- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

What type of white rice do you usually eat?

- ○ Don't usually eat white rice
- ○ Regular
- ○ Converted or parboiled
- ○ Other – Specify type and brand

7. (Continued) Please fill in your average total use, during the past month, of each specified food.

Macaroni (white) and cheese (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

Other pasta made with white flour, e.g., spaghetti, noodles, pasta salad (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

Whole grain pasta, e.g., spaghetti, noodles, pasta salad (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

Barley (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

Bulgur or tabouli, kasha (buckwheat) (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

Other grain products, e.g., couscous, etc. (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ One cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2–3 cups per day
- ○ 4 or more cups per day

Pancakes, waffles, or French toast (3 pieces)
- ○ Never
- ○ Less than once per month
- ○ 1–3 servings per month
- ○ 1 serving per week
- ○ 2–4 servings per week
- ○ 5–6 servings per week
- ○ 1 serving per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

French fried potatoes or hash browns (small order or 1/2 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 servings per day
- ○ 4 or more servings per day

Scalloped potatoes (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

Potatoes, baked, boiled, or mashed (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

Olean-containing potato chips or corn chips (small bag or 1 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

Regular potato chips or corn chips (small bag or 1 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

7. (Continued) Please fill in your average total use, during the past month, of each specified food.

Crackers, e.g., Triscuits, Wheat Thins, Saltines, Ritz (5)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Pizza (2 slices)

- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Tortillas (1)

- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

BEVERAGES

CARBONATED BEVERAGES—Consider the serving size as one 12 oz. (about 350 ml.) glass, bottle or can for these carbonated beverages.

8. Please fill in your average total use, during the past month, of each specified food.

LOW-CALORIE (Sugar-free types)

Low-calorie cola, e.g., Diet Coke with caffeine (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4 or more cans per day

Low-calorie caffeine-free soda (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4 or more cans per day

Other low-calorie carbonated beverage, e.g., Diet 7-Up, Fresca, diet ginger ale (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4 or more cans per day

REGULAR TYPES (not sugar-free)

Coke, Pepsi, or other cola with sugar (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4 or more cans per day

Caffeine-Free Coke, Pepsi, or other cola with sugar (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4 or more cans per day

Other carbonated beverage with sugar, e.g., 7-Up (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4 or more cans per day

8. (Continued) Please fill in your average total use, during the past month, of each specified food.

OTHER BEVERAGES

Non-carbonated fruit drinks with added sugar (not sport drinks) – lemonade, Kool Aid, Five Alive, etc. (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4 or more glasses per day

Sport drinks – Gatorade, Powerade (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 bottles per month
- ○ 1 bottle per week
- ○ 2–4 bottles per week
- ○ 5–6 bottles per week
- ○ 1 bottle per day
- ○ 2–3 bottles per day
- ○ 4 or more bottles per day

Beer, regular (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4–5 cans per day
- ○ 6+ cans per day

Light beer, e.g., Bud Light (12 oz. glass, bottle, can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4–5 cans per day
- ○ 6+ cans per day

Malt liquor, e.g., Olde English, Colt 45 (12 oz. can)

- ○ Never
- ○ Less than once per month
- ○ 1–3 cans per month
- ○ 1 can per week
- ○ 2–4 cans per week
- ○ 5–6 cans per week
- ○ 1 can per day
- ○ 2–3 cans per day
- ○ 4–5 cans per day
- ○ 6+ cans per day

Red wine (4 oz. glass)

- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4–5 glasses per day
- ○ 6+ glasses per day

White wine (4 oz. glass)

- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4–5 glasses per day
- ○ 6+ glasses per day

Liquor, e.g., whiskey, gin, etc. (1 drink or shot)

- ○ Never
- ○ Less than once per month
- ○ 1–3 drinks per month
- ○ 1 drink per week
- ○ 2–4 drinks per week
- ○ 5–6 drinks per week
- ○ 1 drink per day
- ○ 2–3 drinks per day
- ○ 4–5 drinks per day
- ○ 6+ drinks per day

