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Association between glycemic load and cognitive function in community-dwelling older adults: results from the Brain in Motion study

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Association between glycemic load and cognitive function in community-dwelling older adults: results from the *Brain in Motion* study

by

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A THESIS

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Abstract

Background: Impaired glucose tolerance is a risk factor for non-age-related cognitive decline and is also associated with measures of physical activity (PA) and cardiorespiratory fitness (CRF). A low glycemic load (GL) diet can aid in the management of blood glucose levels, but little is known about its effect on cognition with poor glucoregulation.

Objective: The aim of this thesis was to assess the relation between GL and cognitive function by glucoregulation, and possible mediatory effects by CRF and PA, in older adults.

Design: A cross-sectional analysis of 194 cognitively healthy adults aged ≥55 years (mean=65.7, SD=6.1) was conducted. GL was assessed using a quantitative food frequency questionnaire, and glucoregulation was characterized on the HOMA-IR index. Subjects also completed a cognitive assessment, CRF testing, a validated self-reported PA questionnaire, and a blood draw. Multiple linear regression models adjusted for significant covariates were used to evaluate the relation between GL and cognition, and mediation analysis was used to assess potential mediatory effects by CRF and PA.

Results: GL was inversely associated with global cognition (β=-0.014; 95% CI -0.024, -0.0036) and figural memory (β =-0.035; 95% CI -0.052, -0.018) in subjects with poor glucoregulation. Neither CRF nor PA mediated these relations. In subjects with good glucoregulation, no association was found between GL and cognitive function ($p>0.05$).

Conclusions: A low GL diet is associated with better cognitive function in older adults with poor glucoregulation. This study provides supportive evidence for the role of GL in maintaining better cognitive function during the aging process.

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
<	Less Than
>	Greater Than
≤	Less Than or Equal To
≥	Greater Than or Equal To
=	Equals
±	Plus or Minus
Δ	Change
β	Regression Coefficient
ADRDA	Alzheimer's Disease and Related Disorders Association
AGE	Advanced Glycated End Products
APOE	Apolipoprotein E
BDI	Beck Depression Inventory
BDNF	Brain-Derived Neurotrophic Factor
BIM	Brain in Motion
BMI	Body Mass Index
C-DHQ I	National Cancer Institute Diet History Questionnaire modified for Canadian populations
CHREB	Conjoint Health Research Ethics Board
CI	Confidence Interval
CRF	Cardiorespiratory Fitness
CVD	Cardiovascular Disease
DAG	Diacylglycerol
DHQ I	National Cancer Institute Diet History Questionnaire
D-KEFS	Delis-Kaplan Executive Function System
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4^{th} Edition
FFQ	Food Frequency Questionnaire
FIRI	Fasting Insulin Resistance Index
gAUC	Area under the blood glucose curve
GI	Glycemic Index
GL	Glycemic Load
G-WWB	Guar gum supplemented White Wheat Bread
HbA_{1c}	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
hr	Hour
IGT	Impaired Glucose Tolerance
IR	Insulin Resistance
IQ	Intelligence Quotient
kcal	Kilocalorie
LDL	Low-Density Lipoprotein
log	Logarithm
MCI	Mild Cognitive Impairment

LTPAQ	Lifetime Total Physical Activity Questionnaire
MAP	Mean Arterial Pressure
MeSH	Medical Subject Heading
MET	Metabolic Equivalent
mmHg	Millimetre of Mercury
mmol	Millimole
MMSE	Mini-Mental State Examination
n	Sample size
NAART	North American Adult Reading Test
NART	National Adult Reading Test
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
OR	Odds Ratio
p	P-value
PA	Physical Activity
PKC	Protein Kinase C
pmol	Picomole
QUICKI	Quantitative Insulin Sensitivity Check Index
r	Correlation Coefficient
R^2	Coefficient of Determination
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SA	Selective Attention
SD	Standard Deviation
SEE	Standard Error of the Estimate
SQL	Structured Query Language
T2DM	Type 2 Diabetes Mellitus
TICS	Telephone Interview for Cognitive Status
$\dot{V}O_2$	Oxygen Consumption
$\dot{V}O_2max$	Maximal Aerobic Capacity
WAIS-III	Wechsler Adult Intelligence Scale, 3^{rd} Edition
WAIS-R	Wechsler Adult Intelligence Scale Revised
WASI	Wechsler Abbreviated Scale of Intelligence
WHR	Waist-to-Hip Ratio
wk	Week
WM	Working Memory
WMS	Wechsler Memory Scale
WMS-III	Wechsler Memory Scale, 3^{rd} Edition
WWB	White Wheat Bread
x	Times
$\bar{x}$	Sample mean

Chapter One: **Introduction**

1.1 Introduction

Cognitive decline is a process that naturally occurs as part of aging (1); however, it is also considered a precursor to the development of neurodegenerative diseases and dementia (2). Alzheimer's disease is the most common form of dementia with no known cause or cure, and is characterized by a decline in various cognitive abilities that directly affect an individual's overall health and quality of life (1). Cognitive decline is therefore a public health concern for the aging population. Pharmaceutical interventions have generally been unsuccessful in preventing or slowing age-related cognitive decline, placing a priority on focusing research on lifestyle interventions (3). Risk factors associated with poorer cognitive function include impaired glucose tolerance (IGT) (4), unhealthy dietary patterns (5), physical inactivity (6), and low cardiorespiratory fitness (CRF) (7).

IGT is a metabolic condition characterized by the body's decreased efficiency in properly controlling blood glucose levels, usually as a result of pancreatic beta cell dysfunction and/or insulin resistance (IR) and is a pre-diabetic state that may develop into type 2 diabetes mellitus (T2DM) (4). Fortunately, glucoregulation has been shown to improve with beneficial lifestyle changes, such as increasing physical activity (PA) levels and modifying diet, in individuals with IGT (8). An effective way of managing blood glucose levels when glucose tolerance is an issue is by consuming a diet that is characterized by a low glycemic load (GL) (9). A low GL diet produces gradual rises in postprandial blood glucose levels that are sustained for longer durations compared to a high GL diet that spikes blood glucose levels (10). Considering the association between IGT and cognition, low GL diets may improve cognitive function, prevent cognitive decline, and reduce dementia risk in IGT individuals.

Low GL dietary patterns may also indirectly be beneficial for CRF and PA levels. CRF is a measure of the body's efficiency in uptake, delivery, and usage of oxygen during sustained PA (11). Better regulation of blood glucose levels in IGT individuals via low GL diets can fuel the body during PA more efficiently (12), thereby creating a good physiological environment to improve CRF and promote longer and/or more frequent PA sessions. However, GL in the realm of sports nutrition is a relatively new concept that has yet to be comprehensively studied (12). Considering the separate associations of CRF and PA with cognition, the relation between GL and cognitive function has the potential to be mediated by CRF and PA levels.

Addressing GL, CRF, and PA together can provide insights into the combined effects of these lifestyle factors on cognition rather than considering each factor alone. A multi-factorial research approach has been less widely used in dementia research, yet recent suggestions have been made to target dementia prevention in this manner (13). This project examined the effects of dietary GL on cognitive function by glucoregulation in older adults and assessed possible mediatory effects of CRF and PA, which has not been studied.

1.2 Literature Review

The literature review was conducted using the online medical journal database PubMed that provides access to MEDLINE. The following medical subject heading (MeSH) terms were used to perform three searches: (1) glycemic load, glycemic index, cognitive function, cognitive deficit, cognitive aging, aging/psychology, dementia, aged, and middle aged (Table 1); (2) exercise, sports, dance therapy, tai ji, yoga, cognitive function, cognitive deficit, cognitive aging, aging/psychology, dementia, aged, and middle aged (Table 2); (3) physical fitness, oxygen consumption/physiology, cognitive function, cognitive deficit, cognitive aging, aging/psychology, dementia, aged, and middle aged (Table 3). Search results were reviewed, beginning at a publication date of January 1968, and relevant articles, up to a publication date of

April 12, 2017, were included as appropriate. Articles were included if the study population were cognitively healthy older adults (≥50 years) and analyses were conducted on associations between cognitive function and measures of GL, CRF, and PA. Articles included are summarized in Tables 1-3.

1.2.1 Dietary Glycemic Load and Cognitive Function in Older Adults

Diet composition is an important modifiable lifestyle factor that is related to cognitive functioning (14-18). Various nutrients, such as folate, vitamin D, and flavonoids, elicit positive effects on cognition, but the effects of such nutrients need to be assessed in the context of overall diet (14). Diets that are composed of a relatively low percent of carbohydrates and high percent of fat and protein are associated with better cognitive function and reduced risk of cognitive impairment (15, 16). The Mediterranean Diet is a dietary profile that has been heavily studied in relation to cognition and is characterized by high intake of fruits, vegetables, legumes, and grains and low intake of saturated fat, dairy, meat, and sweets (17, 18). Adherence to this diet is associated various positive health outcomes such as better cognitive performance and less cognitive decline (17, 18). The Mediterranean Diet can be a low GL diet by consuming complex carbohydrates, and this combination has been shown to more greatly reduce the risk of T2DM than each dietary pattern alone (19).

Cognitive function and impairments in glucoregulation, such as with T2DM, are strongly related because of the brain's reliance on glucose for energy (20). The brain is the main consumer of glucose in the body, using approximately 20 percent of glucose-derived energy despite accounting for close to two percent of body weight (21). Under normal dietary conditions, glucose is the brain's sole energy source, and unlike muscle, the brain uses glucose at a constant rate (22). Glucose is vital for the brain since it cannot be replaced as an energy source (21). However, glucose utilization by the brain can be supplemented when glucose levels are low, such as during prolonged starvation or strenuous PA (23, 24). During prolonged starvation, the liver converts fatty acids to ketone bodies (22), and lactate is generated by muscle during strenuous PA (25). Under these hypoglycemic conditions, ketone bodies and lactate are used by the brain for energy (23, 24).

As glucose is almost solely the energy source of the brain, the regulation of blood glucose levels are integral for proper brain function (26). Dietary glucose is consumed in the form of carbohydrate-containing foods, absorbed through intestinal epithelial cells, and transported throughout the body in the blood (27). Glycemic index (GI) is a measure of the postprandial effect of a carbohydrate-containing food on blood glucose levels (10). Low GI foods produce a gradual rise and longer-sustained levels of blood glucose after consumption compared to high GI foods which generate a spike followed by a fast reduction that can dip below baseline blood glucose levels (28). GL is a weighted measure of GI that is calculated by multiplying a food's GI by the number of grams of available carbohydrates in the food's serving and dividing by 100 (10). The GI of foods and GL as a more useful characterization of overall diet are fairly new concepts that were developed for use by people with diabetes (28). Only recently has there been research exploring their effects in people without diabetes.

GL has the potential to have an effect on cognition since glucoregulation is vital for the functioning of the brain and dietary GL directly affects blood glucose levels (26). There are a small number of studies that have investigated the effect of GL on cognition in an older population, utilizing methods of assessing GL's effect acutely, with the administration of test meals (29-32), or long-term, with an evaluation of overall diet (33-36) (Table 1).

In healthy, older adults, a repeated measures, crossover study (2000) showed no difference in cognitive performance following a low GL versus a high GL meal (29), but another intervention study (2012) found consuming a low GL meal resulted in better selective attention scores, but had no effect on working memory test scores (31). Psychomotor skill was also noted to improve following a low GL meal in both healthy and T2DM older adults (32). Moreover, Papanikolaou et al. (30) assessed T2DM individuals and found better cognitive scores to be achieved following a low GL meal on measures of delayed verbal and working memory, executive function, and auditory selective attention, yet there was no effect on sustained attention. Individuals with high gAUC (29, 30) and poor pancreatic beta cell function (29) had worse test scores, and subjects with better glucoregulation performed better on the cognitive tests (31). It is also interesting to note that Nilsson et al. (31) found individuals with good, compared to worse, glucoregulation had better cognitive performance on the selective attention test following a high GL meal compared to a low GL meal. These findings highlight the importance of proper blood glucose control on cognition although these studies testing GL acutely produced mixed results.

Assessing GL from a dietary perspective rather than testing individual meals has resulted in stronger associations with cognition. Power et al. (36) conducted the first study to examine GL and cognitive function in the elderly and found lower dietary GL to be associated with higher *Mini-Mental State Examination* (MMSE) scores and fewer MMSE errors, indicating better cognitive function. In addition, the risk of mild cognitive impairment (MCI) (MMSE score ≤ 24) was estimated to be significantly greater with the consumption of a higher versus a lower GL diet (36). Although the MMSE is not a comprehensive cognitive assessment, these findings introduce a novel association of GL and cognition in an older population.

Similarly, Simeon et al. (35) were first to detect an association between GL and cognitive performance in a large female cohort, finding GL to be negatively associated with *Telephone*

Interview for Cognitive Status (TICS) score and higher dietary GL to increase risk of a lower TICS score, which was used as a measure of cognition. Higher GL has also been shown to be related to poorer perceptual speed and spatial ability, yet no significant associations were found between GL and rate of cognitive decline (34). Mixed results of the latter study, conducted by Seetharaman et al., could be attributed to a poorly designed food frequency questionnaire (FFQ) that only measured a handful of GL foods.

Moreover, GL was examined in relation to Alzheimer's disease risk in a large prospective cohort study of 939 individuals (33). The study, with a mean follow-up period of 6.3 years, found no association between GL and risk of Alzheimer's disease, but it was insufficiently powered to detect a significant relation (33). An interesting finding from the analysis was that the proportion of individuals suffering from T2DM decreased with increasing GL (33), which is contradictory to the relation between improved glucose regulation with lower GL diets (8).

Although the current literature concerning the relation between GL and cognitive performance in an older population has produced some null results (29), the majority of findings highlight that dietary GL is inversely associated with cognitive function (30-32, 34-36). This finding is biologically plausible as higher GL diets cause greater fluctuations in blood glucose levels, which is particularly problematic for individuals with poor glucoregulation, and proper glucoregulation is integral for brain function (26).

1.2.2 Physical Activity Levels and Cognitive Function in Healthy Older Adults

PA is defined as the movement of skeletal muscles that require energy expenditure beyond a resting bodily state, encompassing a wide range of daily activities that can be categorized as occupational, leisure, or household (37). PA has been characterized in a variety of different ways that generally include continuous measures of frequency, duration, and intensity and is assessed via methods such as self-administered recall questionnaires, researcher-led interviews, or accelerometers (38). Often, the term 'physical activity' and 'exercise' are incorrectly interchanged; exercise is a subcategory of PA that includes bodily movements which are planned, structured, and repetitive and are performed for the purpose of maintaining or improving physical health (37). Measuring PA by exercise alone can be misleading and an over-simplification as participation in activities that cannot necessarily be classified as exercise can deem an individual as being physically inactive (39). PA measures in research studies therefore include both exercise and non-exercise activities, and higher levels of PA are indicative of higher frequencies, durations, and/or intensities of reported activities (38).

PA has been shown to act as a protective factor for neurological ailments and diseases such as dementia (39, 40), Alzheimer's disease (40, 41), and depression (42), and to elicit benefits in reducing the rate of age-related neurological processes such as cognitive decline (39). As the risk of cognitive decline increases as one ages (1), much research has been conducted assessing the effect of PA on cognition, cognitive decline, and neurodegenerative diseases in older individuals. Observational studies have evaluated the relation cross-sectionally (43-50) and with prospective cohorts (51-60) (Table 2).

Cross-sectional analysis of PA on cognition shows a general positive trend between higher PA levels and better cognitive function (43-45, 47, 49), yet some studies show mixed results (46, 48, 50) (Table 2). Four studies examining at the association of average PA levels, measured across periods ranging from seven to fourteen days, found individuals that have higher levels of PA performed better on specific measures of cognitive performance (43-45, 49), suggesting that effects may be domain-specific (44, 45, 49). Cognitive function domains which have been shown to be beneficially associated with higher PA levels are executive function (44), memory (45), verbal fluency (47, 49), perceptual speed (45), and visuospatial abilities (45). In contrast to these findings, three studies found no relation between levels of PA and cognitive function test scores (46, 48, 50). However, two of these studies revealed significant associations between PA intensity and scores from domain-specific cognitive tasks, but with conflicting results (46, 48). Brown et al. (48) found measures of PA that were performed at the highest intensities to be positively associated with cognitive measures of memory, processing speed, and verbal fluency, while Lindwall et al. (46) only found light intensity exercise was associated with better memory, vocabulary, and MMSE scores. While cross-sectional research shows a significant relation between greater PA involvement and cognitive function in older adults, results highlight an importance in evaluating which measures of PA level (frequency, duration, or intensity) provide the greatest contribution to the relation.

Prospective cohort studies, with follow-up periods that range from two to twenty-six years, collectively show significant associations between levels of PA and measures of cognitive function (54, 56, 57, 59) (Table 2). Individuals who reported higher PA levels at baseline were found to perform cognitively better at follow-up compared to individuals with lower or no reported baseline PA levels (54, 56, 57, 59). Notably, a study of approximately five thousand men and women from Iceland found very strong associations between PA levels and cognitive performance: participants who were physically active in their midlife years, defined as reporting any PA, performed significantly better on cognitive tasks assessing processing speed, memory, and executive function twenty-six years later compared to participants with no reports of PA (56). Moreover, not only has overall level of PA been associated with cognition, but duration of PA sessions were found to be a significant predictor of cognitive performance, specifically individuals whose PA sessions were thirty minutes or greater performed better on cognitive tasks than individuals with lower durations (59). Baseline PA levels were also associated with baseline cognitive function in the study conducted by Ku et al. (58).

Prospective studies have also examined the relation between PA levels and cognition through the evaluation of rates of cognitive decline among individuals with differing levels of PA across follow-up periods ranging from one to eleven years (51-55, 58, 60) (Table 2). Higher levels of PA at baseline were inversely related with cognitive decline, measured as declines in cognitive assessment scores between baseline and follow-up (51, 55, 60), as well as positively associated with a reduced risk of subsequent cognitive decline (52, 58). Weuve et al. (54) assessed decline in global cognition, as well as decline in performance of the cognitive domains of verbal fluency, memory, and attention, in sixteen thousand American women across a two-year follow-up and found a significant trend between higher PA levels and less cognitive decline in all cognitive measures excluding verbal fluency. Additionally, in an analysis considering intensity and duration of PA in men, no association was found between either measure and cognitive function at baseline, however, individuals that showed the greatest negative change in either intensity or duration over the ten year study period exhibited the greatest cognitive decline, while those showing increases in PA duration or intensity showed no decline in cognition (53).

Results from both cross-sectional and prospective analyses support an overall consensus that engaging in PA is beneficial for cognitive function of older adults and can serve as a protective factor in age-related cognitive decline. Systematic reviews of the topic show overall effects that are in accordance with these study findings. One recent (2014) meta-analysis of seventeen prospective studies showed results of a protective effect against cognitive decline in the comparison of subjects with higher to lower levels of PA (39). Additionally, another meta-analysis (2011) of fifteen prospective studies found participants who report either low-to-moderate or high levels of PA have a 35% and 38% reduced risk of cognitive decline, respectively, in comparison to sedentary individuals (6). Lastly, a third recent (2014) systematic review found 26 of 27 studies reviewed reported a positive association between PA and maintaining or improving cognitive function (61).

There is a rich amount of research evidence that addresses the relation between PA and cognitive function in older adults. While some mixed results have been produced, a greater number of studies have collectively shown that participating in PA is beneficial for cognition and can significantly reduce the risk of cognitive decline.

1.2.3 Cardiorespiratory Fitness and Cognitive Function in Healthy Older Adults

CRF is a measure of how efficiently the body uptakes, transports, and uses oxygen during prolonged PA and is correlated with participation in regular aerobic exercise (62). Physical activity that is performed at a sustained elevated heart rate for the purpose of building endurance of the heart and lungs is characterized as aerobic exercise (62). Improving and maintaining CRF is particularly important for older adults as a decline in various aspects of cardiovascular functioning, such as maximal heart rate and cardiac output, can occur in late adulthood, even without the presence of cardiovascular complications (63).

Maximal aerobic capacity ($\dot{V}O_2max$) is considered the 'gold standard' measure of CRF (64). It is a measure of the body's maximum rate of oxygen consumption during peak exercise as oxygen consumption does not increase further with an increase in exercise intensity (65). $\dot{V}O_2max$ is thought to limit an individual's ability to perform intense exercise that relies on the lungs and heart for oxygen uptake and delivery (66). Aerobic exercise, therefore, strengthens the heart and lungs, which in turn increases $\dot{V}O_2max$ and CRF (62).

It is proposed that better CRF is associated with higher cerebral blood flow, glucose utilization, and Brain-Derived Neurotrophic Factor (BDNF) (67). Cerebral blow flow supplies the brain with its metabolic needs – such as its primary energy source: glucose – and removes waste, and BDNF acts as a mediator in structural neural changes (67). Better glucose delivery and usage by the brain, as well as structural changes such as neuro- and synaptogenesis, can affect cognitive capacity and elicit beneficial effects on cognition (67). It is therefore reasonable for CRF and cognitive performance to be positively associated.

A number of cross-sectional (68-82) and prospective cohort studies (83, 84) have studied the relation between CRF and cognition. These studies collectively show that fitter older adults, indicated by higher measures of $\dot{V}O_2$max, perform better on measures of cognitive performance and show less cognitive decline over time, yet benefits on specific cognitive domains are inconsistent between studies (68-84) (Table 3).

A recent (2016) cross-sectional study of 877 older individuals evaluated the association between $\dot{V}O_2$max and cognition, both globally and with the cognitive domains of memory, executive function, and motor skills (80). Higher CRF was a strong predictor of better memory, executive function, and global cognition, but not motor skills, however results of this domain approached significance (80). While this study shows strong associations between CRF and cognition, a limitation of the protocol was that $\dot{V}O_2$max was estimated by an equation using a ratio between maximum and resting heart rate, and is therefore an indirect measure of CRF (80). Similarly, Boots et al. (77) used the formula estimate of $\dot{V}O_2$max developed by Jurca et al. (85) that accounts for age, sex, body mass index (BMI), resting heart rate, and self-reported PA and used a subset of the study's sample to validate the estimate against $\dot{V}O_2$max values obtained from graded exercise testing. The CRF formula estimate was found to be well correlated with direct measures of $\dot{V}O_2$max and in the study's sample of 315 individuals, associations between higher estimated CRF and better performance on measures of speed and flexibility, verbal learning and memory, and visuospatial abilities were found to be significant (77). While both these studies are notable for having considerably large sample sizes, they are limited by their indirect measures of CRF, which may not accurately predict $\dot{V}O_2max$. However, a recent (2015) systematic review of 19 different equations used to predict maximal aerobic capacity concluded the accuracy of these indirect measures to be moderate to high, and close estimations of $\dot{V}O_2max$ can therefore be achieved through usage of validated formulas (86).

Cross-sectional studies have showed significant associations between higher CRF levels and cognitive measures of flexibility (75, 77), visuospatial ability (69, 77), psychomotor performance (81), memory (72, 76, 77, 80, 82), working memory (70, 72, 74), recognition (81), speed (70-72, 77), verbal learning/ability (71, 77), attention (73), perception (71), executive function (71, 73, 74, 76, 78-82), and overall cognitive function (68, 71, 73, 80) (Table 3). While each study reviewed found some relation between fitness level and cognition, specific patterns of findings are inconsistent across studies. Associations with cognitive measures of attention were not found in three studies (69, 71, 78), yet Netz et al. (73) found a significant correlation. Moreover, executive function, which is hypothesized and shown in various studies to be sensitive to fitness and PA, was associated with CRF in nine of the studies reviewed (71, 73, 74, 76, 78-82), providing good evidence for the hypothesis. However, Newson & Kemps (70) found no relation with this cognitive domain, even though their neuropsychological assessment included some of the same tests as the other studies.

Furthermore, two prospective cohort studies individually followed a group of healthy, older adults every two (84) or six years (83) and assessed cognitive decline over time as a function of baseline CRF. Analysis from the two studies produced conflicting results. Wendell et al. (84) assessed cognitive performance on measures of memory, attention, perceptuomotor speed, language, and executive function and found an association between lower baseline $\dot{V}O_2max$ and greater cognitive decline specifically for measures of memory. On the contrary, Barnes et al. (83) found significant positive associations between baseline CRF and cognitive performance on all tasks included in their study, specifically measures of attention/executive function, verbal memory, and verbal fluency. Additionally, a systematic review (2006) of CRF and cognitive performance in older adults found no overall relation between the two measures from cross-sectional studies and found CRF to be negatively predictive of cognition using pre-post comparisons from exercise trials (87).

The contradictory nature of these findings poses challenges in making sense of underlying relations. Etnier et al. (87) suggest that CRF may mediate the relation between PA and cognition, but increases in CRF may not show cognitive benefits, as CRF is a gross, and not very sensitive, measure of physiological changes. Another possible explanation for the conflicting results is the small sample sizes of the majority of reviewed studies, which may not be well powered to detect significant associations. However, as many studies suggest, $\dot{V}O_2max$ may truly be associated with cognitive performance, but its role may be a preliminary one in a cascading series of events that eventually affect cognition (87). The effect of PA and CRF on cognitive performance needs to be further explored with the consideration of potential co-factors, such as diet, to better understand underlying mechanisms and potential dose-response relations.

1.3 Research Aims and Hypotheses

This project aimed to explore the effect of dietary GL on cognitive function by glucoregulation in community-dwelling older adults and to assess possible mediatory effects of PA and CRF using a cross-sectional study design.

Aim 1: To assess the relation of dietary GL by glucoregulation on global cognition and specific cognitive domains at study baseline.

Hypothesis 1: Consuming a diet characterized by a lower GL will be associated with higher cognitive domain and global cognition scores. The association between lower GL and cognitive function may be stronger in subjects with poorer glucoregulation.

Aim 2: To assess mediation by CRF and/or PA in the relations of GL and global and domain-specific cognitive function, if significant.

Hypothesis 2: CRF and/or PA has the potential to be a mediator of the relation between GL and cognitive function, but since GL has not been studied in combination with CRF or PA on cognitive function, it is unclear if such a relation exists. CRF and/or PA may mediate the relation between GL and cognitive function.

1.4 Chapter One Figures and Tables

Table 1. Literature review summary: Effect of dietary glycemic load on cognitive function in older adults

Author, year (ref), country	Population (sample size, mean age)	Study Design	Glycemic Load Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Clinical Studies							
Kaplan RJ et al., 2000 (29), Canada	n=20 men and women 72.3 years	Repeated measures, counterbalanced, crossover study.	3 test meals: 1) Glucose drink (GL 71) 2) Instant mashed potatoes (GL 59) 3) Barley (GL 18) and placebo (GL 0)	1) Word list recall 2) Paragraph recall 3) Trails Part B Adult Form 4) Attention test	Cognitive performance.	Pancreatic beta cell function, IR, gAUC, and BMI.	Cognitive performance did not differ between intervention meals on all tests. High gAUC, poor pancreatic beta cell function, and low IR was associated with poor baseline verbal declarative memory and visuomotor performance ($p<0.05$).
Papanikolaou Y et al., 2006 (30), Canada	n=21 men and women with T2DM 65.0 years	Repeated measures, counterbalanced, crossover study.	2 test meals: 1) White bread (GL 50) 2) Cheese and tomato pasta (GL 28)	1) Hopkins Verbal Learning Test (revised) 2) Paragraph recall 3) Verbal Paired Associates subtest of WMS 4) Digit Span Forward 5) Trail-making Test 6) Test of Everyday Attention	Cognitive performance.	Age, BMI, Shipley (intelligence) score, BDI (depression) score, HbA_{1c} levels, and day of testing.	Low GL meal resulted in better scores on measures of delayed verbal memory, working memory, executive function, and auditory selective attention ($p<0.05$). Higher gAUC was associated with poorer measures of verbal memory ($p<0.05$).
Nilsson A et al., 2012 (31), Sweden	n=40 men and women 62.9 years	Randomised, crossover, balanced trial.	2 test breads: 1) White wheat bread (WWB) (GL 50) 2) Guar gum supplemented white wheat bread (G-WWB) (GL 23)	2 cognitive tests developed for the study: 1) Working Memory (WM) Test (reading sentences) 2) Selective Attention (SA) Test (computerized picture test)	WM and SA test scores.	N/A	G-WWB (lower GL) resulted in better SA test scores than WWB (higher GL) in the late postprandial phase ($p<0.01$). WWB resulted in better SA test scores than G-WWB in subjects with better compared to worse glucoregulation ($p<0.05$). No differences in WM test scores.
Lamport DJ et al., 2013 (32), UK	n=24 men and women with T2DM 61.0 years n=10 healthy men and women 56.2 years	Randomised, crossover, counterbalanced trial with diabetes status as the between group difference.	2 isocaloric test meals: 1) Glucose drink (GL 71) 2) Toast and yogurt (GL 12) and water placebo (GL 0)	1) Visual Spatial Learning Test 2) Visual Verbal Learning Test 3) Corsi Block Tapping Test 4) Power of Hanoi 5) Grooved Pegboard 6) Psychomotor Test 7) Source Monitoring Test 8) Paragraph Recall	Cognitive performance.	Age, NART score, BMI, height, weight, stress score, sleep score, depression score, MMSE score, and waist circumference.	Psychomotor test score was better after consumption of low GL meal for both healthy and T2DM subjects ($p=0.029$). No other differences were found between meal type and cognitive performance.

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; gAUC, area under the blood glucose curve; GL, glycemic load; G-WWB, guar gum supplemented white wheat bread; HbA_{1c}, glycated haemoglobin; IR, insulin resistance; MMSE, Mini-Mental State Examination; NART, National Adult Reading Testing; SA, selective attention; T2DM, type 2 diabetes mellitus; WWB, white wheat bread; WM, working memory; WMS, Wechsler Memory Scale.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Glycemic Load Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Cohort Studies							
Luchsinger JA et al., 2007 (33), USA	n=939 men and women 75.9 years	Prospective cohort study beginning in 1992, 6.3-year mean follow-up.	61 item semi-quantitative FFQ previously validated in the community.	Diagnosis of dementia based on DSM-IV criteria and Clinical Dementia Rating. Diagnosis of Alzheimer's Disease based on NINCDS-ADRDA criteria.	Risk of Alzheimer's Disease.	History of diabetes, hypertension, heart disease, and smoking, BMI, fasting plasma total cholesterol and triglycerides, HDL, LDL, and APOE genotype.	GL, after adjustment for caloric intake, was not associated with risk of Alzheimer's disease.
Seetharaman S et al., 2015 (34), Sweden	n=838 men and women 63.1 years	Prospective cohort study beginning in 1986, 16-year follow-up.	FFQ of daily consumption of white bread slices, sweetened beverages & lumps/teaspoons of sugar in coffee, ice cream, cake/biscuits, and pastries.	In-person comprehensive cognitive assessment administered 5 times over 16 years.	Cognitive abilities.	Age, gender, education, waist circumference, depressive symptoms, CVD, and T2DM.	Higher GL was associated with poorer overall perceptual speed ($p=0.03$) and spatial ability ($p=0.03$). GL was not related to rate of cognitive decline.
Simeon V et al., 2015 (35), Italy	n=1514 women 71.1 years	Prospective cohort study beginning in 1997, 11- to 16-year follow-up.	FFQ of 47 dishes/food items validated within the study's framework.	TICS test ('93 revised version) carried out via telephone.	TICS score.	Marital status, HDL, total cholesterol, systolic blood pressure, diabetes, total PA, smoking habits, coffee consumption, energy intake (not from alcohol), and Italian Mediterranean Index score.	GL was negatively associated with TICS score ($p=0.026$). Estimate of the odds ratio of a lower TICS score, comparing a higher to lower GL diet, is 1.005 (95% CI 1.001, 1.011, $p=0.034$).
Cross-sectional Studies							
Power SE et al., 2015 (36), Ireland	n=208 men and women 75.1 years	Cross-sectional cohort study.	Semi-quantitative FFQ of 147 single food items/beverages validated for Irish population. Stratified by 5 dietary patterns, labelled as: 1) Low-fat Western (GL 154) 2) Western (GL 147) 3) Traditional Irish (GL 139) 4) Low-fat prudent (GL 128) 5) Prudent (GL 122)	MMSE	MMSE score.	Age, sex, diabetes, healthy food diversity score, hypertension, smoking status, BMI, nutritional status, number of cardiovascular medications, residential property price, and energy intake.	Consuming a prudent (lower GL) versus Western (higher GL) diet pattern resulted in higher MMSE scores ($p<0.05$). GL was positively associated with number of MMSE errors ($p<0.001$). Estimate of the odds ratio of MCI (MMSE≤24), comparing high and low GL diets, is 4.52 (95% CI 1.28, 19.85, $p=0.027$).

Abbreviations: ADRDA, Alzheimer's Disease and Related Disorders Association; APOE, Apolipoprotein E; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th Edition; FFQ, food frequency questionnaire; GL, glycemic load; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; PA, physical activity; T2DM, type 2 diabetes mellitus; TICS, Telephone Interview for Cognitive Status.

Table 2. Literature review summary: Effect of physical activity on cognitive function in healthy older adults from observational studies

Author, year (ref), country	Population (sample size, mean age)	Study Design	Physical Activity Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Cohort Studies							
Yaffe K et al., 2001 (51), USA	n=5925 women 71.1 years	Prospective cohort study, beginning in 1986, average 7.5-year follow-up.	PA was assessed with number of city blocks walked and flights of stairs climbed each day for exercise. In addition, the Paffenbarger Scale was used to report weekly frequency and duration in past year of 33 different physical activities. Total kilocalories expended per week were calculated.	1) Modified MMSE	Cognitive function.	Age, education level, depression, history of hypertension or diabetes, estrogen use, smoking, baseline functional limitation, self-reported health status, and medical comorbidities.	Women who walked a greater number of city blocks showed less cognitive decline and a significant trend for a greater reduction in odds of cognitive decline. Women with higher PA levels had a lower percentage decline in the modified MMSE score compared to women with lower PA levels.
Lytle ME et al., 2004 (52), USA	n=1146 men and women 76.8 years	Prospective cohort study, beginning in 1987, 2-year follow-up.	Self-report of engagement in exercise program including type, frequency, and duration, but no measures of intensity. Exercise level variable was coded as: 1) High exercise (aerobic exercise ≥ 30 mins ≥ 3x/week); 2) Low exercise (all other exercise groups); 3) No exercise.	1) MMSE	Cognitive decline, defined as decline in MMSE score ≥ 3 points.	Age, sex, education, and self-rated health status.	High exercise level was associated with reduced risk of subsequent cognitive decline (OR=0.39; 95% CI 0.19, 0.78)
van Gelder BM et al., 2004 (53), Finland, Italy, and the Netherlands	n=295 men 75.0 years	Prospective cohort study, beginning in 1984, 10-year follow-up.	Self-administered questionnaire including questions on frequency, duration, and pace of walking and bicycling in previous week, average amount of time per week spent on hobbies and gardening, and average amount of time spent on odd jobs and sports. Average amount of time spent weekly on farming or forestry was also asked for Finnish and Italian men. Total daily duration of PA, mean intensity scores, and changes in these two variables were calculated.	1) MMSE	Change in cognitive function.	Age, education, country, alcohol consumption, smoking status, mental activities, PA intensity, PA duration, activities of daily living, depression, BMI, use of antihypertensive drugs, HDL, total cholesterol, blood pressure, and baseline cognitive functioning.	At baseline, no association was found between cognitive function and either PA duration or intensity. Lowest intensity quartile showed greatest cognitive decline than other quartiles. Men whose PA duration decreased >60 min/day or whose PA intensity decreased >0.5 SDs showed the greatest cognitive decline. Men who increased their PA duration or intensity did not show cognitive decline.

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; MMSE, Mini-Mental State Examination; OR, odds ratio; PA, physical activity; SD, standard deviation.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Physical Activity Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Weuve J et al., 2004 (54), USA	n=16466 women 74.3 years	Prospective cohort study, beginning in 1986, 2-year follow-up.	Questionnaire asking women to estimate time spent engaging in leisure-time PA in past year. Each activity was assigned a MET value, and energy expenditure was subsequently estimated. Sample divided into quintiles based on average energy expended in MET-hours/week: 1)<5.2; 2)5.2-10.0; 3)10.1-16.2; 4)16.3-26.0; 5)>26.0.	1) TICS 2) Delayed recall test 3) East Boston Memory Test 4) Category fluency test 5) Digit Span Backwards test	Cognitive tests arranged into 5 cognitive function scores: TICS, category fluency, working memory and attention, verbal memory, and global cognition score.	Age at cognitive assessment, education, husband's education, alcohol consumption, smoking, aspirin use, ibuprofen use, vitamin E supplementation, antidepressant use, poor mental health, history of osteoarthritis, history of emphysema or chronic bronchitis, low vitality, balance problems, moderate to severe bodily pain, health limitations in walking a block, high blood pressure, elevated cholesterol level, T2DM, coronary heart disease, coronary artery bypass graft surgery, congestive heart failure, transient ischemic attack, and carotid endarterectomy.	There was a statistically significant trend for higher mean scores for all 5 cognitive function scores with higher levels of long-term PA (p<0.001). On all cognitive function scores except category fluency (p=0.05), there was a significant trend for higher levels of PA and less cognitive decline (p<0.001 for all).
Middleton LE et al., 2008 (55), Canada	n=7595 men and women 76.1 years	Prospective cohort study, beginning in 1991, 5-year follow-up.	Self-administered questionnaire assessed level of PA/exercise frequency and intensity. Participants were classified into either 'high exercise' (≥3 x/week, at least as intense as walking) or 'low/no exercise' (all other exercisers and non-exercisers).	1) Modified MMSE	Change in modified MMSE score.	Age and number of years in formal education.	High exercise group showed less cognitive decline from baseline to 5-year follow-up than low/no exercise group (p<0.001). High exercise group had less risk of cognitive decline (10.3% versus 15.8% in low/no exercise group) and higher chance of cognitive improvement (89.7% versus 84.2% in low/no exercise group) (p<0.001).
Chang M et al., 2010 (56), Iceland	n=4945 men and women 51.3 years at baseline	Prospective cohort study, beginning in 1967, 26-year follow-up.	At baseline, participants were asked two questions: 1) If they regularly participated in sports or exercised at any time during their adult life and 2) How many hours per week they exercised during winter and summer time. PA groups were defined as a) no PA; b) ≤ 5 hours of PA/week; c) ≥ 5 hours or more of PA per week.	1) Digit symbol substitution test 2) Figure comparison task 3) Stroop test (modified) 4) California Verbal Learning Test 5) Digits Backwards task 6) Cambridge Neuropsychological Test Automated Battery Spatial Working Memory test (shortened version) 7) MMSE	Composite scores for speed of processing, memory, and executive function.	Midlife measures: age at time of examination, blood pressure, BMI, serum cholesterol, self-reported smoking status, and resting heart rate. Late-life measures: high depressive symptoms, education, and APOE allele genotype.	Two groups (≤ 5 hours of PA/week and ≥ 5 hours or more of PA/week) that were physically active in midlife had significantly faster processing speed (p<0.0001), better memory (p<0.0001), and better executive function (p<0.0001).