Plain water, bottled or tap including mineral water and soda water (1 cup or glass)

- ○ Never
- ○ Less than once per month
- ○ 1–3 glasses per month
- ○ 1 glass per week
- ○ 2–4 glasses per week
- ○ 5–6 glasses per week
- ○ 1 glass per day
- ○ 2–3 glasses per day
- ○ 4–5 glasses per day
- ○ 6+ glasses per day

Herbal tea (8 oz. cup), Not green tea

- ○ Never
- ○ 1 cup per week or less
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 cups per day
- ○ 3 cups per day
- ○ 4 cups per day
- ○ 5 cups per day
- ○ 6+ cups per day

Green tea (8 oz. cup)

- ○ Never
- ○ 1 cup per week or less
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 cups per day
- ○ 3 cups per day
- ○ 4 cups per day
- ○ 5 cups per day
- ○ 6+ cups per day

Iced tea (12 oz. glass, bottle, can) e.g., Nestea, Lipton, Tetley, etc.

- ○ Never
- ○ 1 cup per week or less
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 cups per day
- ○ 3 cups per day
- ○ 4 cups per day
- ○ 5 cups per day
- ○ 6+ cups per day

8. (Continued) Please fill in your average total use, during the past month, of each specified food.

Tea (8 oz. cup), Not herbal, green or iced

- ○ Never
- ○ 1 cup per week or less
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 cups per day
- ○ 3 cups per day
- ○ 4 cups per day
- ○ 5 cups per day
- ○ 6+ cups per day

Decaffeinated coffee (8 oz. cup)

- ○ Never
- ○ 1 cup per week or less
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 cups per day
- ○ 3 cups per day
- ○ 4 cups per day
- ○ 5 cups per day
- ○ 6+ cups per day

Regular coffee with caffeine (8 oz. cup), Not latte, cappuccino, mocha, iced coffee, espresso, etc.

- ○ Never
- ○ 1 cup per week or less
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 cups per day
- ○ 3 cups per day
- ○ 4 cups per day
- ○ 5 cups per day
- ○ 6+ cups per day

Coffee drinks with caffeine - e.g., latte, cappuccino, mocha, iced coffee, etc. (8 oz. cup) or espresso (1 oz. cup)

- ○ Never
- ○ 1 cup per week or less
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 cups per day
- ○ 3 cups per day
- ○ 4 cups per day
- ○ 5 cups per day
- ○ 6+ cups per day

If you drink tea, how often is it decaffeinated?

- ○ Almost never or never
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

If you drink coffee, how often is it decaffeinated?

- ○ Almost never or never
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

How often are your coffees or coffee drinks purchased outside of home or work (i.e., ready-to-drink)?

- ○ Almost never or never
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

Where do you usually purchase your ready-to-drink coffee or coffee drinks?

- ○ Starbucks or Second Cup
- ○ Timothy's, Tim Hortons, Coffee Time, Country Style
- ○ Other, please specify

0 1 2 3 4 5 6 7 8 9

If you make your coffee at home or work, how is it usually prepared?

- ○ Paper filter drip
- ○ Permanent filter (plastic or metal) drip
- ○ Percolated
- ○ French press (e.g., Bodum)
- ○ Instant
- ○ Other, please specify

0 1 2 3 4 5 6 7 8 9

a
b
c

Are there any other caffeinated beverages not mentioned above that you usually drink at least once per week (e.g., Jolt, root beer, hot chocolate, cocoa, etc.)?