Abbreviations: APOE, Apolipoprotein E; BMI, body mass index; MET, metabolic equivalent; MMSE, Mini-Mental State Examination; PA, physical activity; T2DM, type 2 diabetes mellitus; TICS, Telephone Interview for Cognitive Status.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Physical Activity Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Gillum RF; Obisesan TO, 2010 (57), USA	n=5903 men and women ≥60 years (mean not reported)	Prospective cohort study, beginning in 1988, average 8.5-year follow-up.	Leisure time PA was assessed with interview questions asking frequency of exercise in the past month for jogging/running, riding a bicycle or exercise bicycle, swimming, aerobic dancing, other dancing, calisthenics or floor exercises, gardening or yard work, and weightlifting. Four groups based on frequency were formed (0, 1-4, 5-7, ≥8 x/week).	A short index cognitive function was constructed with 6 orientation, 6 recall, and 5 attention items.	Cognitive function.	Age, sex, race/ethnicity, education, census region, urbanization, health status, chronic morbidity, alcohol use, regular source of care at baseline, if participant had a regular personal physician, BMI, systolic blood pressure, smoking, and log C-reactive protein.	Those that were physically inactive had lower cognitive function: 31% (95% CI 25, 37) of those with no leisure time PA had the lowest cognitive function scores compared to 16% (95% CI 12, 22) of those with 5 or more activities/week ($p<0.0001$).
Ku PW et al., 2012 (58), Taiwan	n=1160 men and women ≥67 years (mean not reported)	Prospective cohort study, beginning in 1996, 11-year follow-up.	Participants were asked 'Did you usually engage in any kind of leisure-time physical activity?' Four response categories were: 1) none; 2) 1-2 sessions/week; 3) 3-5 sessions/week; 4) ≥6 sessions/week.	1) Short Portable Mental Status Questionnaire	Cognitive function.	Sex, age, education level attained, cohabitation status, self-perceived social support, alcohol drinking, smoking, number of chronic diseases, and activities of daily living.	Baseline PA levels and change in PA levels were inversely associated with rate of cognitive decline ($p<0.05$). Baseline PA levels were also positively associated with baseline cognitive function scores ($p<0.05$).
Chu DC et al., 2015 (59), Taiwan	n=1268 men and women ≥70 years (mean not reported)	Prospective cohort study, beginning in 1999, 8-year follow-up.	Participants were asked 'Did you usually engage in any kind of leisure-time physical activity?' Four response categories were: 1) none; 2) 1-2 sessions/week; 3) 3-5 sessions/week; 4) ≥6 sessions/week. Duration was reported as 0, 1-14, 15-29 or ≥30 minutes per session and perceived exertion was reported as speed of breathing: no change, slightly fast, or very fast.	1) Short Portable Mental Status Questionnaire	Cognitive function.	Age, gender, years of education, living status, participation in five common leisure activities and frequency (watching TV, listening to radio, reading newspapers/magazines/books, playing chess/cards, and visiting friends/relatives), alcohol consumption, smoking, BMI, number of chronic diseases, activities of daily life, and depressive symptoms.	Those who engaged in high levels of exercise had better cognitive performance ($p<0.001$). Duration of exercise was also significantly associated with cognitive function ($p=0.004$). Level of exercise was associated with rate of cognitive change ($p<0.001$).
Howard EP et al., 2016 (60), USA	n=4620 men and women 81 years	Prospective cohort study, 1-year follow-up.	Hettler's Domains of Wellness were used to assess PA which included 7 items: 1) ≥3 hours of PA in past 3 days 2) Leaving house ≥3 times in past 3 days 3) Participation in exercise program in past 3 days 3a) Biking 3b) Pilates, yoga, Tai Chi 3c) Swimming/aqua fitness 3d) Hiking	1) Cognitive Performance Scale	1-year cognitive decline.	Adjusted for baseline measures related to cognitive performance: 1) Being not independent in decision making 2) Short-term memory problems 3) Being not independent in being understood by others	Participation in any of the 7 PA items showed a reduced risk of cognitive decline (OR 0.46-0.72, $p<0.05$ for all).

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PA, physical activity.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Physical Activity Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Cross-sectional Studies							
Vance DE et al., 2005 (43), USA	n=158 men and women 75.1 years	Cross-sectional cohort study.	Questionnaire covering past 2 weeks consisting of type and duration of various items including sedentary activities, leisure activities, and household chores.	1) MMSE 2) Usual Field of View 3) Benton Visual Retention Test 4) Trail-Making Test Park B 5) Rey-Osterrieth Complex Figure Copy and Recall Tests	Cognitive performance.	N/A	Greater PA was predictive of better cognitive performance (standardized coefficient=0.32 ($p<0.05$)). Sedentary behaviour was predictive of more depressive symptoms (standardized coefficient=0.18 ($p<0.05$)) and depressive symptoms had a direct relation to cognition (standardized coefficient=-0.34 ($p<0.05$)), with more depressive symptoms predicting lower cognitive function.
Bixby WR et al., 2007 (44), USA	n=120 men and women 78.9 years	Cross-sectional cohort study.	Yale Physical Activity Survey covers various PAs including household chores, recreation, and structured exercise. Participants reported activity type, frequency, and duration during a typical week. A summary score, called the Yale Index, was calculated to represent total PA an individual engaged in during a typical 7-day period.	1) Stroop Color-Word test	Stroop test performance.	Age, years of education, and IQ.	The Yale Index was positively associated to tasks of the Stroop test that require executive function: color-word (ΔR^2=0.02, p=0.04) and interference (ΔR^2=0.04, p=0.01). The Yale Index was unrelated to non-executive tasks of the Stroop test (word and color).
Buchman AS et al., 2008 (45), USA	n=521 men and women 82.3 years	Cross-sectional cohort study.	PA was quantified using an actigraph worn on the wrist by participants for 10 days. Average total daily PA was calculated from the actigraph data collected.	19 cognitive tests used to assess various cognitive domains and global cognition.	Performance on cognitive tests.	Gender, years of education, age, BMI, self-report PA, Parkinsonian signs, physical frailty, lower extremity performance, depressive symptoms, number of vascular risk factors, and vascular diseases.	Total daily PA was significantly associated with global cognition in a positive linear way ($p<0.001$) as well as with cognitive sub-measures of episodic memory (p=0.039), semantic memory ($p<0.001$), and working memory (p=0.015). Total daily PA was also significantly associated with perceptual speed ($p<0.001$) and visuospatial abilities (p=0.011) in a non-linear relation.

Abbreviations: BMI, body mass index; IQ, intelligence quotient; MMSE, Mini-Mental State Examination; PA, physical activity.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Physical Activity Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Lindwall M et al., 2008 (46), Sweden	n=813 men and women 75.1 years	Cross-sectional cohort study.	Exercise activities were assessed using two survey questions: 'How often did you exercise with light intensity in the last 12 months?' and 'How often did you exercise more strenuously in the last 12 months?' Four choices of duration were available: 1) never; 2) 1-3 x/month; 3) several x/week; 4) everyday. New variables were created to measure change in exercise status.	1) MMSE 2) Free recall task 3) Recognition of positions task 4) Vocabulary task 5) Digit cancellation task 6) Digit span task 7) Comparing figures task	Cognitive function test scores.	Age, education, depression, functional status, and co-morbidity.	There was a significant main effect of light exercise on free recall ($p=0.05$), vocabulary ($p<0.01$), digit span ($p<0.01$), and MMSE ($p<0.001$). Gender-specific analyses showed a significant effect for all cognitive tests except the comparing figures task for men, but not for women. No effects of strenuous exercise on any cognitive function test were found. Effect of light exercise change on MMSE was significant for men ($p<0.001$), but not for women ($p=0.84$).
Lam LCW et al., 2009 (47), China	n=782 men and women 72.0 years	Cross-sectional cohort study.	Questionnaire assessing leisure-time PA was administered that asked about type, frequency, and duration of exercise practiced. Exercise groups were created as 1) No exercise; 2) Walking and stretching; 3) Aerobic exercise; 4) Mind-body exercise.	1) Clinical Dementia Rating 2) Chinese version of Alzheimer's Disease Assessment Scale-Cognitive subscale 3) MMSE 4) Digit and visual span test 5) Category verbal fluency test	Cognitive function.	Age and education.	Aerobic and mind-body exercise groups with exercise habits greater than 5 years compared to the stretching exercise group had higher cognitive test scores on MMSE, 10-min delayed recall, visual backward span, and category verbal fluency ($p<0.05$). Cognitive profiles between aerobic and mind-body exercise groups were not significantly different ($p>0.05$). Physical exercise greater than 5 years compared to no exercise was significantly associated with category verbal fluency scores ($p=0.037$).
Brown BM et al., 2012 (48), Australia	n=217 men and women 69.5 years	Cross-sectional cohort study.	PA was quantified using an actigraph worn on the waist by participants for 7 days. Two PA scores were calculated for each participant: average PA per day and highest intensity of PA per day.	1) MMSE 2) Digit Span task from WAIS-III 3) Digit Symbol Coding from WAIS-III 4) Logical Memory I and II 5) California Verbal Learning Test 6) Rey Complex Figure Test 7) Controlled Oral Word Association Task 8) Stroop Test	Cognitive functioning scores.	Age, gender, years of education, APOE ε4 allele carriage, BMI, and self-reported cardiovascular disease.	Highest intensity of PA was positively associated with digit symbol coding scores ($p<0.05$), Rey Complex Figure Test score ($p<0.05$), and verbal fluency score of the Controlled Oral Word Association Test ($p<0.05$). No associations were found between average PA and cognitive function test scores.
Wilbur J et al., 2012 (49), USA	n=174 men and women 66.0 years	Cross-sectional cohort study.	PA was quantified using an actigraph worn on the hip by participants for 7 days. Mean daily PA was defined as: 1) sedentary; 2) light (<3.0 METs); 3) moderate (3.0-6.0 METs); 4) vigorous (>6.0 METs).	1) East Boston Memory Test 2) Stroop Neuropsychological Screening Test 3) Numbers Comparison Test 4) Category Fluency Test	Performance on cognitive function tests assessing episodic memory and executive function.	Age, education, sex, marital status, employment, country of origin, and number of chronic health problems.	Lower word fluency scores were negatively associated with minutes per day of light intensity PA ($r=-0.51$), minutes per day of moderate/vigorous PA ($r=-0.56$), and counts per minute ($r=-0.62$).

Abbreviations: APOE, Apolipoprotein E; BMI, body mass index; MET, metabolic equivalent; MMSE, Mini-Mental State Examination; PA, physical activity; WAIS-III, Wechsler Adult Intelligence Scale 3rd Edition.

Author, year (ref), country	**Population (sample size, mean age)**	**Study Design**	**Physical Activity Measure**	**Cognitive Function Measure**	**Outcome Measure**	**Covariates**	**Findings**
Young JC et al., 2016 (50), UK	n=50 men and women 68.1 years	Cross-sectional cohort study with 12-month follow-up.	PA and exercise was assessed with the Physical Activity Scale for the Elderly. 27 participants were classified as 'supervets', defined as engaging in high-effort endurance exercise via running, swimming, and/or cycling for ≥20 years. The other 23 participants were nonsedentary controls.	1) Simple Reaction Time 2) Digit Symbol Substitution Task 3) Trail Making A and B 4) Controlled Oral Word Association Test 5) 20-Word Item Episodic Memory Task 6) Backward Digit Span 7) Prospective Memory Card Sort Task 8) Focal and Non-Focal Prospective Memory Task 9) Map Test of Everyday Attention 10) Rapid Visual Information Processing 11) Stroop-Switch Task	Performance on cognitive function tests assessing speed of processing, executive function, memory, and attention.	N/A	No differences were found in cognitive performance on measures of speed of processing, executive function, memory, or attention between the supervet group and nonsedentary controls.

Abbreviations: PA, physical activity.

Table 3. Literature review summary: Effect of cardiorespiratory fitness on cognitive function in healthy older adults from observational studies

Author, year (ref), country	Population (sample size, mean age)	Study Design	Cardiorespiratory Fitness Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Cohort Studies							
Barnes DE et al., 2003 (83), USA	n=349 men and women 68.7 years	Prospective cohort study, beginning in 1993, 6-year follow-up.	Peak $\dot{V}O_2$ Subjects split into lowest, middle, and highest tertile of peak $\dot{V}O_2$ by gender. For females, the peak $\dot{V}O_2$ tertiles were 12.3-18.6, 18.7-22.7, and 22.8-36.1 ml/kg/min, and 14.8-23.4, 23.5-28.9, and 29.0-45.7 ml/kg/min for males.	Baseline: 1. Modified MMSE 6 year follow-up: 1. MMSE 2. Trail-Making Test Part B 3. Stroop Interference Test 4. Digit Symbol Test 5. California Verbal Learning Test 6. Verbal fluency task	Cognitive function.	Age, gender, education, NAART, annual household income, hypertension, thyroid disorder, self-rated health, smoking status, and baseline modified MMSE score.	No association between baseline modified MMSE score and peak $\dot{V}O_2$. Baseline tertile peak $\dot{V}O_2$ was positively associated with a lower decline in MMSE score ($p=0.002$) and better scores on all cognitive tests ($p<0.006$) at 6-year follow-up. Linear regression adjusted for covariates showed similar results: baseline $\dot{V}O_2$ was positively associated with a lower decline in MMSE score, better scores on all tests assessing attention/executive function, and immediate recall on the California Verbal Learning Test ($p<0.05$ for all analyses).
Wendell CR et al., 2014 (84), USA	n=615 men and women 56.1 years	Prospective cohort study, beginning in 1985, 2-year follow-up.	$\dot{V}O_2$max (measured only at baseline) Mean $\dot{V}O_2$max=28.4±6.9 ml/kg/min.	Administered at baseline and follow-up assessments: 1. Blessed-Information-Memory-Concentration 2. MMSE 3. Digits Forward and Digits Backward portion of Digit Span subtest of WAIS-R 4. California Verbal Learning Test 5. Benton Visual Retention Test 6. Trail Making Test Part A and B 7. Letter Fluency and Category Fluency 8. Boston Naming Test 9. Card Rotations Test	Trajectory of performance on measures of memory, attention, perceptuomotor speed, language, and executive function.	Age, sex, years of education, race, BMI, depressive symptoms, antihypertensive medications, hypertension, CVD, and inflammatory disease.	A significant interaction of $\dot{V}O_2$max and age was found for scores on Blessed-Information-Memory-Concentration ($p=0.014$), Benton Visual Retention Test ($p<0.0001$), and California Verbal Learning Test ($p=0.005$), indicating that a lower $\dot{V}O_2$max at baseline was associated with significantly greater cognitive decline on multiple measures of visual memory and verbal memory.
Cross-sectional Studies							
Dustman RE et al., 1990 (68), USA	n=30 men 54.9 years	Cross-sectional cohort study.	$\dot{V}O_2$max Median split of subjects into 'High Fit' and 'Low Fit' groups. High fit mean $\dot{V}O_2$max=49.8±5.5 ml/kg/min; low fit mean $\dot{V}O_2$max=29.1±3.8 ml/kg/min.	1. Sternberg reaction time 2. Stroop Color Interference 3. Symbol Digit Modalities 4. Trails B	Composite cognitive score of mean standard scores from 4 cognitive tests.	Years of education.	Cognitive performance was better in the High Fit group compared to the Low Fit group ($p<0.02$).

Abbreviations: CVD, cardiovascular disease; MMSE, Mini-Mental State Examination; NAART, North American Adult Reading Test; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_2$max, maximal aerobic capacity; WAIS-R, Wechsler Adult Intelligence Scale Revised.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Cardiorespiratory Fitness Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Shay KA; Roth DL, 1992 (69), USA	n=48 men 65.0 years	Cross-sectional cohort study.	$\dot{V}O_2$max Median split of subjects into 'High Fit' and 'Low Fit' groups. High Fit mean $\dot{V}O_2$max=29.7±3.4 ml/kg/min; Low Fit mean $\dot{V}O_2$max=20.8±3.0 ml/kg/min.	1. WAIS-R 2. WMS Visual Reproduction test 3. Stroop color test 4. WAIS-R Vocabulary task 5. WMS Logical Memory test 6. Verbal Fluency task 7. Trail-making test 8. Hooper Visual Organization test 9. WAIS-R Digit Symbol test 10. Rey-Osterrieth Complex Figure Reproduction Test 11. Critical flicker fusion threshold 12. Finger-tapping speed	Domain-specific (visuospatial, attention and concentration, verbal memory, and sensorimotor) cognitive function.	WAIS-R vocabulary score.	High Fit subjects performed significantly better only on tasks requiring visuospatial abilities (p=0.004).
Newson RS; Kemps EB, 2008 (70), Australia	n=48 men and women 70.8 years	Cross-sectional cohort study.	$\dot{V}O_2$max Median split of subjects into 'High-fitness' and 'Low-fitness' groups. High-fitness mean $\dot{V}O_2$max=31.15±6.66 ml/kg/min; Low-fitness mean $\dot{V}O_2$max=12.88±7.85 ml/kg/min.	1. Simple reaction time task 2. Stroop task 3. Map Search Test 4. Letter-Number Sequencing subtest of WAIS-III 5. Corsi Blocks Backward task 6. Digit Symbol Substitution Test 7. Boxes Test 8. Zoo Map Test 9. Six Elements Test 10. Names Test 11. Doors Test	Composite cognitive scores of mean standard z-scores on measures of simple reaction time, attention, working memory, speed of processing, executive function, and memory.	Age, gender, education, general well-being, exercise engagement, and crystallised intelligence (revised NART and Spot-the-Word Test).	The High-fitness group had higher cognitive scores on measures of simple reaction time (p<0.05), attention (p<0.05), working memory (p<0.001), and speed of processing (p<0.01). There was no difference in cognitive scores between fitness groups on measures of executive function or memory.
Brown AD et al., 2010 (71), Canada	n=42 women 65.1 years	Cross-sectional cohort study.	$\dot{V}O_2$max Subjects split into 'Fit' and 'Sedentary' groups based on age-predicted $\dot{V}O_2$max values. Fit group mean $\dot{V}O_2$max=28.0±4.7 ml/kg/min; Sedentary group mean $\dot{V}O_2$max=20.0±3.0 ml/kg/min.	1. Vocabulary subtest of WASI 2. D-KEFS Verbal Fluency test 3. Matrix reasoning subtest of WASI 4. Benton Judgment of Line Orientation Test 5. Buschke Selective Reminding Task 6. Medical College of Georgia Complex Figures Test 7. Symbol Digit Modalities Test 8. D-KEFS Color-Word Interference Test 9. Auditory Consonant Trigrams 10. Sorting Test	Overall cognitive function assessed by the summation of the domain-specific (verbal knowledge, spatial reasoning, memory, processing speed, complex attention, and executive function) z-scores.	Age and education.	Cognitive function was positively correlated with $\dot{V}O_2$max (r=0.41, p=0.008). Positive correlations between $\dot{V}O_2$max and specific cognitive domains were also observed for cognitive speed (r=0.391, p=0.013), verbal ability (r=0.300, p=0.06), perception (r=0.351, p=0.026), and executive function (r=0.304, p=0.056). The Fit group, compared to the Sedentary group, had significantly better overall cognitive function (p=0.007) as well as better scores on cognitive speed (p=0.014), verbal ability (p=0.03), perception (p=0.003), but not executive function (p=0.071).

Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; NART, National Adult Reading Test; $\dot{V}O_2$max, maximal aerobic capacity; WAIS-III, Wechsler Adult Intelligence Scale 3rd Edition; WAIS-R, Wechsler Adult Intelligence Scale Revised; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Cardiorespiratory Fitness Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
McAuley E et al., 2011 (72), USA	n=86 men and women 65.1 years	Cross-sectional cohort study.	3 separate measures of $\dot{V}O_2$max: 1. Maximal graded exercise test 2. Rockport 1-mile walk test 3. Equation-derived estimate by a formula accounting for age, sex, BMI, resting heart rate, and self-reported PA that was developed in 2005 by Jurca et al.(85).	1. Modified flanker paradigm 2. Spatial working memory task	Domain-specific (processing speed and spatial working memory) cognitive function.	N/A	Three measures of CRF were significantly correlated with each other (r=0.66, p=p<0.001). Higher fitness was significantly associated with better processing speed for all three fitness measures: Exercise test-derived (r=-0.34, p=0.05), Rockport-derived (r=-0.36, p=0.001), and equation-derived (r=-0.26, p=0.02). Higher fitness was significantly associated with better spatial memory for the exercise test-derived measure (r=-0.23, p=0.05) and equation-derived measure (r=-0.29, p=0.02), but not the Rockport-derived measure (r=-0.15, p=0.23).
Netz Y et al., 2011 (73), Israel	n=38 men and women 77.5 years	Cross-sectional cohort study.	$\dot{V}O_2$max Median split of subjects into 'Low Fitness' and 'Moderate Fitness' groups. Low fitness mean $\dot{V}O_2$max=13.42±4.4 ml/kg/min; moderate fitness mean $\dot{V}O_2$max=25.26±4.3 ml/kg/min.	Mindsteams computerized battery comprised of: 1. Go-NoGo Response Inhibition 2. Verbal Memory 3. Stroop Interference 4. Nonverbal Memory 5. Catch Game 6. Visual Spatial Imagery	Normalized summary cognitive scores for measures of memory, attention, visual-spatial abilities, executive function, and global cognition.	N/A	Significantly better cognitive scores were observed for the Moderate Fitness group compared to the Low Fitness group for measures of attention (p=0.036) and global cognition (p=0.04). Significant correlations were found between $\dot{V}O_2$max and scores on measures of executive function (r=0.39, p=0.02), attention (r= 0.37, p=0.02), and global cognition (r=0.38, p=0.02).
Weinstein AM et al., 2012 (74), USA	n=142 men and women 66.4 years	Cross-sectional cohort study.	$\dot{V}O_2$max Mean $\dot{V}O_2$max=21.3±4.8 ml/kg/min.	1. Modified Stroop task 2. Spatial Working Memory task	Performance on cognitive function tasks.	Age, sex, and education.	Higher $\dot{V}O_2$max was predictive of less Stroop % interference (p<0.05), indicating better performance on the Stroop task. Higher $\dot{V}O_2$max was also predictive of better Spatial Working Memory 3-Item accuracy (p<0.01), indicating better performance on the Spatial Working Memory task.
Berryman N et al., 2013 (75), Canada	n=48 men and women 70.5 years	Cross-sectional analysis of a larger training intervention study.	$\dot{V}O_2$max Mean $\dot{V}O_2$max=24.3±4.9 ml/kg/min.	1. MMSE 2. Modified Stroop Color-Word test	Global cognitive function as well as measures of processing speed and inhibition/ flexibility of executive function.	Age, education, fat-free mass, and gender.	A significant partial correlation was found between $\dot{V}O_2$max and the flexibility score of the Stroop test (r=-0.325, p=0.031), indicating higher levels of CRF are associated with cognitive flexibility.