Other caffeinated beverages	Usual serving size in ounces	Servings per week
(a)		
(b)		
(c)		

SWEETS, BAKED GOODS & MISCELLANEOUS

9. Please fill in your average total use, during the past month, of each specified food.

Chocolate candy bar or packet, (e.g., Hershey's, M&M's)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

Other mixed candy bars, (e.g., Snickers, Milky Way, Reeses)
- ○ Never
- ○ Less than once per month
- ○ 1–3 candy bars per month
- ○ 1 candy bar per week
- ○ 2–4 candy bars per week
- ○ 5–6 candy bars per week
- ○ 1 candy bar per day
- ○ 2–3 candy bars per day
- ○ 4 or more candy bars per day

Candy without chocolate (e.g., 1 pack mints, Lifesavers)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2–3 times per day
- ○ 4 or more times per day

Jams, jellies, preserves, syrup, or honey (1 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2–3 tbs. per day
- ○ 4 or more tbs. per day

Peanut butter (1 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2–3 tbs. per day
- ○ 4 or more tbs. per day

Almond butter (1 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2–3 tbs. per day
- ○ 4 or more tbs. per day

Popcorn (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 cup per day
- ○ 2 or more cups per day

Pretzels (1 oz., or small bag)
- ○ Never
- ○ Less than once per month
- ○ 1–3 servings per month
- ○ One serving per week
- ○ 2–4 servings per week
- ○ 5–6 servings per week
- ○ One serving per day
- ○ 2 or more servings per day

Cookies, home baked (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cookies per month
- ○ 1 cookie per week
- ○ 2–4 cookies per week
- ○ 5–6 cookies per week
- ○ 1 cookie per day
- ○ 2–3 cookies per day
- ○ 4 or more cookies per day

Cookies, fat-free or reduced fat (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cookies per month
- ○ 1 cookie per week
- ○ 2–4 cookies per week
- ○ 5–6 cookies per week
- ○ 1 cookie per day
- ○ 2–3 cookies per day
- ○ 4 or more cookies per day

Cookies, other ready made (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cookies per month
- ○ 1 cookie per week
- ○ 2–4 cookies per week
- ○ 5–6 cookies per week
- ○ 1 cookie per day
- ○ 2–3 cookies per day
- ○ 4 or more cookies per day

Brownies (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2 or more per day

9. (Continued) Please fill in your average total use, during the past month, of each specified food.

Doughnuts (1)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4 or more per day

Cake, home baked (slice)
- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ 1 or more slices per day

Cake, ready made (slice)
- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ 1 or more slices per day

Pie, homemade (slice)
- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ 1 or more slices per day

Pie, ready made (slice)
- ○ Never
- ○ Less than once per month
- ○ 1–3 slices per month
- ○ 1 slice per week
- ○ 2–4 slices per week
- ○ 5–6 slices per week
- ○ 1 or more slices per day

Sweet roll, coffee cake or other pastry, home baked (serving)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Sweet roll, coffee cake or other pastry, ready made (serving)
- ○ Never
- ○ Less than once per month
- ○ 1–3 times per month
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Once per day
- ○ 2 or more servings per day

Peanuts (small packet or 1 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2 or more servings per day

Almonds (small packet or 1 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2 or more servings per day

Walnuts (1 oz. or 14 halves)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2 or more servings per day

Other nuts (small packet or 1 oz.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2 or more servings per day

Oat bran, added to food (1 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2 or more servings per day

Other bran, added to food (1 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2 or more servings per day

Wheat germ (1 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2 or more servings per day

Chowder, cream or cheese soup (1 cup)
- ○ Never
- ○ Less than once per month
- ○ 1–3 cups per month
- ○ 1 cup per week
- ○ 2–4 cups per week
- ○ 5–6 cups per week
- ○ 1 or more cups per day

9. (Continued) Please fill in your average total use, during the past month, of each specified food.