Abbreviations: BMI, body mass index; CRF, cardiorespiratory fitness; MMSE, Mini-Mental State Examination; PA, physical activity; $\dot{V}O_2$max, maximal aerobic capacity.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Cardiorespiratory Fitness Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Hayes SM et al., 2014 (76), USA	n=28 men and women 64.1 years	Cross-sectional cohort study.	Peak $\dot{V}O_2$ Peak $\dot{V}O_2$ mean=30.0±8.5 ml/kg/min.	1. Trail Making and Verbal Fluency from D-KEFS 2. Mental Arithmetic and Digit Span Backwards form WAIS-III 3. Wisconsin Card Sorting Test (computerized) 4. Face-name memory task 5. Brief Visuospatial Memory Test Revised 6. Faces subtest of WMS-III 7. California Verbal Learning Test (2nd edition) 8. Logical Memory subtest of WMS-III	Composite cognitive domain scores of mean standard z-scores on means of executive function, visual memory, verbal memory, and face-name memory.	Premorbid intellectual function, depression, and gender.	Peak $\dot{V}O_2$ was shown to predict executive function score (R^2=0.174, p<0.05), face-name memory score (R^2=0.205, p<0.05), and visual memory score (R^2=0.335, p<0.005). No association between peak $\dot{V}O_2$ and verbal memory score was found.
Boots EA et al., 2015 (77), USA	n=315 men and women 58.6 years	Cross-sectional analysis of a longitudinal cohort study.	Estimated by a formula accounting for age, sex, BMI, resting heart rate, and self-reported PA that was developed in 2005 by Jurca et al.(85). Formula measure of CRF was validated within the study's sample using $\dot{V}O_2$ measurements obtained from 85 subjects who underwent graded exercise testing. The formula measure of CRF was found to be significantly associated with $\dot{V}O_2$ (r=0.71, p<0.001).	1. Rey Auditory Verbal Learning Test 2. Delayed Recall task 3. Digit Span and Letter-Number Sequencing subtests of WAIS-III 4. Stroop Color-Word Test Interference Trial 5. Trail-Making Test A and B 6. Block Design and Matrix Reasoning subtests of WASI 7. Judgment of Line Orientation Test 8. Reading subtest of Wide-Range Achievement Test (3rd edition) 9. Vocabulary and Similarities subtests from WASI 10. Boston Naming Test 11. MMSE	Domain-specific (memory, attention, executive function, language, and visuospatial ability) cognitive function.	Sex and education.	A significant association between higher CRF and better performance on cognitive domains of visuospatial ability (p<0.001), speed and flexibility (p=0.033), and verbal learning and memory (p=0.022) was found.
Dupuy O et al., 2015 (78), Canada	n=36 women 62.9 years	Cross-sectional cohort study.	$\dot{V}O_2$max Subjects split into 'Higher Fit' and 'Lower Fit' groups based on age- and gender-referenced $\dot{V}O_2$max norms. Higher Fit mean $\dot{V}O_2$max=30.1±1.5 ml/kg/min; Lower Fit mean $\dot{V}O_2$max=21.4±7.1 ml/kg/min.	1. Digit Symbol Substitution Test 2. Trail Making test 3. Modified Stroop color test 4. Computerized Modified Stroop task	Domain-specific (psychomotor speed, attention, and executive function) cognitive function.	N/A	An association between higher fitness level and better performance on the section of the computerized Stroop task that requires executive control was seen (p<0.05). No association was seen between fitness and the non-executive control section of the Stroop task or any of the other cognitive tasks.

Abbreviations: BMI, body mass index; CRF, cardiorespiratory fitness; D-KEFS, Delis-Kaplan Executive Function System; MMSE, Mini-Mental State Examination; PA, physical activity; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_2$max, maximal aerobic capacity; WAIS-III, Wechsler Adult Intelligence Scale 3rd Edition; WASI, Wechsler Abbreviated Scale of Intelligence; WMS-III, Wechsler Memory Scale 3rd Edition.

Author, year (ref), country	Population (sample size, mean age)	Study Design	Cardiorespiratory Fitness Measure	Cognitive Function Measure	Outcome Measure	Covariates	Findings
Gauthier CJ et al., 2015 (79), Canada	n=54 men and women 63.0 years	Cross-sectional cohort study.	$\dot{V}O_2$max Mean $\dot{V}O_2$max=29.04±6.92 ml/kg/min.	1. Modified Stroop task	Reaction time on modified Stroop task as a measure of executive function.	N/A	$\dot{V}O_2$max was inversely associated with reaction time on the modified Stroop task (p=0.018, R^2=0.113), indicating higher fitness is associated with better executive function.
Freudenberger P et al., 2016 (80), Austria	n=877 men and women 65.0 years	Cross-sectional cohort study.	$\dot{V}O_2$max Mean $\dot{V}O_2$max=26.34±4.6 ml/kg/min.	1. Bäumler's Lern-und-Gedächtnistest 2. Purdue Pegboard Test 3. Wisconsin Card Sorting Test 4. Trail Making Test-Part B 5. Digit Span Backward 6. Alters Konzentrationstest 7. Computerized complex reaction time task	Global and domain-specific (memory, executive function, and motor skills) cognitive function.	Model 1: age, sex, years of education, and treatment with Calcium channel antagonists or beta-blockers. Model 2: Covariates of model 1 plus hypertension, diabetes, total cholesterol, smoking status, and BMI.	Higher $\dot{V}O_2$max was associated with better memory (p<0.0001), executive function (p=0.003), motor skills (p=0.018), and global cognition (p<0.0001) in model 1. Addition of covariates of model 2 had no effect on results except for association between $\dot{V}O_2$max and motor skills, which was no longer significant (p=0.078).
Bauermeister S; Bunce D, 2016 (81), UK	n=225 men and women 63.8 years	Cross-sectional cohort study.	$\dot{V}O_2$max estimated by the Rockport Fitness Walking Test(88). Mean $\dot{V}O_2$max=25.46±15.73 ml/kg/min.	1. Simple Reaction Time Task 2. Two-Choice Reaction Time Task 3. Four-Choice Reaction Time Task 4. Eriksen Flanker Task 5. Stroop Arrow Task 6. Stroop Word Task 7. Simple Visual Search Task 8. Complex Visual Search Task 9. Immediate Word Recognition 10. Delayed Word Recognition	Domain-specific (psychomotor performance, executive function, visual search, and recognition) cognitive function.	Age and NAART.	Significant age by $\dot{V}O_2$max interactions were found for performance on the Four-Choice Reaction Time Task (psychomotor performance), Flanker and Stroop tasks (executive function), and Immediate Word Recognition (p<0.05 for all). Younger age and higher aerobic fitness showed better cognitive function scores on these tasks.
Hayes SM et al., 2016 (82), USA	n=28 men and women 64.1 years	Cross-sectional cohort study.	$\dot{V}O_2$max Mean $\dot{V}O_2$max=30.0±8.5 ml/kg/min.	1. D-KEFS Trail Making 2. D-KEFS Verbal Fluency 3. WAIS-III Arithmetic 4. WAIS-III Digit Span Backwards 5. Computerized Wisconsin Card Sorting Test 6. Face-Name Memory Task 7. Brief Visuospatial Memory Test Revised 8. Faces Subtest of WMS-III 9. California Verbal Learning Test (2nd edition) 10. Logical Memory Subtest of WMS-III	Domain-specific (executive function, face-name memory, visual memory, and verbal memory) cognitive function.	Age and sex.	$\dot{V}O_2$max was positively associated with cognitive domain z-scores of executive function (β=0.040, p<0.05), face-name memory (β=0.102, p<0.05), and visual memory (β=0.095, p<0.005).

Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; NAART, North American Adult Reading Test; $\dot{V}O_2$max, maximal aerobic capacity; WAIS-III, Wechsler Adult Intelligence Scale 3rd Edition; WMS-III, Wechsler Memory Scale 3rd Edition.

Chapter Two: **Research Method**

2.1 Overview

Research conducted for this project uses a subset of data collected through the *Brain in Motion* (BIM) study, a quasi-experimental study assessing the effect of a 6-month aerobic exercise intervention on cerebrovascular regulation and cognitive function in community-dwelling older adults. The BIM study's methods and protocol were previously published (89). Recruitment began in May 2010 and was carried out via media, poster, and newspaper advertisements at the University of Calgary and surrounding areas. Final participants completed the study in April 2016.

2.2 Ethics Approval

The BIM study was approved by the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary: Ethics Protocol ID #22502. Research conducted for this project was approved by CHREB and added to the BIM ethics protocol on May 9, 2016.

2.3 Study Design, Population, and Sample Size

The BIM study was an 18-month long study consisting of pre-exercise, exercise, and post-exercise phases as outlined in Figure 1. Participants were English-speaking men and women aged 55-86 years who, at the time of recruitment, were inactive, as defined by engaging in less than 30 minutes of moderate exercise four days per week or 20 continuous minutes of vigorous exercise two days per week. Participants were non-smokers for at least 12 months with a BMI of less than 35 kg/m^2, were free of neurological, cardiovascular, cerebrovascular, and obstructive airway diseases, had no history of major surgery or trauma within the past 6 months, and were deemed able and safe by a study physician to participate in the exercise intervention. Participants were also free of cognitive impairment, as indicated by a score of 24 or greater on the *Montreal Cognitive Assessment* (90), were able to walk independently and go up and down at least 20 stairs, and provided written consent. This project used a cross-sectional analysis of data collected at the first time point (Phase 1A month 0) and is comprised of participants that were administered the cognitive assessment, maximal aerobic capacity test, and PA questionnaire, completed the FFQ, and provided a blood sample (n=194).

2.4 Data Collection

2.4.1 Cognitive Assessment

Cognitive function was assessed using data collected from a two-hour long cognitive assessment administered by a trained BIM staff member at Phase 1A. The assessment was comprised of a cognitive battery of 7 tasks that tested 6 cognitive domains (89). The seven tasks were the *Color Word Interference*, *Card Sorting*, and *Verbal Fluency* tasks of the *Delis-Kaplan Executive Function System*, *Symbol-Digit Modalities Test*, *Buschke Selective Reminding*, *Medical College of Georgia Complex Figure*, and *Auditory Consonant Trigrams*. Cognitive domains were determined using confirmatory factory analysis in which each factor needed to meet a threshold of 0.4 for inclusion in the structure. The six cognitive domains derived were concept formation, executive processing speed/inhibition, verbal memory, verbal fluency, figural memory, and complex attention. Completed cognitive assessments were scored by trained BIM staff members using a standardized scoring guide and entered into the data management system FileMaker Pro version 11.1 (FileMaker Inc., 2010). Data were exported into Microsoft Excel version 14.7.3 (Microsoft Corp., 2010) to calculate z-scores. Z-scores were computed from raw scores and averaged for tasks within each of the six cognitive domains. A global cognition score was computed as the average of the six cognitive domain z-scores. Participants who had a missing score in any task, because of an inability or refusal to complete the task, were excluded from computation of the task's associated cognitive domain z-score and subsequent global cognition z-score (n=4).

2.4.2 Dietary History Questionnaire

Dietary intake was measured using the *National Cancer Institute Diet History Questionnaire* (DHQ I) modified for Canadian populations (C-DHQ I), which is a self-administered quantitative FFQ of past 12-month dietary intake (91). The questionnaire has 146 questions that cover 124 food items and includes portion size and dietary supplements. GL was added to the DHQ I nutrient database using published values (92) as described by Flood et al. (93). The DHQ I was previously validated in the United States as a reliable assessment of diet in adults (94). The C-DHQ I food list was evaluated against dietary intake data from a large population-based Canadian survey and demonstrated to be representative of food intake in Canada (95), and the nutrient database was modified to reflect the Canadian Nutrient File version 2001b (96). At Phase 1A, participants were given the questionnaire to complete at home and asked to return the completed C-DHQ I at their next visit to the research lab. Completed questionnaires were scanned on a Teleform© scanner, exported into a Structured Query Language (SQL) database, and analyzed with the analysis program Diet*Calc version 1.4.3 (National Cancer Institute, 2005) to generate nutrient estimates. A copy of the C-DHQ I is presented in Appendix A.

2.4.3 Lifetime Total Physical Activity Questionnaire

Past year PA was assessed using the *Lifetime Total Physical Activity Questionnaire* (LTPAQ), which is an interview-administered questionnaire that measures all domains of PA (occupational, household, and recreational), all parameters of activity (frequency, intensity, and duration) from childhood to the time of the interview that was previously assessed as a reliable measure of total lifetime PA (97). The LTPAQ was administered at Phase 1A by a trained interviewer. Prior to the interview, participants received two recall calendars as memory aids, one focusing on educational and occupational activities and the other on major life events. The calendars were brought to the interview and used by the interviewer to help with recall of lifetime PA patterns. For occupational activities, participants reported the duration, frequency, and perceived intensity for paid or volunteer jobs they held for at least 8 hours per week for 4 months of the year over their lifetime. Transportation to and from the workplace was also reported. For household activities, participants reported a duration and frequency for household and seasonal activities, such as gardening, that were performed for at least 7 hours per week for 4 months of the year. Lastly, for recreational activities, participants reported a duration, frequency, and perceived intensity for exercise and sports activities performed at least 2 hours per week for at least 4 months of the year and done at least 10 times during their lifetime. Completed LTPAQs were coded and entered into Blaise©, a computer-assisted interviewing system and survey processing tool, exported into an SQL database, and transferred into Stata/IC version 13.1 (StataCorp, 2013). A code was written and run in Stata/IC to extract activities performed within the past 12 months to use for this project. Intensities of the reported activities performed as occupational, household, and recreational PA were assigned a MET value according to the *Compendium of Physical Activities* (98), and these data were combined to create the total PA variable expressed as MET-hours/week done in the previous 12 months. PA variables by type of activity (occupational, household, and recreational) had many zero-value observations and were not used in analyses. A copy of the LTPAQ is presented in Appendix B.

2.4.4 Maximal Aerobic Capacity Test

CRF was assessed by a maximal aerobic capacity test that measures $\dot{V}O_2$max. $\dot{V}O_2$max tests have been determined to be valid and reliable measures of maximum rate of oxygen consumption, which is a strong predictor of CRF (99). Tests were conducted by two trained BIM staff members under the supervision of a medical doctor at Phase 1A. Participants were instructed to abstain from vigorous exercise, alcohol, and caffeine for at least 6 hours prior to the test, eating a heavy meal within 3-4 hours of the test, and smoking at least 2 hours prior to the test. The test was conducted on a motorized treadmill with the participant attached to a breathing monitoring system. A Parvo Medics True One® metabolic cart was used to control the test and collect the testing data. Following a warm up period, the treadmill gradually increased in incline and speed following the Bruce protocol (100). Subjects were tested until maximal oxygen consumption was reached, defined as a steady rate of oxygen consumption despite an increase in workload (100). At this point, the treadmill's incline and speed were reduced, initiating a cool down period. Blood pressure measurements were manually taken at various points throughout the test, including at rest, standing, during exercise, and after cool-down. Testing data was exported from the metabolic cart and stored in Microsoft Excel version 14.7.3 (Microsoft Corp., 2010).

2.4.5 Demographics and Covariates

At baseline, socio-demographic, health, and lifestyle information was obtained during onsite screening. Information on age, sex, marital status, education, retirement status, household income, and smoking history was collected. Overall intellectual level was measured using the *North American Adult Reading Test* (NAART). The NAART has been validated as a reliable measure of verbal intelligence, which is highly correlated with overall intellectual level, and used as a better measure of intelligence than reported education (101). Anthropometric measurements of height, weight, waist and hip circumference, and body fat percentage were taken by a trained staff member prior to beginning the maximal aerobic capacity test. During a separate visit, a 12-hour fasted blood sample was taken by a study nurse and sent to Calgary Laboratory Services for analysis. Blood profile measures obtained include cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, glucose, and insulin.

2.4.6 Glucoregulation

Glucoregulation was assessed using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), a validated measure of IR in both people with diabetes and normal glucoregulatory individuals that is extensively used in epidemiological studies (102, 103). HOMA-IR was calculated using participants' fasting glucose and fasting insulin concentrations using the equation defined by Matthews et al. (104):

$$\text{HOMA-IR} = \frac{\text{fasting glucose (mmol/L)} * 0.144 \text{ (unit conversion)} * \text{fasting insulin (pmol/L)}}{22.5}$$

The top 25% of the sample (HOMA-IR>2.35) was classified as having poor glucoregulation and the remaining 75% (HOMA-IR≤2.35) as having good glucoregulation. This method is standard practice since there are no universally established cut-offs for classifying IR on the HOMA-IR scale (105). HOMA-IR threshold values between 1.55-2.73 for 66th-90th percentile cut-offs were reported by larger studies of various populations (106). The HOMA-IR threshold value of 2.35 as a 75th percentile cut-off used for this project is within this range, suggesting an appropriate classification of the poor glucoregulation group.

2.5 Statistical Analyses

All statistical analyses were performed using Stata/IC version 13.1 (StataCorp, 2013). The study sample characteristics were first assessed with descriptive statistics using means ± standard deviations and frequencies for continuous and categorical variables, respectively. Between group differences (good versus poor glucoregulation) were analyzed with t-tests for continuous variables and chi square/Fisher's exact tests for categorical variables.

Distributions of continuous predictor and outcome variables were explored for potential outliers. Extreme outliers in total energy intake were identified and removed by the method described by Kipnis et al. (108). The distribution of total energy intake was right-skewed and a natural logarithm transformation was applied, which normally distributed the variable. Log-transformed estimated energy intakes that fell outside two interquartile ranges from the first and third quartile cut-offs were identified as extreme outliers. One extreme outlier (energy intake= 342.7 kcal) was identified and the subject's dietary data were excluded from further analyses.

Collinearity among covariates was first assessed with Spearman's correlations, ANOVA, and chi square tests. A decision was made on which variable would be considered during the modeling process for highly correlated continuous variables and highly associated categorical variables. Correlated/associated variables were separately regressed on global cognition with the inclusion of age, sex, and caloric intake-adjusted GL, and the variable included in the model with the greatest coefficient of determination (model R^2) was chosen. As such, covariates considered were: age, sex, marital status, NAART, body fat percentage, waist-to-hip ratio (WHR), smoking status, alcohol consumption, caffeine intake, LDL, HDL, mean arterial pressure (MAP), $\dot{V}O_2max$, and total past-year PA. GL was adjusted for energy intake using the nutrient density method (109) and expressed in units of GL/1000 kcal. In addition, residual confounding of total energy intake (log kcal/day) was evaluated during modeling by determining its impact on the GL regression coefficient. Total energy intake was retained in the model if a change of ≥15% was observed in the coefficient.

Multiple linear regression models adjusted for significant covariates were used to evaluate the relation between GL and cognition by glucoregulation. Covariates were considered significant and included in the model if their addition generated a ≥15% change in the regression coefficient of GL and improved the adjusted model R^2. Stepwise regression modeling was carried out using backward elimination (110) and two-way and three-way covariate interactions were considered. Final models adjusted for age, sex, NAART, WHR, marital status, and energy intake. Bootstrapped estimates of the standard errors run with 1000 replications were used to minimize the effect of influential observations due to the relatively small sample size. Linear regression assumptions were evaluated for validity of the final models using histograms, Q-Q plots, and the Shapiro-Wilk test (107) to assess normality of the residuals, residual-versus-fitted plots, Breusch-Pagan (111), and Cook-Weisberg (112) tests to assess homoscedasticity, variance inflation factors to assess multicollinearity (VIF<10), and scatter plots to assess for a linear relation between independent and dependent variables. Statistical significance of an estimate was fixed at $p<0.05$.

Models resulting in significant associations between GL and cognition were assessed for mediation by CRF and PA. Mediation analysis was conducted using the four-step regression approach proposed by Baron and Kenny (1986) (113). Four linear regression analyses were performed to test the associations among GL, cognition, and the two potential mediators (CRF and PA) as outlined in Figure 2. Each regression model in steps one through four was adjusted for the same covariates (age, sex, NAART, WHR, marital status, and energy intake) and linear regression assumptions were evaluated using the method that was previously mentioned. Bootstrapped estimates of the standard errors were used and run with 1000 replications. The regression coefficient of the explanatory variable in steps one through three must have been statistically significant in order to proceed to step four. The regression model in step four evaluated the form of mediation present. There was evidence of full mediation if the coefficients of GL and the mediator (CRF or PA) were not significant and significant, respectively, and evidence of partial mediation if both coefficients (GL and the mediator) were significant. If at least one of the regression coefficients of the explanatory variable in steps one through three was not significant, it was concluded that there was no evidence of mediation by the potential mediator (CRF and PA).

2.6 Chapter Two Figures and Tables

Figure 1. ***Brain in Motion*** **study design**

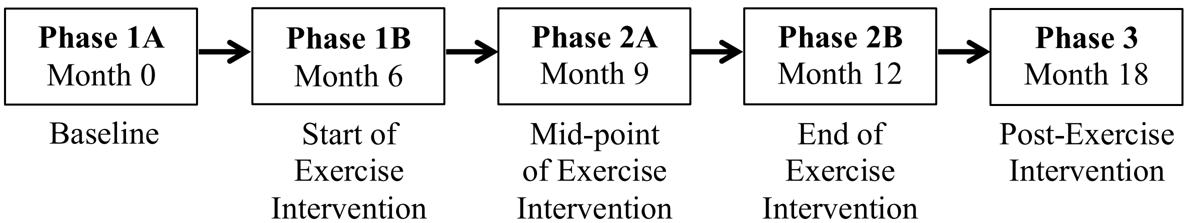
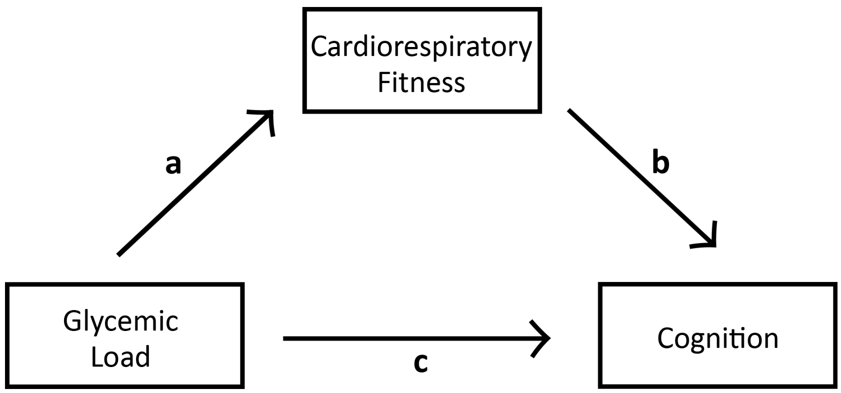
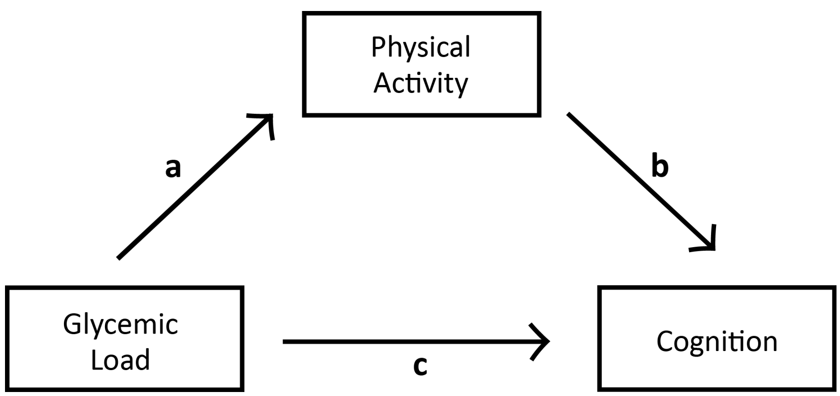


Figure 2. Analytic framework for testing mediation of cardiorespiratory fitness and physical activity in the associations between glycemic load and cognition



Step 1: Linear regression analysis with GL predicting cognition to test for path c
Step 2: Linear regression analysis with GL predicting CRF to test for path a
Step 3: Linear regression analysis with CRF predicting cognition to test for path b
Step 4: Linear regression analysis with GL and CRF predicting cognition



Step 1: Linear regression analysis with GL predicting cognition to test for path c
Step 2: Linear regression analysis with GL predicting PA to test for path a
Step 3: Linear regression analysis with PA predicting cognition to test for path b
Step 4: Linear regression analysis with GL and PA predicting cognition

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All models adjusted for age, sex, NAART, WHR, marital status, and energy intake.
Abbreviations: CRF, cardiorespiratory fitness; GL, glycemic load; NAART, North American Adult Reading Test; PA, physical activity; WHR, waist-to-hip ratio.

Chapter Three: **Manuscript: Association between glycemic load and cognitive function in community-dwelling older adults: results from the *Brain in Motion* study**

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3.1 Preface

Impaired glucoregulation is associated with poorer cognitive function and lower levels of PA and CRF. An effective way of managing blood glucose levels when glucoregulation is an issue is by consuming a low GL diet. GL has been regarded by experts as a valid method of differentiating foods by their glycemic response, and can therefore help individuals with impaired glycemic control. Low GL diets aid in glucoregulation at the gut level by slowing the digestion and absorption of carbohydrates, thereby raising blood glucose more gradually. The effect of GL on cognition may be different in individuals with poor versus good glucoregulation, and CRF and PA could potentially mediate such relations.

This study demonstrates that a low GL diet is associated with better cognitive function in individuals with poor glucoregulation. Moreover, this study found no association between GL and cognition in individuals with good glucoregulation, suggesting the effect of GL on cognition may be limited to those with impaired glycemic control. Lastly, this study found no evidence for mediation by either CRF or PA in the relation between GL and cognition in poor glucoregulatory individuals.

3.2 Declaration

The work outlined in this manuscript was a multi-group collaboration. AG, IC, CMF, TTS, RSL, and MJP conceived the experimental design. Primary supervision for AG was provided by MJP. AG, AVT, LLD, and MHD conducted this research. AG conducted all statistical analyses of the study data, and IC, CMF, TTS, RSL, and MJP advised on the statistical analyses. AG wrote the first draft of the manuscript, and all co-authors contributed to revisions and approved the final version of the manuscript.

3.3 Abstract

Background: Impaired glucose tolerance is a risk factor for non-age-related cognitive decline and is also associated with measures of physical activity (PA) and cardiorespiratory fitness (CRF). A low glycemic load (GL) diet can aid in the management of blood glucose levels, but little is known about its effect on cognition with poor glucoregulation.

Objective: We assessed the relation between GL and cognitive function by glucoregulation and possible mediatory effects by CRF and PA in older adults from the *Brain in Motion Study*.

Design: A cross-sectional analysis of 194 cognitively healthy adults aged ≥55 years (mean=65.7, SD=6.1) was conducted. GL was assessed using a quantitative food frequency questionnaire, and glucoregulation was characterized on the HOMA-IR index. Subjects also completed a cognitive assessment, CRF testing, a validated self-reported PA questionnaire, and a blood draw. Multiple linear regression models adjusted for significant covariates were used to evaluate the relation between GL and cognition, and mediation by CRF and PA was also assessed.

Results: GL was inversely associated with global cognition (β=-0.014; 95% CI -0.024, -0.004) and figural memory (β =-0.035; 95% CI -0.052, -0.018) in subjects with poor glucoregulation. Neither CRF nor PA mediated these relations. In subjects with good glucoregulation, no association was found between GL and cognitive function ($p>0.05$).

Conclusions: A low GL diet is associated with better cognitive function in older adults with poor glucoregulation. This study provides supportive evidence for the role of GL in maintaining better cognitive function during the aging process.

3.4 Introduction

Neuroanatomical and physiological changes that occur as part of the aging process may lead to cognitive decline (1). Declines in some cognitive functions, such as memory and processing speed, are precursors to the diagnosis of neurodegenerative disorders such as Alzheimer's disease, and are public health concerns for the aging population (2). Risk factors associated with poorer cognitive function include impaired glucose tolerance (IGT) (4), unhealthy dietary patterns (5), physical inactivity (6), and low cardiorespiratory fitness (CRF) (7). IGT is characterized by dysregulation of blood glucose levels, which is disadvantageous for the brain, as its primary energy source is glucose (4, 26). Proper glucoregulation is vital in providing energy for better brain function, and controlling blood glucose in those with IGT may promote healthy brain and cognitive aging.

Glucoregulation in IGT individuals has been shown to improve from beneficial lifestyle changes, such as increasing physical activity (PA) levels and improving diet quality (8). Glycemic load (GL), a dietary characterization of the quality and quantity of carbohydrates, can aid in the management of blood glucose levels with IGT (9). High GL can spike postprandial blood glucose that can subsequently fall below preprandial levels. This spike is in contrast to the gradual rise in blood glucose with low GL which can be sustained for a longer duration (10). This latter pattern can elicit cognitive benefits in IGT individuals (26). However, research has been scarce on the associations between low GL diets and cognition (4, 26). Power et al. (36) conducted the first study to examine GL and cognitive function in the elderly and found lower GL to be associated with better cognitive function as measured by the *Mini-Mental State*

Examination (MMSE). Similarly, Simeon et al. (35) found GL to be negatively associated with *Telephone Interview for Cognitive Status* (TICS) score. Although the MMSE and TICS are screening tools for dementia and not cognitive assessments, these findings introduced a novel association of GL and indicators of cognitive disease in an older population.

Low GL may also be associated with CRF and PA, and their effects may be additive on cognition. The glycemic control of type 2 diabetic individuals has been shown to improve following a three-month low GL diet (9), and glucoregulation has been shown to improve with increasing levels of CRF (114) and PA (115, 116). The risk for cognitive dysfunction in IGT is likely to decrease with improved glycemic control, potentially via a low GL diet, improved CRF, and higher PA. Unfortunately, the combination of GL, PA, and CRF has not been studied.

This study is the first to assess the relation between GL and cognitive function with a focus on glucoregulation in older men and women using a comprehensive measure of diet and an extensive cognitive test battery. We hypothesized that lower GL would be associated with higher cognitive function scores, with a stronger association in subjects with poor glucoregulation. In addition, we evaluated mediation by CRF and PA in the relations between GL and cognition in subjects with both good and poor glucoregulation.

3.5 Methods

3.5.1 Study Population

The *Brain in Motion* study is an 18-month long, quasi-experimental study assessing the effect of a six-month aerobic exercise intervention on cerebrovascular regulation and cognitive function in older community-dwelling adults. The study was conducted between May 2010 and April 2016 at the University of Calgary and details of its protocol and methods have been previously published (89). Briefly, the *Brain in Motion* study consisted of three six-month long study periods comprising of pre-exercise, exercise, and post-exercise phases with five individual time points of data collection. Recruitment was carried out via media, poster, and newspaper advertisements at the University of Calgary and surrounding areas. Study participants were English-speaking men and women aged 55-86 years who, at the time of recruitment, were inactive as defined by engaging in less than 30 minutes of moderate exercise four days per week or 20 continuous minutes of vigorous exercise two days per week. Participants were non-smokers for at least 12 months with a BMI of less than 35 kg/m^2, were free of neurological, cardiovascular, cerebrovascular, and obstructive airway diseases, had no history of major surgery or trauma within the past six months, and were deemed able and safe by a study physician to participate in the exercise intervention. Participants were also free of cognitive impairment, as indicated by a score of 24 or greater on the Montreal Cognitive Assessment (90), were able to walk independently and up and down at least 20 stairs, and provided written consent. All study procedures were approved by the University of Calgary Conjoint Health Research Ethics Board. A detailed flow of participants is presented in Figure 3. For this cross-sectional analysis using the data collected at the first time point (pre-exercise month 0), the sample (n=194) is comprised of participants who were administered the cognitive assessment and maximal aerobic capacity test, completed the diet and physical activity questionnaires, and provided a blood sample at baseline.

3.5.2 Dietary Assessment

Dietary intake was measured using the *National Cancer Institute Diet History Questionnaire* (DHQ I) modified for Canadian populations (C-DHQ I) (91). The C-DHQ I is a self-administered quantitative food frequency questionnaire (FFQ) of past-year dietary intake consisting of 146 questions that cover 124 food items and includes portion size and dietary supplements. GL was added to the DHQ I nutrient database using published values (92) as described by Flood et al. (93). The DHQ I was previously validated against biomarkers for energy and protein intake in an adult population in the United States (94). The C-DHQ I food list has been evaluated against dietary intake data collected in a large population-based Canadian survey and demonstrated to be representative of food intake in Canada (95). The C-DHQ I nutrient database has been modified to reflect the Canadian Nutrient File version 2001b (96) and Diet*Calc software (Version 1.4.3, National Cancer Institute, 2005) was used to analyze C-DHQ I responses and generate nutrient estimates.

3.5.3 Cognitive Assessment

A two hour-long cognitive test battery adapted from the previously published *Brain in Motion* study protocol was used to assess cognitive function (89). Trained staff administered the cognitive assessment comprising of seven tasks evaluating six cognitive domains. The battery included the *Color Word Interference*, *Card Sorting*, and *Verbal Fluency* tasks of the *Delis-Kaplan Executive Function System*, *Symbol-Digit Modalities Test*, *Buschke Selective Reminding*, *Medical College of Georgia Complex Figure*, and *Auditory Consonant Trigrams*. Cognitive domains were determined using confirmatory factor analysis in which each factor needed to meet a threshold of 0.4 for inclusion in the structure. Six cognitive domains were derived: concept formation, executive processing speed/inhibition, verbal memory, verbal fluency, figural memory, and complex attention (Table 10). Z-scores were computed from raw scores and averaged for tasks within each of the six cognitive domains. A global cognition score was computed as the average of the six cognitive domain z-scores. Participants who had a missing score in any task, due to inability or refusal to complete the task, were excluded from computation of the task's associated cognitive domain z-score and subsequent global cognition z-score (n=4).

3.5.4 Assessment of Glucoregulation

A 12-hour fasted blood sample was taken by a study nurse and analyzed by Calgary Laboratory Services, Calgary, AB, Canada. Blood profile measures obtained include cholesterol, HDL, LDL, triglycerides, glucose, and insulin. Glucoregulation was assessed using HOMA-IR, a validated measure of insulin resistance in both normal and diabetic individuals that is extensively used in epidemiological studies (102, 103). HOMA-IR was estimated using participants' fasting glucose and fasting insulin concentrations using the equation defined by Matthews et al. (104):

$$\text{HOMA-IR} = \frac{\text{fasting glucose (mmol/L)} * 0.144 \text{ (unit conversion)} * \text{fasting insulin (pmol/L)}}{22.5}$$

The top 25% of the sample (HOMA-IR>2.35) was classified as having worse glucoregulation and the remaining 75% (HOMA-IR≤2.35) as having good glucoregulation. This method is standard practice since there are no universally established cut-offs for classifying insulin resistance on the HOMA-IR scale (105). Our HOMA-IR cut-off of 2.35 is within the range of threshold values reported by larger studies of various populations (106), suggesting an appropriate classification of our poor glucoregulation group.

3.5.5 Assessment of Covariates

3.5.5.1 Demographics

Participants provided age, sex, marital status, education, retirement status, household income, and smoking history during onsite screening. Overall intellectual level was measured using the *North American Adult Reading Test* (NAART). The NAART has been validated as a reliable measure of verbal intelligence, which is highly correlated with overall intellectual level, and used as a better measure of intelligence than reported education (101).

3.5.5.2 Past 12-month Physical Activity

Past year PA was assessed using the *Lifetime Total Physical Activity Questionnaire* (LTPAQ), which is an interview-administered questionnaire that measures all domains of PA (occupational, household, and recreational), all parameters of activity (frequency, intensity, and duration) from childhood to the time of the interview that has been previously assessed as a reliable measure of total lifetime PA (97). Activities performed within the past 12 months were extracted from this questionnaire and used for this particular study. Intensities of the reported activities were assigned a metabolic equivalent (MET) value according to the *Compendium of Physical Activities* (98). These data were combined to create the total PA variable expressed as MET-hours/week done in the previous 12 months.

3.5.5.3 Cardiorespiratory Fitness

Relative $\dot{V}O_2$max (ml/kg/min) was used as an assessment of CRF and measured with the administration of a maximal aerobic capacity ($\dot{V}O_2$max) test. $\dot{V}O_2$max tests have been determined to be valid and reliable measures of maximum rate of oxygen consumption, which is a strong predictor of CRF (99). The test was conducted on a motorized treadmill, which increased in incline and speed following the Bruce protocol (100). Participants were attached to a breathing monitoring system and tested until maximal oxygen consumption was reached, defined as a steady rate of oxygen consumption despite an increase in workload (100). Blood pressure measurements were manually taken at rest and during exercise. Anthropometric measurements of height, weight, waist and hip circumference, and body fat percentage were taken prior to beginning the $\dot{V}O_2$max test.

3.5.6 Statistical Analysis

All statistical analyses were performed using Stata/IC version 13.1 (StataCorp, 2013). The study sample characteristics were first assessed with descriptive statistics. Between group differences (good versus poor glucoregulation) were analyzed with t-tests for continuous variables and chi square/Fisher's exact tests for categorical variables.

The distribution of total energy intake was right-skewed and a natural logarithm transformation was applied which normally distributed the variable. Log-transformed estimated energy intakes that fell outside two interquartile ranges from the first and third quartile cut-offs were identified as extreme outliers and removed as described by Kipnis et al. (108). One extreme outlier (energy intake= 342.7 kcal) was identified and the subject's dietary data were excluded from further analyses. This left 189 participants in the final analysis.

Collinearity among covariates was first assessed with Spearman's correlations, ANOVA, and chi square tests. A decision was made on which variable would be considered during the modeling process for highly correlated continuous variables and highly associated categorical variables. As such, covariates considered were: age, sex, marital status, NAART, body fat (%), waist-to-hip (WHR) ratio, smoking status (ever smoked versus never smoked), alcohol consumption (g/day), caffeine intake (mg/day), LDL (mmol/L), HDL (mmol/L), mean arterial pressure (MAP) (mmHg), $\dot{V}O_2max$ (ml/kg/min), and total past-year PA (MET-hr/wk). GL was adjusted for energy intake using the nutrient density method (109) and expressed in units of GL/1000 kcal. In addition, residual confounding of total energy intake (log kcal/day) was evaluated during modeling by determining its impact on the GL regression coefficient. Total energy intake was retained in the model if a change of ≥15% was observed in the coefficient.

Multiple linear regression models adjusted for significant covariates were used to evaluate the relation between GL and cognition by glucoregulation. Covariates were included in the model if their addition generated a ≥15% change in the regression coefficient of GL and improved the coefficient of determination (adjusted R^2). Stepwise regression modeling was performed using backward elimination and two-way and three-way covariate interactions were considered. Final models adjusted for age, sex, NAART, WHR, marital status, and energy intake. Bootstrapped estimates of the standard errors run with 1000 replications were used to minimize the effect of influential observations. Linear regression assumptions were evaluated for validity of the final models using histograms, Q-Q plots, and the Shapiro-Wilk test (107) to assess normality of the residuals, residual-versus-fitted plots, Breusch-Pagan (111), and Cook-Weisberg (112) tests to assess homoscedasticity, variance inflation factors to assess multicollinearity (<10), and scatter plots to assess for a linear relation between independent and dependent variables. Mediation by CRF and PA was evaluated using the four-step regression approach proposed by Baron and Kenny (1986) (113). Statistical significance of an estimate was fixed at $p<0.05$.

3.6 Results

Characteristics of the study sample are presented in Table 5. Participants had a mean age of 65.7±6.1 years, 52.6% were female, with a moderate to high socioeconomic status on average, and 56.2% were retired. A total of 77.3% of the participants were married with a higher proportion in the good glucoregulation group. The poor glucoregulation group had a higher mean weight, BMI, waist and hip circumference, WHR, triglycerides, total-to-HDL cholesterol ratio, and lower mean HDL. By design, the poor glucoregulation group had higher mean fasting glucose, fasting insulin, and HOMA-IR index score.

Summary measures of dietary intake, CRF, and PA of the participants are presented in Table 6. On average, the poor glucoregulation group had a higher total caloric and fat intake, but differences in other dietary variables were not observed. However, a lower GL was borderline statistically significant for the good glucoregulation group ($p=0.06$). The good glucoregulation group was fitter than the poor glucoregulation group with lower resting systolic blood pressure, MAP, resting heart rate, and higher $\dot{V}O_2max$. Participants' raw cognitive assessment scores by each administered task are presented in Table 7. No group differences were observed on any cognitive task. In addition, four participants had incomplete cognitive assessment data because of their inability or refusal to complete at least one task. The z-score of the cognitive domain evaluated by the task was not estimated because of a missing score, therefore, these subjects also had a missing global cognition z-score. Consequently, 142 and 47 observations in the better and poor glucoregulation groups, respectively, were used in regression analyses.