Ketchup or red chili sauce (1 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2 or more servings per day

Salt added at table (1 shake) (include seasoning salt, garlic salt)
- ○ Never
- ○ Less than once per month
- ○ 1–3 shakes per month
- ○ 1 shake per week
- ○ 2–4 shakes per week
- ○ 5–6 shakes per week
- ○ 1 shake per day
- ○ 2–3 shakes per day
- ○ 4–5 shakes per day
- ○ 6+ shakes per day

Mrs. Dash or other salt substitutes (1 shake at table or in cooking)
- ○ Never
- ○ Less than once per month
- ○ 1–3 shakes per month
- ○ 1 shake per week
- ○ 2–4 shakes per week
- ○ 5–6 shakes per week
- ○ 1 shake per day
- ○ 2–3 shakes per day
- ○ 4–5 shakes per day
- ○ 6+ shakes per day

How many teaspoons of sugar do you add in total, each day, to your beverages or food? (include brown sugar)

Teaspoons

[ ]

Nutrasweet or Equal (1 packet) NOT Sweet 'N Low
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4–5 per day
- ○ 6+ per day

Garlic (1 clove or 4 shakes)
- ○ Never
- ○ Less than once per month
- ○ 1–3 per month
- ○ 1 per week
- ○ 2–4 per week
- ○ 5–6 per week
- ○ 1 per day
- ○ 2–3 per day
- ○ 4–5 per day
- ○ 6+ per day

Low fat mayonnaise/fat free mayonnaise (2 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2 or more tbs. per day

Regular mayonnaise (2 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2 or more tbs. per day

Salad dressing (2 tbs.)
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2–3 tbs. per day
- ○ 4 or more tbs. per day

Type of salad dressing:
- ○ Nonfat
- ○ Low fat
- ○ Olive oil dressing
- ○ Regular

Olive oil added to food or bread (1 tbs.); exclude use in cooking
- ○ Never
- ○ Less than once per month
- ○ 1–3 tbs. per month
- ○ 1 tbs. per week
- ○ 2–4 tbs. per week
- ○ 5–6 tbs. per week
- ○ 1 tbs. per day
- ○ 2–3 tbs. per day
- ○ 4–5 tbs. per day
- ○ 6+ tbs. per day

10. How much of the visible fat on your beef, pork or lamb do you remove before eating?

- ○ Don't eat meat
- ○ Remove all visible fat
- ○ Remove most
- ○ Remove small part of fat
- ○ Remove none

11. What kind of fat is usually used for frying and sautéing at home?

- ○ Don't fry
- ○ Real butter
- ○ Margarine
- ○ Olive oil
- ○ Vegetable oil
- ○ Vegetable shortening
- ○ Lard/bacon fat
- ○ Pam type spray

12. What kind of fat is usually used for baking at home?

- ○ Don't bake
- ○ Real butter
- ○ Margarine
- ○ Olive oil
- ○ Vegetable oil
- ○ Vegetable shortening
- ○ Lard/bacon fat
- ○ Pam type spray

13. How often do you eat food fried, stir-fried in oil, or sautéed at home?

- ○ Never
- ○ Less than once a week
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Daily

14. How often do you eat deep fried food away from home or as take out (e.g., french fries, fried chicken, fish, clams, shrimp, etc.)?

- ○ Never
- ○ Less than once a week
- ○ Once per week
- ○ 2–4 times per week
- ○ 5–6 times per week
- ○ Daily

15. What type of cooking oil is usually used at home (e.g., Wesson Corn Oil)?

(Specify brand and type)

16. Are there any other foods not mentioned above that you usually eat at least once per week?

Include for example: Paté, cream sauce, custard, radishes, fava beans, coconut, mango, horseradish, parsnips, rhubarb, papaya, dates, figs. (Do not include dry spices and do not list something that has been listed in the previous sections.)

Other foods that you usually eat at least once per week	Usual serving size	Servings per week
(a)		
(b)		
(c)		

DIET CHANGES

17. Do you currently follow a special diet?

- ○ No
- ○ Yes → ○ Physician prescribed ○ Self prescribed

a) If yes, for how many years?

(Number of years on diet)

b) If yes, what kind of diet do you follow? (Select more than one if necessary.)