Table 8 provides a summary of the multivariate linear regression analyses on global cognition. In both the good and poor glucoregulation groups, being older was associated with poorer global cognition, with a decrease of 0.023 and 0.046, respectively, in the global cognition z-score for every year increase in age ($p<0.001$ for both). Both subgroups also showed a positive association between intellectual level, indicated by NAART score, and global cognition ($p<0.001$ for both). Moreover, being married was associated with better global cognition in the good glucoregulation group ($\beta=-0.088$; $p=0.01$). The primary exposure of interest, GL, was found to be statistically significant in the poor glucoregulation group, but not in the good glucoregulation group. In the poor glucoregulation group, lower GL was associated with better global cognition, demonstrating an increase of 0.14 in global cognition z-score with a decrease in every 10 GL/1000 kcal, while maintaining total energy intake ($p=0.008$). The level of statistical significance increased when bootstrapping was used to estimate the SEE ($p=0.008$ versus $p=0.014$), demonstrating robustness of the regression coefficient of GL. The partially adjusted model, accounting for age, sex, GL, and caloric intake, explained 16.1% and 35.9% of the variance (adjusted R^2) in global cognition z-scores in the good and poor glucoregulation groups, respectively. The fully adjusted models, with inclusion of NAART, WHR, and marital status, increased the adjusted R^2 in the good and poor glucoregulation groups to 30.6% and 47.8%, respectively.

Linear regression models assessing the separate relations between GL and six cognitive domains in the two subgroups with adjustment for age, sex, NAART, WHR, marital status, and energy intake are presented in Table 9. A negative association between GL and figural memory was found in the poor glucoregulation group. The model revealed for every 10 unit increase in GL/1000 kcal, while keeping total energy intake constant, there would be a 0.035 decrease in figural memory z-score ($p<0.001$). A total of 35.2% of the variance in figural memory z-scores was explained by this model. We did not find a relation between GL and the remaining cognitive domains for the poor glucoregulation group and no relation for the good glucoregulation group.

Further, we explored the statistical relations between GL, figural memory, and global cognition in the poor glucoregulation group with a series of analyses that examined any mediatory effects, if present, by CRF and PA. Lower GL was associated with higher past-year PA (β=-1.50; 95% CI -2.75, -0.26) (model not shown), but past-year PA did not mediate the association between GL and global cognition. Null results were also obtained in the assessment of mediation by PA between GL and figural memory. Moreover, no association was found between GL and CRF, thereby negating mediation by CRF between GL and the two cognitive measures.

3.7 Discussion

We found lower GL to be positively associated with global cognition and figural memory in individuals with poor glucoregulation. These results are consistent with previous epidemiologic research that found associations between consuming a diet characterized by a lower GL and better cognitive functioning in an older population (34-36). However, no previous study has assessed the association between GL and cognition comparing non-diabetic older adults with good *versus* poor glucoregulation. Our study suggests the effect of GL on cognition may be limited to individuals who have poor glucoregulation.

Our results are biologically plausible, since glucose is the primary energy source of the brain, and impairments in glycemic control have been shown to impact cognitive function negatively (4). Individuals with poor glucoregulation experience greater fluctuations in blood glucose levels than those with good glucoregulation (117). The difference in glucoregulation between individuals with poor and good glucoregulation is the blunted clearance of glucose from blood into tissue because of pancreatic beta cell dysfunction (impaired insulin release) and/or insulin resistance at the level of the tissue (4). Insulin also acts as a vasodilator to enhance glucose delivery to tissues (118). This function is weakened in individuals with impaired glucoregulation, resulting in decreased tissue perfusion that can lead to tissue atrophy (119). Impairments in glucose metabolism are strongly associated with brain atrophy (120-122) and reduced hippocampal volumes (123, 124), both of which are correlated with cognitive dysfunction or decline (125, 126).

Moreover, endothelial dysfunction is present in impaired glucoregulatory and type 2 diabetic individuals (127), and is associated with impairments in cognitive function (128). Elevated blood glucose levels cause vascular damage through several mechanisms including increases in oxidative stress, decreases in nitric oxide bioavailability, and formation of advanced glycation end products, all of which contribute to inflammation (129). Chronic inflammation is associated with neurodegenerative disorders and increases risk of cognitive dysfunction (130). Hence, well-regulated blood glucose levels are integral for proper brain and cognitive function (26).

A low GL diet provides a manner in which individuals with poor glucoregulation can aid in the regulation of blood glucose at the gut level. Low GL foods contain complex carbohydrates that take longer to digest, resulting in the gradual rise of blood glucose levels (10). Previous studies that have investigated the effect of test meals with varying GL found higher cognitive performance in subjects following a lower GL meal compared to a higher GL meal (30-32), yet one study found no differences between test meals (29). However, it is probable that consistent consumption of a low GL diet by individuals with poorer glucoregulation can reduce blood glucose fluctuations and subsequently reduce risk of cognitive decline in this population.

Learning and memory are thought to be most susceptible to metabolic brain disorders (131). As such, the cognitive domain of memory would likely be the first to be affected by chronic impairments in glucoregulation. Willette et al. (132) found HOMA-IR to be negatively associated with glucose metabolism in large regions of the frontal, parietal, and temporal lobes in older adults with a risk of Alzheimer's disease. These investigators also found HOMA-IR to be predicted by left medial temporal lobe glucose metabolism, which was negatively associated with memory performance (132). Moreover, glycemic control and blood glucose levels were found to be positively associated with memory performance in non-diabetic older individuals with the former relation being partly mediated by hippocampal volume and microstructure (133). While our analyses revealed a significant inverse association between GL and figural memory in the poor glucoregulation group, we found no evidence or trend for an association with verbal memory. This result may suggest that figural memory is more susceptible to consequences of impairments in blood glucose regulation.

Our study found a 0.14 SD increase in global cognition for every 10 GL/1000 kcal decrease in individuals with poor glucoregulation. A meta-analysis of GL on parameters of obesity reported daily dietary GL of 14 studies ranged from 75 to 280 (134). As such, the alteration of diet composition to elicit a change of 10 GL/1000 kcal is feasible. Furthermore, the clinical relevance of a 0.14 SD increase in global cognition is a significant reduction in cognitive decline risk. Kaffashian et al. (135) reported dementia risk was associated with a 0.03 SD decline in global cognition over 10 years. In addition, Rawlings et al. (136) found a 0.15 SD greater decline in global cognition over 20 years in diabetic compared to non-diabetics individuals. An increase in global cognition of 0.14 SD could have great clinical importance, but a longitudinal study would be more appropriate in evaluating the effect of GL on cognitive decline.

We observed a null finding in the mediation of CRF and PA in the significant relations of GL and cognition. Evidence of mediation requires CRF and PA to be separately associated with GL, which we did not observe. It is likely that diet quality and measures of physical fitness and activity are not strongly correlated in older adults. Instead, GL, CRF, and PA may elicit a synergistic, rather than a mediatory, effect on cognition in this population.

A notable strength of this study was our comprehensive cognitive battery that captured six cognitive domains as well as global cognition. The cognitive assessment was administered in-person by trained psychometricians, and our measures of cognition used validated tests that were designed to provide extensive and reliable cognitive scores. Moreover, a wide range of exposure and outcome data were collected from participants of the *Brain in Motion* study, allowing us to investigate the effect of numerous covariates on the relation between glucoregulation and cognitive function in our analyses. Our study design was also unique in combining physiologic measures with the cognitive assessment. The quality of our cognitive variables and full assessment of covariates provided strength to our data collection, analyses, and conclusions.

Limitations of the study were that participants were predominantly Caucasian, well-educated, and with a middle to high socioeconomic status. This mostly homogenous volunteer and relatively small sample limits the generalizability of our results to a broader group of older adults. Despite having only 49 subjects in the poor glucoregulation group, we observed a strong association when we used bootstrapping to estimate the standard errors, which allowed us to address the issues in our analysis related to the small sample size.

Another limitation of this study is the use of self-reported measure of diet. FFQs are prone to underestimate dietary intake, but are an important tool in assessing overall habitual intake. GL has been regarded by experts as a valid method of differentiating foods by their glycemic response, and the best predictor of the glycemic response is GL/1000 kcal (137). However, the evaluation of GL must always be considered in the context of overall diet (137), hence the use of the C-DHQ I was necessary for the aim of our study.

Lastly, our cross-sectional design is a limitation to making inferences about causal relations. A prospective longitudinal study with multiple time points of data collection or a randomized control trial would be more appropriate in evaluating causal relations.

In conclusion, our results suggest the importance of a lower GL diet on cognitive function in older adults that may be limited to those with poor glucoregulation. Further research is needed to explore possible causal relations between GL and cognition in an older population with poorer glucoregulation. Since glucoregulation has been shown to improve when diet (8) in IGT individuals is modified, improvements in glucoregulation may mediate the relation between lower GL and better cognitive function in this population. A study with a more sensitive measure of longer-term glucoregulation, such as glycated hemoglobin (HbA_{1c}), could also be used to strengthen results.

3.8 Acknowledgements

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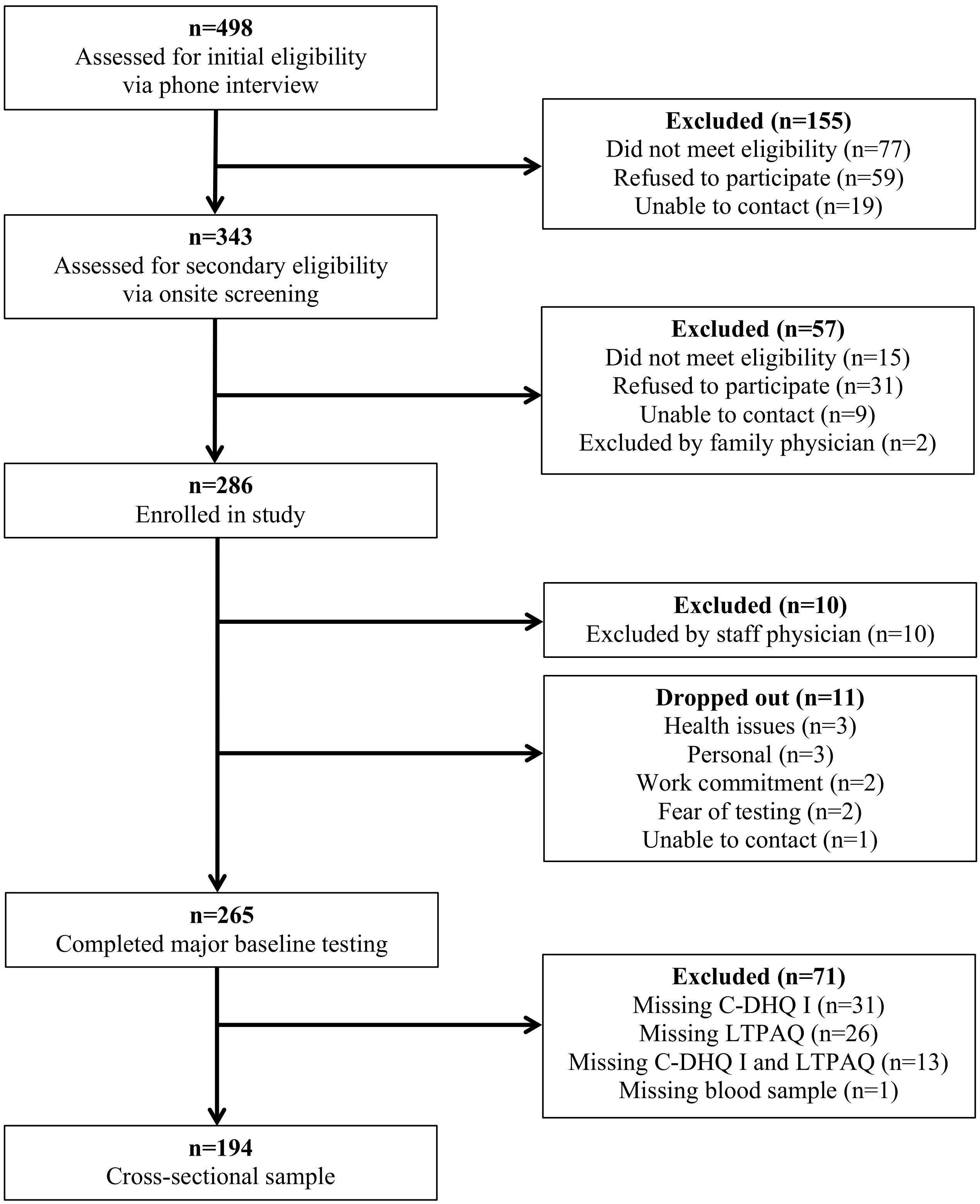
3.9 Chapter Three Figures and Tables

Figure 3. Participant flowchart



Abbreviations: C-DHQ I, National Cancer Institute Diet History Questionnaire modified for Canadian Populations; LTPAQ, Lifetime Total Physical Activity Questionnaire.

Table 4. Characteristics and descriptive statistics of the study participants, cross-sectional sample from the *Brain in Motion* study, Alberta, Canada, 2010-2016, n=194

Characteristic	Total n=194		Good glucoregulation n=145		Poor glucoregulation n=49		
	n	$\bar{x}$(SD)/%	n	$\bar{x}$(SD)/%	n	$\bar{x}$(SD)/%	P-value[1]
Socio-Demographics							
Sex (M/F)	194	92/102	145	64/81	49	28/21	0.12
Age (years)	194	65.7(6.1)	145	65.6(6.3)	49	66.1(5.8)	0.61
Marital Status (%)	194		145		49		
Married	150	77.3	120	82.7	30	61.2	<0.01
Divorced	19	9.8	12	8.3	7	14.3	
Widowed	10	5.2	4	2.8	6	12.3	
Single	5	2.5	4	2.8	1	2.0	
Other	10	5.2	5	3.4	5	10.2	
Education Level (%)	194		145		49		
Secondary School or less	42	21.6	34	23.4	8	16.3	0.35
College/University Degree	109	56.2	82	56.6	27	55.1	
Graduate Degree	43	22.2	29	20.0	14	28.6	
Education (years)	193	15.9(2.5)	144	15.7(2.5)	49	16.4(2.7)	0.13
Retirement Status (%)	194		145		49		
Retired	109	56.2	81	55.9	28	57.1	0.30
Semi-retired	25	12.9	16	11.0	9	18.4	
Not Retired	60	30.9	48	33.1	12	24.5	
Household Income (%)	191		142		49		
$20,000 to $59,999	54	28.3	36	25.4	18	36.7	0.06
$60,000 to $99,999	47	24.6	38	26.8	9	18.4	
$100,000 to $139,999	48	25.1	31	21.8	17	34.7	
$140,000 to $179,999	15	7.9	13	9.2	2	4.1	
Over $180,000	27	14.1	24	16.9	3	6.1	
Premorbid Intelligence							
NAART	194	110.6(6.3)	145	110.3(6.4)	49	111.5(6.1)	0.26
Anthropometrics							
Weight (kg)	194	78.5(14.6)	145	75.6(13.4)	49	87.2(14.8)	<0.001
BMI (kg/m^2)	194	27.3(3.8)	145	26.4(3.3)	49	29.9(3.7)	<0.001
Body Fat (%)	194	32.4(7.2)	145	31.8(7.2)	49	34.0(7.2)	0.07
Waist Circumference (cm)	194	96.7(12.2)	145	93.6(11.0)	49	105.8(10.9)	<0.001
Hip Circumference (cm)	194	102.6(8.4)	145	100.9(7.5)	49	107.6(9.0)	<0.001
WHR	194	0.94(0.08)	145	0.93(0.08)	49	0.98(0.07)	<0.001
Substance Abuse							
Smoking Status (%)	194		145		49		
Ever Smoked	89	45.9	64	44.1	25	49.0	0.40
Never Smoked	105	54.1	81	55.9	24	51.0	
Alcohol Consumption (g/day)	193	11.5(16.6)	144	9.8(13.2)	49	16.4(23.3)	0.02

Blood Profile							
Lipids (mmol/L)							
Cholesterol	194	5.3(0.9)	145	5.3(0.9)	49	5.1(1.06)	0.24
HDL	194	1.6(0.5)	145	1.7(0.5)	49	1.3(0.4)	<0.001
LDL	194	3.1(0.8)	145	3.1(0.7)	49	3.1(1.0)	0.86
Total-to-HDL Ratio	194	3.6(1.1)	145	3.4(0.9)	49	4.1(1.2)	<0.001
Triglycerides	194	1.3(0.6)	145	1.2(0.5)	49	1.7(0.7)	<0.001
Glucoregulation							
Fasting Glucose (mmol/L)	194	5.5(0.7)	145	5.3(0.5)	49	6.1(0.9)	<0.001
Fasting Insulin (pmol/L)	194	57.6(40.8)	145	41.9(13.9)	49	104.1(56.2)	<0.001
HOMA-IR (index score)	194	2.1(1.8)	145	1.4(0.5)	49	4.1(2.6)	<0.001

[1]P-values from statistical tests comparing between glucoregulation group differences using t-tests for continuous variables and chi square/Fisher's exact tests for categorical variables.
Abbreviations: NAART, North American Adult Reading Test; WHR, waist-to-hip ratio; $\bar{x}$, sample mean.

Table 5. Summary measures of diet, cardiorespiratory fitness, and physical activity in the study population from *Brain in Motion* study

	Total n=194		Good glucoregulation n=145		Poor glucoregulation n=49		
Variable	**n**	**$\bar{x}$(SD)/%**	**n**	**$\bar{x}$(SD)/%**	**n**	**$\bar{x}$(SD)/%**	**P-value[1]**
Diet (daily means)							
Glycemic Load (GL units)	193	88.3(34.1)	144	85.6(32.8)	49	96.4(36.9)	0.06
Caloric Intake (kcal)	193	1613.2(617.1)	144	1548.7(591.7)	49	1802.6(656.6)	0.01
Total fat (g)	193	61.1(29.9)	144	57.8(28.6)	49	71.0(31.7)	0.01
Carbohydrates (g)	193	191.2(70.9)	144	187.3(70.1)	49	202.4(72.8)	0.20
Fiber (g)	193	18.8(7.8)	144	19.1(8.3)	49	17.9(6.2)	0.33
Protein (g)	193	66.0(29.1)	144	64.2(27.5)	49	71.2(33.0)	0.15
Caffeine (mg)	193	435.0(334.4)	144	424.4(335.3)	49	466.3(333.3)	0.45
Cardiorespiratory Fitness							
Blood Pressure (mmHg)							
Resting Systolic	194	129.3(13.5)	145	127.7(13.4)	49	134.3(12.5)	<0.01
Resting Diastolic	194	77.8(8.3)	145	77.2(8.3)	49	79.8(7.8)	0.05
Resting MAP	194	95.0(9.0)	145	94.1(9.1)	49	98.0(8.0)	<0.01
Heart Rate (beats/min)							
Resting	194	72.4(10.6)	145	71.0(9.7)	49	76.7(12.0)	<0.01
Maximum	194	155.5(14.5)	145	156.3(15.5)	49	153.0(10.8)	0.17
$\dot{V}O_2$max (ml/kg/min)	194	26.1(5.5)	145	26.7(5.6)	49	24.4(4.7)	0.01
RER	194	1.17(0.09)	145	1.17(0.09)	49	1.15(0.08)	0.27
Past-Year Physical Activity							
Total MET-hr/wk	194	85.8(52.4)	145	89.7(54.1)	49	74.2(45.4)	0.07

[1]P-values from t-tests comparing between glucoregulation group differences.
Abbreviations: MAP, mean arterial pressure; MET, metabolic equivalent; RER, respiratory exchange ratio; $\dot{V}O_2$max, maximal aerobic capacity; $\bar{x}$, sample mean.

Table 6. Study participants' cognitive assessment scores

	Total n=194		Good glucoregulation n=145		Poor glucoregulation n=49		
Cognitive Assessment Task	**n**	**$\bar{x}$(SD)**	**n**	**$\bar{x}$(SD)**	**n**	**$\bar{x}$(SD)**	**P-value[1]**
Executive Function: Processing Speed and Inhibition							
Symbol-Digit Modalities Test: Written Score	194	48.8(8.0)	145	48.2(7.9)	49	50.4(8.1)	0.10
Symbol-Digit Modalities Test: Oral Score	194	55.9(9.5)	145	55.3(9.2)	49	57.5(10.1)	0.15
D-KEFS Color Word Interference: Color Reading Time	192	30.7(5.5)	144	30.9(5.8)	48	30.3(4.5)	0.51
D-KEFS Color Word Interference: Word Reading Time	192	22.6(3.7)	144	22.6(4.6)	48	22.6(3.7)	0.96
D-KEFS Color Word Interference: Switching Time	192	64.1(16.3)	144	63.8(16.8)	48	65.1(15.1)	0.65
D-KEFS Color Word Interference: Inhibition Time	192	60.1(12.2)	144	60.0(12.4)	48	60.6(11.7)	0.76
Executive Function: Concept Formation							
D-KEFS Card Sorting: Number of Correct Sorts	194	4.8(1.5)	145	4.8(1.5)	49	5.1(1.5)	0.20
D-KEFS Card Sorting: Free Sorting Description Score	194	18.3(6.2)	145	18.1(6.2)	49	18.8(6.3)	0.49
D-KEFS Card Sorting: Recognition Description Score	194	17.5(6.5)	145	17.5(6.1)	49	17.4(7.7)	0.91
Verbal Memory							
Buschke Selective Reminding: Total Score	194	47.7(7.2)	145	47.7(6.9)	49	47.9(8.2)	0.89
Buschke Selective Reminding: Delayed Recall Score	194	8.0(2.3)	145	8.0(2.3)	49	8.0(2.3)	0.88
Buschke Selective Reminding: Cued Recall Score	193	9.0(1.8)	145	9.0(1.8)	48	9.0(1.8)	0.96
Verbal Fluency							
D-KEFS Verbal Fluency: Letter Fluency Score	194	42.6(11.5)	145	43.0(11.6)	49	41.3(11.1)	0.37
D-KEFS Verbal Fluency: Category Fluency Score	194	41.3(7.5)	145	41.6(6.9)	49	40.2(9.0)	0.26
D-KEFS Verbal Fluency: Category Switching Score	194	14.5(2.5)	145	14.7(2.5)	49	13.9(2.6)	0.05
Figural Memory							
MCG Complex Figure: Immediate Recall	194	28.0(5.8)	145	27.7(6.0)	49	28.9(5.0)	0.24
MCG Complex Figure: Delayed Recall	194	27.5(5.9)	145	27.2(6.1)	49	28.2(5.4)	0.33
Complex Attention							
Auditory Consonant Trigrams: Total Correct Score	193	48.3(5.9)	144	48.3(5.8)	49	48.3(6.0)	0.97
Auditory Consonant Trigrams: Perseverations Score	193	6.6(4.0)	144	6.5(3.9)	49	6.9(4.5)	0.61

[1]P-values from t-tests comparing between glucoregulation group differences.

Abbreviations: D-KEFS, Delis-Kaplan Executive Function System; MCG, Medical College of Georgia; $\bar{x}$, sample mean.

Table 7. Summary of the final models for multivariate linear regression analyses on global cognition by glucoregulation status

Variable	Age-, Sex- and Caloric Intake-Adjusted Model				Fully Adjusted Model			
	β[1] (SEE)	95% CI	P-value	Adj. R^2	β[1] (SEE)	95% CI	P-value	Adj. R^2
Good glucoregulation (n=142)								
Glycemic Load (GL/1000 kcal)	0.004 (0.004)	-0.003, 0.011	0.22	16.1%	0.003 (0.003)	-0.004, 0.010	0.38	30.6%
Age	-0.022 (0.006)	-0.033, -0.011	<0.001		-0.023 (0.006)	-0.034, -0.012	<0.001	
Sex[2]	0.22 (0.07)	0.09, 0.36	0.001		0.16 (0.10)	-0.04, 0.35	0.11	
Log (Caloric Intake)	0.20 (0.11)	-0.01, 0.41	0.06		0.16 (0.10)	-0.03, 0.35	0.09	
NAART					0.025 (0.005)	0.015, 0.036	<0.001	
WHR					-0.41 (0.58)	-1.54, 0.72	0.48	
Marital Status[3]					-0.088 (0.035)	-0.157, -0.019	0.01	
Constant	-0.42 (0.92)	-2.22, 1.38	0.65		-2.19 (1.30)	-4.74, 0.36	0.09	
Poor glucoregulation (n=47)								
Glycemic Load (GL/1000 kcal)	-0.017 (0.005)	-0.027, -0.006	0.002	35.9%	-0.014 (0.005)	-0.024, -0.004	0.008	47.8%
Age	-0.047 (0.010)	-0.067, -0.027	<0.001		-0.046 (0.010)	-0.065, -0.026	<0.001	
Sex[2]	-0.03 (0.12)	-0.26, 0.21	0.81		0.05 (0.15)	-0.25, 0.35	0.75	
NAART					0.034 (0.008)	0.017, 0.050	<0.001	
WHR					-0.004 (1.44)	-2.82, 2.82	0.99	
Marital Status[3]					-0.039 (0.042)	-0.12, 0.04	0.35	
Constant	4.09 (0.83)	2.47, 5.72	<0.001		0.09 (2.07)	-3.98, 4.15	0.97	

[1]Regression coefficients interpreted as the change in global cognition z-score for every unit increase in the variable.
[2]Sex variable coded as 0, male; 1, female.
[3]Marital status variable coded as 1, married; 2, widowed; 3, divorced; 4, single; 5, other.
Abbreviations: Adj., adjusted; NAART, North American Adult Reading Test; WHR, waist-to-hip ratio.

Table 8. Summary of multivariate linear regression models between glycemic load and 6 cognitive domains by glucoregulation

Outcome Variable	n	β[1] (SEE)	95% CI	P-value	Adjusted R^2
Good glucoregulation					
Executive Function: Processing Speed and Inhibition	143	0.00002 (0.008)	-0.015, 0.015	0.99	17.7%
Executive Function: Concept Formation	144	0.003 (0.008)	-0.012, 0.018	0.69	16.1%
Verbal Memory	144	0.003 (0.007)	-0.011, 0.017	0.67	19.8%
Verbal Fluency	144	0.001 (0.006)	-0.011, 0.013	0.89	17.9%
Figural Memory	144	0.012 (0.009)	-0.006, 0.029	0.19	3.9%
Complex Attention	143	-0.003 (0.002)	-0.007, 0.001	0.19	3.1%
Poor glucoregulation					
Executive Function: Processing Speed and Inhibition	48	-0.014 (0.011)	-0.036, 0.009	0.23	40.5%
Executive Function: Concept Formation	49	-0.012 (0.012)	-0.036, 0.012	0.33	14.6%
Verbal Memory	48	0.003 (0.013)	-0.022, 0.027	0.84	20.8%
Verbal Fluency	49	-0.014 (0.011)	-0.036, 0.008	0.22	25.6%
Figural Memory	49	-0.035 (0.009)	-0.052, -0.018	<0.001	35.2%
Complex Attention	49	-0.004 (0.006)	-0.015, 0.008	0.53	0.1%

All models adjusted for age, sex, NAART, WHR, marital status, and energy intake.
[1]Regression coefficients interpreted as the change in the cognitive domain z-score for every 1 GL unit increase.

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Table 9. Summary of cognitive domains assessed and corresponding tasks administered for the cognitive assessment

Cognitive Domain	Cognitive Assessment Task	Test Description
Executive Function: Processing Speed and Inhibition	*Symbol-Digit Modalities Test*	Simple substitution task pairing specific numbers with given geometric figures. Administered in written and oral forms for 90 seconds each.
	D-KEFS[1] *Color Word Interference*	Subject is presented a Stroop effect worksheet and asked to orally complete the task following 4 rules separately.
Executive Function: Concept Formation	*D-KEFS Card Sorting*	Subject performs 2 tasks: free-sorting of a card set into categories and recognizing categories card set was sorted into by test administrator.
Verbal Memory	*Buschke Selective Reminding*	Subject is read 12 unrelated words and asked to perform 4 tasks: 1. Memory test: learning of words rehearsed for 6 trials 2. Cued recall 3. Multiple choice recognition 4. Oral delayed recall 30 minutes after task 3
Verbal Fluency	*D-KEFS Verbal Fluency*	Subject is presented 3 conditions separately and asked to say as many words that meet the condition in 60 seconds.
Figural Memory	*Medical College of Georgia Complex Figure*	Subject is given a complex figure and instructed to perform 3 tasks: copy the figure, draw it from memory immediately, and then again after 30 minutes.
Complex Attention	*Auditory Consonant Trigrams*	Subject hears 3 consonants followed by a number and is instructed to subtract from that number for several seconds and then asked to recall the letters.

[1]Delis-Kaplan Executive Function System

Chapter Four: **Additional Analyses**

4.1 Testing Age Effects on Regression Analyses

To compare the effect of age on global cognition by glucoregulation, multiple linear regression analyses were performed on the good glucoregulation group, poor glucoregulation group, and total study sample (Table 10). Models were adjusted for age, sex, NAART, WHR, marital status, GL, and energy intake. Regression results for the poor and good glucoregulation groups were previously reported in Chapter Three (Table 7). The regression coefficient of age for the total sample was -0.026 (95% CI -0.036, -0.016), which was similar to that of the good glucoregulation group (β=-0.023; 95% CI -0.034, -0.012). In the poor glucoregulation group, age had a stronger negative association with global cognition (β=-0.046; 95% CI -0.065, -0.026). The confidence intervals for the poor and good glucoregulation groups do not overlap at the point estimates, which provides evidence that the two regression coefficients of age are significantly different from each other. These results show that increased age is associated with poorer global cognition and that individuals with poor glucoregulation show poorer global cognition with age compared to those with good glucoregulation.

4.2 Other Glucoregulation Indices

4.2.1 QUICKI and FIRI Classification

Glucoregulation was additionally assessed using the Quantitative Insulin Sensitivity Check Index (QUICKI) (138) and the Fasting Insulin Resistance Index (FIRI) (139). Like HOMA-IR, QUICKI and FIRI provide an estimate of glucoregulation using fasting glucose and fasting insulin concentrations. QUICKI and FIRI have been shown to be well correlated (r=0.82 and r=-0.82, respectively) with measures of IR obtained from hyperinsulinemic euglycemic glucose clamp, which is the gold standard measure of IR (140).

QUICKI was calculated using the equation defined by Katz et al. (138):

$$\text{QUICKI} = \frac{1}{\log(\text{fasting glucose (mmol/L)}/0.0555 \text{ (unit conversion)}) + \log(\text{fasting insulin (pmol/L)} * 0.144 \text{ (unit conversion)})}$$

A threshold value of 0.339 on the QUICKI scale was used to dichotomize the study sample into good and poor glucoregulation groups. This threshold value falls in between QUICKI values reported for healthy adults ($\bar{x}$=0.366±0.029) and adults with T2DM or glucose intolerance ($\bar{x}$=0.310±0.040) (141), and was used as a cut-off value to classify IR by other studies (142, 143). As such, individuals were classified as having poor glucoregulation if QUICKI≤0.339 or as having good glucoregulation if QUICKI>0.339. This threshold value resulted in dichotomizing the study sample at the 31st percentile on the QUICKI scale.

FIRI was calculated using the equation defined by Duncan et al. (139):

$$\text{FIRI} = \frac{\text{fasting glucose (mmol/L)} * 0.144 \text{ (unit conversion)} * \text{fasting insulin (pmol/L)}}{25}$$

Based on upper limits of normal for fasting glucose and fasting insulin concentrations of 6.1 mmol/L and 11.2 mU/L, respectively, the threshold value of 2.7 on the FIRI scale was used to dichotomize the study sample into good and poor glucoregulation groups (144). As such, individuals were classified as having worse glucoregulation if FIRI≥2.7 or as having good glucoregulation if FIRI<2.7. This threshold value resulted in dichotomizing the study sample at the 85th percentile on the FIRI scale.

4.2.2 Statistical Analyses

Multiple linear regression models adjusted for age, sex, NAART, WHR, marital status, and energy intake were used to evaluate the relation between GL and cognition by glucoregulation evaluated by QUICKI and FIRI. Bootstrapped estimates of the standard errors run with 1000 replications were used to minimize the effect of influential observations due to the relatively small sample size. Linear regression assumptions were evaluated for validity of the final models using histograms, Q-Q plots, and the Shapiro-Wilk test (107) to assess normality of the residuals, residual-versus-fitted plots, Breusch-Pagan (111), and Cook-Weisberg (112) tests to assess homoscedasticity, variance inflation factors to assess multicollinearity (VIF<10), and scatter plots to assess for a linear relation between independent and dependent variables. Statistical significance of an estimate was fixed at $p<0.05$.

4.2.3 Results

Table 10 and Table 11 provide summaries of the multivariate linear regression analyses on global cognition and the six cognitive domains by glucoregulation as assessed by QUICKI and FIRI, respectively. Glucoregulation classification by QUICKI and FIRI resulted in poor glucoregulation groups of n=60 and n=29, respectively. In individuals with poor glucoregulation as classified by QUICKI, there was evidence of an inverse relation between GL and figural memory. The model revealed for every 10 unit increase in GL/1000 kcal, while keeping total energy intake constant, there would be a 0.028 decrease in figural memory z-score (p=0.01). A total of 11.1% of the variance in figural memory z-scores was explained by this model. No relations between GL and the remaining cognitive domains or global cognition was found for the poor glucoregulation group as classified by QUICKI. In individuals with poor glucoregulation as classified by FIRI, there was evidence of an inverse relation between GL and global cognition. The model revealed for every 10 unit increase in GL/1000 kcal, while keeping total energy intake constant, there would be a 0.020 decrease in global cognition z-score (p=0.04). A total of 50.1% of the variance in global cognition z-scores was explained by this model. No relations between GL and the cognitive domains were found for the poor glucoregulation group as classified by FIRI, nor were any associations found between GL and cognition in the good glucoregulation groups as classified by either QUICKI or FIRI.

4.3 Chapter Three Tables and Figures

Table 10. Summary of multivariate linear regression analyses on global cognition in the total study sample (n=189) and by glucoregulation status

	Total n=189				Good glucoregulation n=142				Poor glucoregulation n=47			
Variable	**β[1] (SEE)**	**95% CI**	**P-value**	**Adj. R^2**	**β[1] (SEE)**	**95% CI**	**P-value**	**Adj. R^2**	**β[1] (SEE)**	**95% CI**	**P-value**	**Adj. R^2**
Glycemic Load (GL/1000 kcal)	-0.0010 (0.0027)	-0.0063, 0.0043	0.71	31.7%	0.003 (0.003)	-0.004, 0.010	0.38	30.6%	-0.014 (0.005)	-0.024, -0.004	0.008	47.8%
Age	-0.026 (0.005)	-0.036, -0.016	<0.001		-0.023 (0.006)	-0.034, -0.012	<0.001		-0.046 (0.010)	-0.065, -0.026	<0.001	
Sex[2]	0.14 (0.08)	-0.009, 0.30	0.06		0.16 (0.10)	-0.04, 0.35	0.11		0.05 (0.15)	-0.25, 0.35	0.75	
Log (Caloric Intake)	0.14 (0.08)	-0.014, 0.30	0.08		0.16 (0.10)	-0.03, 0.35	0.09					
NAART	0.029 (0.004)	0.020, 0.037	<0.001		0.025 (0.005)	0.015, 0.036	<0.001		0.034 (0.008)	0.017, 0.050	<0.001	
WHR	-0.13 (0.44)	-1.00, 0.73	0.76		-0.41 (0.58)	-1.54, 0.72	0.48		-0.004 (1.44)	-2.82, 2.82	0.99	
Marital Status[3]	-0.066 (0.026)	-0.12, -0.02	0.01		-0.088 (0.035)	-0.157, -0.019	0.01		-0.039 (0.042)	-0.12, 0.04	0.35	
Constant	-2.30 (0.97)	-4.20, -0.40	0.02		-2.19 (1.30)	-4.74, 0.36	0.09		0.09 (2.07)	-3.98, 4.15	0.97	

[1]Regression coefficients interpreted as the change in global cognition z-score for every unit increase in the variable.
[2]Sex variable coded as 0, male; 1, female.
[3]Marital status variable coded as 1, married; 2, widowed; 3, divorced; 4, single; 5, other.
Abbreviations: Adj., adjusted; NAART, North American Adult Reading Test; WHR, waist-to-hip ratio.

Table 11. Summary of multivariate linear regression models between glycemic load and cognition by glucoregulation assessed by QUICKI

Outcome Variable	n	β[1] (SEE)	95% CI	P-value	Adjusted R^2
Good glucoregulation					
Global Cognition	131	0.025 (0.003)	-0.004, 0.009	0.45	33.2%
Executive Function: Processing Speed and Inhibition	132	0.0002 (0.0076)	-0.015, 0.015	0.98	18.6%
Executive Function: Concept Formation	133	0.0021 (0.0075)	-0.013, 0.017	0.78	18.6%
Verbal Memory	133	0.0027 (0.0073)	-0.012, 0.017	0.71	22.1%
Verbal Fluency	133	0.0026 (0.0059)	-0.009, 0.014	0.66	20.0%
Figural Memory	133	0.0082 (0.0088)	-0.009, 0.025	0.35	3.2%
Complex Attention	132	-0.0032 (0.0022)	-0.008, 0.001	0.15	2.6%
Poor glucoregulation					
Global Cognition	58	-0.0099 (0.0052)	-0.02, 0.0003	0.06	31.9%
Executive Function: Processing Speed and Inhibition	59	-0.0044 (0.011)	-0.025, 0.016	0.68	32.2%
Executive Function: Concept Formation	60	-0.015 (0.012)	-0.039, 0.010	0.23	6.9%
Verbal Memory	59	0.0089 (0.010)	-0.012, 0.029	0.39	9.8%
Verbal Fluency	60	-0.0096 (0.010)	-0.029, 0.010	0.34	23.4%
Figural Memory	60	-0.028 (0.011)	-0.05, -0.007	0.01	11.1%
Complex Attention	60	-0.0027 (0.0049)	-0.012, 0.007	0.58	0.01%

All models adjusted for age, sex, NAART, WHR, marital status, and energy intake.

[1]Regression coefficients interpreted as the change in the cognitive domain z-score for every 1 GL unit increase.

Abbreviations: NAART, North American Adult Reading Test; WHR, waist-to-hip ratio.

Table 12. Summary of multivariate linear regression models between glycemic load and cognition by glucoregulation assessed by FIRI

Outcome Variable	n	β[1] (SEE)	95% CI	P-value	Adjusted R^2
Good glucoregulation					
Global Cognition	162	0.00061 (0.0030)	-0.0053, 0.0065	0.84	28.7%
Executive Function: Processing Speed and Inhibition	163	-0.0029 (0.0074)	-0.017, 0.011	0.70	17.1%
Executive Function: Concept Formation	164	0.0031 (0.0067)	-0.010, 0.016	0.64	13.6%
Verbal Memory	164	0.0016 (0.0061)	-0.010, 0.014	0.79	18.1%
Verbal Fluency	164	-0.0019 (0.006)	-0.014, 0.010	0.75	18.4%
Figural Memory	164	0.0044 (0.0079)	-0.011, 0.020	0.58	3.9%
Complex Attention	163	-0.0018 (0.002)	-0.0058, 0.0022	0.37	3.2%
Poor glucoregulation					
Global Cognition	27	-0.020 (0.0096)	-0.039, -0.001	0.04	50.1%
Executive Function: Processing Speed and Inhibition	28	-0.017 (0.017)	-0.049, 0.016	0.31	43.6%
Executive Function: Concept Formation	29	-0.021 (0.018)	-0.056, 0.014	0.24	4.5%
Verbal Memory	28	0.019 (0.019)	-0.019, 0.057	0.34	14.3%
Verbal Fluency	29	-0.025 (0.015)	-0.055, 0.005	0.10	45.0%
Figural Memory	29	-0.028 (0.016)	-0.060, 0.004	0.09	19.9%
Complex Attention	29	-0.010 (0.0096)	-0.029, 0.009	0.29	4.6%

All models adjusted for age, sex, NAART, WHR, marital status, and energy intake.
[1]Regression coefficients interpreted as the change in the cognitive domain z-score for every 1 GL unit increase.
Abbreviations: NAART, North American Adult Reading Test; WHR, waist-to-hip ratio.

Chapter Five: **Discussion and Conclusion**

5.1 Discussion

The aim of this project was to assess the associations of dietary GL on global cognition and six cognitive domains by glucoregulation and to evaluate if CRF and/or PA mediated significant relations. GL was found to be inversely associated with global cognition and figural memory in individuals with poor glucoregulation. Neither CRF nor PA mediated these two relations. Further, no relations were found between GL and the remaining cognitive domains for the poor glucoregulation group, and no relations were found between GL and any cognitive measure in individuals with good glucoregulation. These results are consistent with previous epidemiological research that found associations between consuming a diet characterized by a lower GL and better cognitive functioning in an older population (34-36). However, no previous study assessed the association between GL and cognition in older adults without diabetes comparing those with good versus poor glucoregulation. This study's results add a novel finding to the literature that suggests the effect of GL on cognition may be limited to individuals who have poor glucoregulation.