- ○ Weight reduction (low calorie)
- ○ Low cholesterol
- ○ Low sodium
- ○ Diabetic
- ○ Low fat
- ○ Low triglyceride
- ○ Ulcer
- ○ High Potassium
- ○ Other → (Specify type of diet)

18. How has your use of the following foods and beverages changed over the PAST TEN YEARS?

Whole milk	**Butter**	**Margarine**
○ Use has decreased	○ Use has decreased	○ Use has decreased
○ Use about the same	○ Use about the same	○ Use about the same
○ Use has increased	○ Use has increased	○ Use has increased
Eggs	**Fish**	**Red meat**
○ Use has decreased	○ Use has decreased	○ Use has decreased
○ Use about the same	○ Use about the same	○ Use about the same
○ Use has increased	○ Use has increased	○ Use has increased
Fruits	**Vegetables**	**Whole wheat bread**
○ Use has decreased	○ Use has decreased	○ Use has decreased
○ Use about the same	○ Use about the same	○ Use about the same
○ Use has increased	○ Use has increased	○ Use has increased
Whole grains	**Sugar**	**Alcohol**
○ Use has decreased	○ Use has decreased	○ Use has decreased
○ Use about the same	○ Use about the same	○ Use about the same
○ Use has increased	○ Use has increased	○ Use has increased

Thank you!

Please check to make sure you have not accidentally skipped any pages.

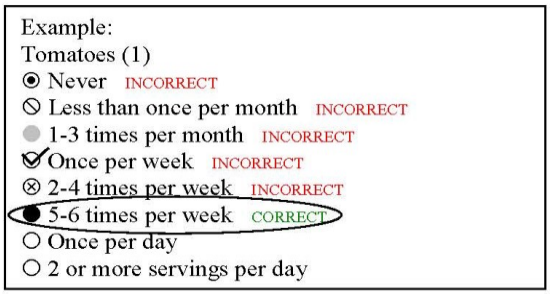
PLEASE DO NOT WRITE IN THIS AREA

05749

Appendix 5: FFQ instructions and serving sizes

Instructions for Completing the Dietary Assessment Booklet

- Please use the **pencil provided** to fill out the dietary assessment booklet.
- When responding to questions, please completely colour in the appropriate circle.



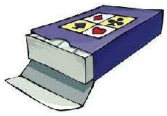
- Ensure that only one circle is filled in for each question.
- If you need to change your response, ensure that you completely erase your previous response.
- Follow the arrows corresponding to the response you selected. These will guide you to the next question you need to answer.
- For the section entitled **Vitamins** please respond according to your lifelong history of supplement intake.
- For the rest of the sections, please respond to the questions according to your average intake of the specified foods over the past month.
- Remember to specify the **brand** and **type** of food in the green boxes when requested.
- If there are any other foods *not* mentioned in the booklet that you consume on a weekly basis, please record them in the table on page 22, question 16.
- Refer to the sheet provided, entitled **Serving Sizes** to aid you in determining your intake of the specified foods.

Serving Sizes

- ½ cup of ice cream is about the size of a tennis ball

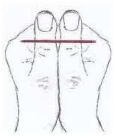
- 1 ounce of cheese is about the size of 4 dice laid out as a square

- 3 ounces of meat, fish or tofu (1 serving) is about the size and thickness of a deck of playing cards

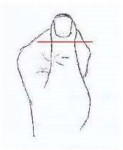


- 1 cup of cooked rice or cooked pasta will fill two of your palms

- 1 tablespoon (tbs.) is equal to the size of your top two thumbs, above the top knuckle



- 1 teaspoon (tsp.) is equal to the size of one of your top thumbs, slightly less than above the top knuckle (3 tsp = 1 tbs.)



- 8 ounces of liquid is equivalent to one cup (250 ml)
- 12 ounces of liquid is equivalent to 1½ cups (375 ml)
- 16 ounces of liquid is equivalent to 2 cups (500 ml)

Conversions

1 cup = 8 oz
8 oz = 250 mL
1 pint = 16 ounces
1 oz = 30 g = 2 TB
1 tbs. = 15 mL = 3 tsp
1 tsp = 5 mL