Secondary analyses were conducted to explore the significant relations observed between age and cognitive function, as well as to compare models assessing glucoregulation by two other indices. The former analysis revealed that age was negatively associated with global cognition, and poor glycemic control increased the association twofold in the negative direction. It is well documented that impairments in cognitive function are related to both older age (145, 146) and poor blood glucose regulation (4, 147). The aging brain experiences structural and physiologic changes that can negatively affect cognitive abilities (146). These changes can progress more rapidly with impairments in glucoregulation since the regulation of blood glucose levels is integral for proper brain function (26), and dysregulation of blood glucose can lead to vascular changes associated with cognitive function (129). Therefore, it would be expected for the combination of greater age and impaired glucoregulation to be more strongly related to cognition than each variable alone, which is consistent with the associations observed.

Moreover, glucoregulation was additionally assessed using the QUICKI and FIRI indices. Compared to classification by HOMA-IR, QUICKI was less conservative and FIRI was more conservative in classifying the study sample as having poor glucoregulation. Reclassification of the poor glucoregulation group into different sample sizes could result in different findings considering the small sample size of the original grouping. Regression analyses using assessment of glucoregulation by QUICKI found GL to be inversely associated with figural memory with poor glucoregulation, but the relation between GL and global cognition was just shy of statistical significance in this group ($p=0.06$). This finding is consistent with the primary analysis of this project that found GL to be more strongly associated with figural memory ($p<0.001$) compared to global cognition ($p=0.008$) in poor glucoregulatory individuals.

Classification by FIRI, however, only found an association between GL and global cognition in the poor glucoregulation group, and the p-value was considerably higher ($p=0.04$) compared to analyses using HOMA-IR ($p=0.008$). The small sample size of the poor glucoregulation group by FIRI ($n=29$) reduced the power of analyses conducted, which could account for the weak and null associations observed. In comparing the three glucoregulation indices, Bastard et al. (140) found HOMA-IR, QUICKI, and FIRI to be well and equally correlated with measures of IR obtained from hyperinsulinemic euglycemic glucose clamp, the gold standard measure of IR. Yet, Vaccaro et al. (148) found HOMA-IR to be superior to QUICKI in correlations with insulin sensitivity assessed by an intravenous glucose tolerance test. The challenge in assessing IR using simple indices lies in the classification cut-offs, which are not well established for the indices. It would be helpful for researchers and clinicians for future research to establish these IR cut-offs.

Establishing cut-offs of simple indices of IR are important to identify IGT or T2DM. The presence of these two conditions are associated with cognitive impairments through mechanisms that are not fully understood (149). In IGT and T2DM, blood glucose levels are elevated due to the blunted clearance of glucose from blood into tissue because of pancreatic beta cell dysfunction and/or insulin resistance (4). The effects of elevated blood glucose seem to play an important role in the mechanism of the association between impaired glucoregulation and cognitive dysfunction (149).

Chronic hyperglycemia can lead to endothelial dysfunction and cause vascular damage through several pathways (129) (Figure 4). A major contributor to endothelial dysfunction is oxidative stress (129), which promotes physiologic strain as antioxidant defenses cannot keep up with free radical production (150). Elevated blood glucose levels promote oxidative stress by increasing the generation of reactive oxygen species, reactive nitrogen species, lipid peroxidation, protein oxidation, and decreasing antioxidant levels (149). In addition, the activation of the diacylglycerol protein kinase C pathway and an increase in production of advanced glycated end products promotes oxidative stress markers (129). The consequence of oxidative stress on vascular function is an imbalance in vascular homeostasis due to increased vasoconstriction and impaired vasodilation (129). Endothelial dysfunction can lead to decreases in tissue perfusion and tissue atrophy (119). Impairments in glucose metabolism are strongly associated with brain atrophy (120-122) and reduced hippocampal volumes (123, 124), both of which are correlated with cognitive dysfunction or decline (125, 126). Cognitive impairment in diabetic rats was corrected with administration of antioxidants (151), suggesting the role of oxidative stress on cognitive function with impaired glucoregulation.

Moreover, elevated blood glucose levels can increase flux of the polyol pathway(149, 152). This pathway converts intracellular glucose to sorbitol, which is unable to pass freely through cell membranes due to its polarity, resulting in an accumulation of sorbitol inside cells (152). Cognitive impairment seen in rats with sorbitol accumulation in brain tissue was reduced when treated with an inhibitor that reduced sorbitol concentrations (153). Although the mechanisms in the negative effect of hyperglycemia on cognitive function are not fully understood in humans, animal studies suggest an important role of oxidative stress and polyol pathway flux in observed cognitive impairments with blood glucose dysregulation.

The strong associations between hyperglycemia and cognitive dysfunction (4) suggest the importance of glycemic control in preventing impairments in cognitive function. GL provides a manner in which individuals with impaired glucoregulation can aid in the regulation of blood glucose at the gut level. Low GL foods contain complex carbohydrates that take longer to digest, resulting in the gradual rise of blood glucose levels (10). In addition, low GL foods prevent insulin spikes that are followed by spikes in postprandial blood glucose, which can subsequently fall below preprandial levels, a response pattern that is seen with high GL foods (4). A low GL diet can be an important strategy in managing glycemia in individuals with blood glucose dysregulation. Jenkins et al. (9) found glycemic control improved in diabetic individuals following a 3-month low GL diet. Furthermore, studies investigating the effect of test meals with varying GL found higher cognitive performance in subjects following a lower GL meal compared to a higher GL meal (30-32), yet one study found no differences between test meals (29). However, it is probable that consistent consumption of a low GL diet by individuals with poorer glucoregulation can reduce blood glucose fluctuations, as observed by Jenkins et al. (9), and may subsequently reduce risk of cognitive decline in this population.

This project found an inverse association between GL and figural memory in individuals with poor glucoregulation. Learning and memory are thought to be most susceptible to metabolic brain disorders (131). As such, the cognitive domain of memory would likely be the first to be affected by chronic impairments in glucoregulation. Willette et al. (132) found HOMA-IR to be negatively associated with glucose metabolism in large regions of the frontal, parietal, and temporal lobes in older adults with a risk of Alzheimer's disease. This negative association was strongest for the left medial temporal lobe where glucose metabolism, as predicted by HOMA-IR, was found to be positively associated with memory performance (132). Other studies noted improvements in memory with better glycemic control in people with diabetes (20). Moreover, glycemic control and blood glucose levels were found to be positively associated with memory performance in older individuals without diabetes with the former relation being partly mediated by hippocampal volume and microstructure (133). The importance of glucose in memory functions has been widely studied, which suggests better glycemic control is beneficial for memory (154). While our analyses revealed a significant inverse association between GL and figural memory in the poor glucoregulation group, we found no evidence or trend for an association with verbal memory. This result may suggest that figural memory is more susceptible to consequences of impairments in blood glucose regulation. However, a study with a larger sample size would help to explore this speculation.

A low GL diet can be effective in improving glycemic control in individuals with impairments in glucoregulation (9), which has the potential to be clinically important for cognitive function. This project found a 0.14 SD increase in global cognition for every 10

GL/1000 kcal decrease in individuals with poor glucoregulation. An alteration of diet composition to elicit a change of 10 GL/1000 kcal is feasible. For example, a white bagel (94g) contains 240 kcal and has a GL of 33 (92). Substituting a bagel for 2/3 cup of quick oats would reduce GL by 11 while maintaining caloric intake (92). Furthermore, a 0.14 SD increase in global cognition has the potential to reduce cognitive decline risk. Kaffashian et al. (135) reported dementia risk was associated with a 0.03 SD decline in global cognition over 10 years. Rawlings et al. (136) found a 0.15 SD greater decline in global cognition over 20 years in people with diabetes compared to people without diabetes. An increase in global cognition of 0.14 SD could therefore have great clinical importance. However, this project explored the association between GL and cognition cross-sectionally and changes in cognitive function or decline risk that could arise from altering dietary GL will likely be different from 0.14 SD. A longitudinal study would be more appropriate in evaluating these relations.

A null finding was also observed in the mediation of CRF and PA in the significant relations of GL and cognition. Table 10 presents the stepwise mediation analysis results not included in the manuscript. The mediation approach proposed by Baron and Kenny (113) requires the mediator to be associated with both the predictor and outcome variable. As such, CRF and PA must be separately associated with both GL and cognition, which was not observed. In evaluating the associations of the mediators with GL and cognition, the only association that was found to be significant was between GL and PA. This analysis found a positive relation between GL and PA, however only 9.7% of the variation in global cognition was explained by this model. Since the coefficients of the exposure variables in steps one through three in the four mediation analyses conducted were not unanimously significant, it was concluded that there was no evidence of mediation by CRF or PA. It is likely that diet quality and measures of physical fitness and activity are not strongly correlated in older adults. Instead, GL, CRF, and PA may elicit a synergistic, rather than a mediatory, effect on cognition in this population.

In addition to the primary aim of this project, well-documented associations between cognition and several covariates were found significant in the final models. In both the good and poor glucoregulation groups, being younger and more educated were separately associated with better global cognition. Additionally, being married was associated with better global cognition in the good glucoregulation group. These three covariates collectively explained a large portion of the variance in global cognition. In the good glucoregulatory group, age, NAART, and marital status described 33.7%, 40.8%, and 10.1%, respectively, of the variance in global cognition that was explained by the final model (adjusted R^2=30.6%). Similarly, age and NAART explained 64.0% and 30.5%, respectively, of the explained variance in global cognition (adjusted R^2=47.8%) in the poor glycemic control group. Relations of cognition with age and education are well established (145, 146, 155-157). Cognitive function, specifically fluid abilities, decline with age as structural and physiological changes occur within the aging brain (146), and cognitive reserve, which is positively associated with educational attainment, is inversely related to susceptibility of age-related and pathologic brain changes (157, 158). These relations are consistent with the associations found between age, NAART, and global cognition in the study sample. Moreover, the social support and cognitive challenges in cohabiting with a partner can serve a protective effect against cognitive decline in older age (159). This can explain the increased risk for cognitive impairment associated with singlehood in mid- and late-life (159).

5.2 Strengths and Limitations

This study is the first to assess the relation between GL and cognitive function, both domain-specific and globally, with a focus on glucoregulation in older adults without T2DM. A notable strength of this project was the comprehensive cognitive battery that captured six cognitive domains as well as global cognition. The cognitive assessment was administered in-person by trained psychometricians, and the measures of cognition used validated tests that were designed to provide extensive and reliable cognitive scores. The BIM study also collected a wide range of exposure and outcome data from participants, allowing the effects of numerous covariates on the relation between glucoregulation and cognitive function to be evaluated during analyses. The study design was also unique in combining physiologic measures with the cognitive assessment. The quality of the cognitive variables and full assessment of covariates provided strength to data collection, analyses, and overall conclusions.

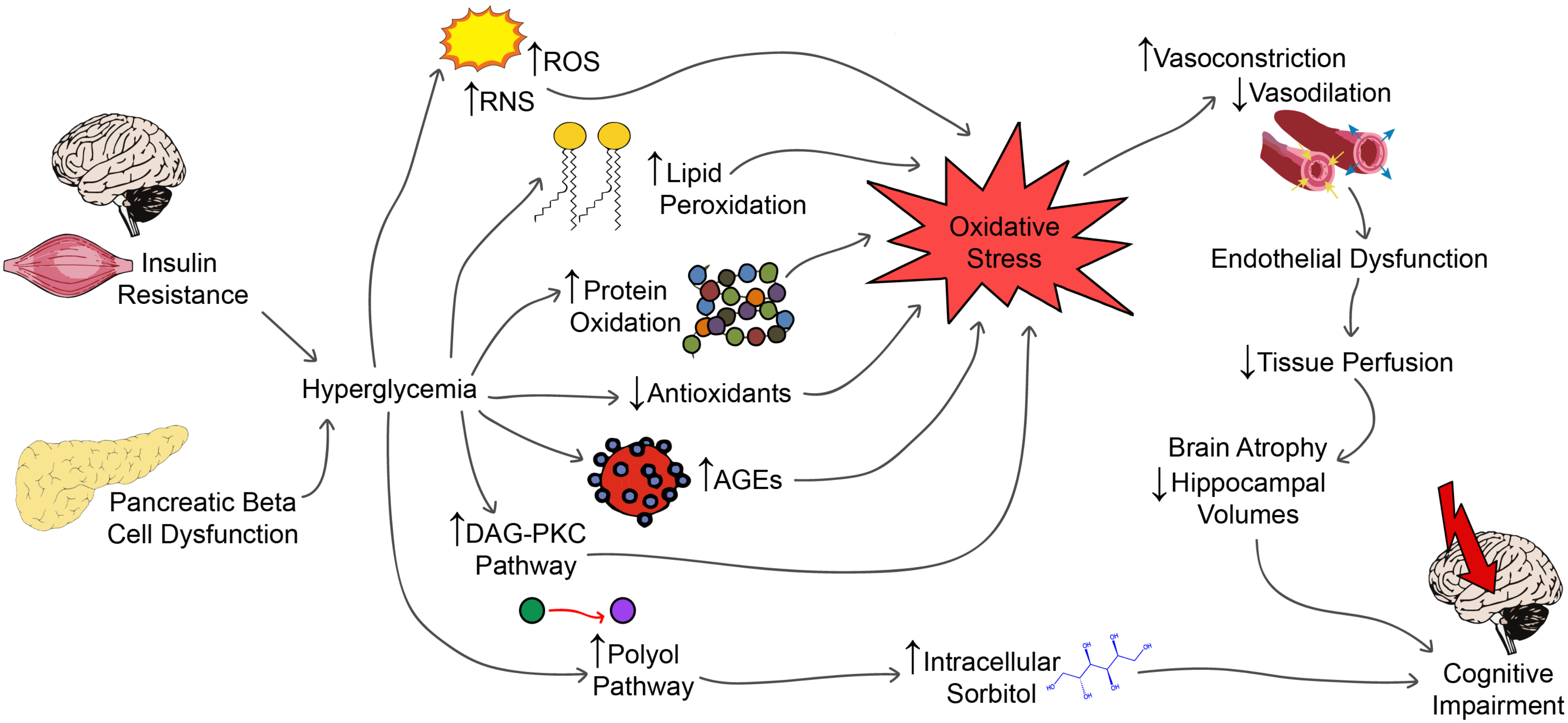
Limitations of the study were that participants were predominantly Caucasian, well-educated, and with a middle to high socioeconomic status. This mostly homogenous volunteer and relatively small sample limits the generalizability of results to a broader group of older adults. Yet, with only 49 subjects in the poor glucoregulation group, a strong association was observed, and 47.8% of the variance in global cognition was explained by the final model. Another limitation of this study is the use of self-reported measure of diet. FFQs are prone to underestimate dietary intake, but are an important tool in assessing overall habitual intake. Experts have regarded GL as a valid method of differentiating foods by their glycemic response, and the best predictor of the glycemic response is GL/1000 kcal (137). However, the evaluation of GL must always be considered in the context of overall diet (137), hence the use of the C-DHQ I was necessary for the aim of this project. Lastly, inferences about causal relations cannot be made because of the study's cross-sectional design.

5.3 Future Directions

Evaluating casual relations between GL and cognitive function in older adults would be useful for public health strategies in reducing cognitive decline risk. In addition, it would be beneficial to assess if improvements in glucoregulation mediate the relation between lower GL and better cognitive function in an older population. A more sensitive measure of longer-term glucoregulation, such as glycated hemoglobin (HbA_{1c}), in addition to a more precise measure of dietary intake, such diet diaries, could strengthen analyses. Further research is also needed to determine whether a dose-response relation exists between GL and cognitive function.

5.4 Chapter Four Tables and Figures

Figure 4. Mechanistic implications of hyperglycemia on cognitive function



Abbreviations: AGE, advanced glycated end products; DAG, diacylglycerol; PKC, protein kinase C; RNS, reactive nitrogen species; ROS, reactive oxygen species.

Table 13. Mediation analysis results testing the mediator effects of cardiorespiratory fitness and physical activity in the significant associations between glycemic load and cognition in poor glucoregulation

Step #	Exposure Variable	Outcome Variable	β[1] (SEE)	95% CI	P-value	Adj. R^2
Mediation Analysis #1						
1	Glycemic Load	Global Cognition	-0.014 (0.005)	-0.024, -0.004	0.008	47.8%
2	Glycemic Load	Cardiorespiratory Fitness	0.003 (0.056)	-0.11, 0.11	0.96	40.7%
3	Cardiorespiratory Fitness	Global Cognition	-0.010 (0.016)	-0.041, 0.021	0.53	39.7%
Mediation Analysis #2						
1	Glycemic Load	Figural Memory	-0.035 (0.009)	-0.052, -0.018	<0.001	35.2%
2	Glycemic Load	Cardiorespiratory Fitness	0.003 (0.056)	-0.11, 0.11	0.96	40.7%
3	Cardiorespiratory Fitness	Figural Memory	0.026 (0.037)	-0.047, 0.099	0.48	19.2%
Mediation Analysis #3						
1	Glycemic Load	Global Cognition	-0.014 (0.005)	-0.024, -0.004	0.008	47.8%
2	Glycemic Load	Physical Activity	-1.50 (0.63)	-2.75, -0.26	0.02	9.7%
3	Physical Activity	Global Cognition	0.0021 (0.0012)	-0.0002, 0.0045	0.08	43.4%
Mediation Analysis #4						
1	Glycemic Load	Figural Memory	-0.035 (0.009)	-0.052, -0.018	<0.001	35.2%
2	Glycemic Load	Physical Activity	-1.50 (0.63)	-2.75, -0.26	0.02	9.7%
3	Physical Activity	Figural Memory	0.002 (0.003)	-0.004, 0.008	0.50	19.1%

[1]Regression coefficients interpreted as the change in the outcome variable for every 1 unit increase in the exposure variable.
All models adjusted for age, sex, NAART, WHR, marital status, and energy intake.
Glycemic load variable expressed in units of GL/1000 kcal. Cardiorespiratory fitness variable expressed as maximal aerobic capacity in units of ml/kg/min. Physical activity variable expressed as average daily physical activity performed in past 12 months in units of MET-hr/wk.
Abbreviations: Adj., adjusted; NAART, North American Adult Reading Test; WHR, waist-to-hip ratio.

Chapter Six: **References**

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Appendix A: National Cancer Institute Diet History Questionnaire modified for Canadian populations

Brain In Motion Study

Adapted from the National Institutes of Health Diet History Questionnaire

DIET HISTORY QUESTIONNAIRE

GENERAL INSTRUCTIONS

- Answer each question as best you can. If you are not sure, please estimate. A guess is better than leaving a blank.
- **Shade** bubbles like this: ●
- If you make a mistake, put an X through the incorrect bubble.
- Please use ball point pen, not a felt pen.
- If you fill **NEVER** or **NO** for a question, please follow any arrows or instructions that direct you to the next question.

Please fill in the corresponding bubble for your gender below.

○ **MALE** ○ **FEMALE**

The questions in the Diet History Questionnaire use measurements like cups, ounces, tablespoons and teaspoons. Refer below to convert these measurements to their metric equivalents.

1 cup	= 240 mL	1 tablespoon	= 15 mL
1 ounce	= 30 mL	1 teaspoon	= 5 mL

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PLEASE MAKE SURE TO FILL OUT **EACH** QUESTION

1. Over the past 12 months, how often did you drink **tomato juice** or **vegetable juice**?

- ○ NEVER (GO TO QUESTION 2)

○ 1 time per month or less	○ 1 time per day
○ 2-3 times per month	○ 2-3 times per day
○ 1-2 times per week	○ 4-5 times per day
○ 3-4 times per week	○ 6 or more times per day
○ 5-6 times per week	

1a. Each time you drank **tomato juice** or **vegetable juice**, how much did you usually drink?

- ○ Less than 3/4 cup (6 ounces)
- ○ 3/4 to 1 1/4 cups (6 to 10 ounces)
- ○ More than 1 1/4 cups (10 ounces)

2. Over the past 12 months, how often did you drink **orange juice** or **grapefruit juice**?

- ○ NEVER (GO TO QUESTION 3)

○ 1 time per month or less	○ 1 time per day
○ 2-3 times per month	○ 2-3 times per day
○ 1-2 times per week	○ 4-5 times per day
○ 3-4 times per week	○ 6 or more times per day
○ 5-6 times per week	

2a. Each time you drank **orange juice** or **grapefruit juice**, how much did you usually drink?

- ○ Less than 3/4 cup (6 ounces)
- ○ 3/4 to 1 1/4 cups (6 to 10 ounces)
- ○ More than 1 1/4 cups (10 ounces)

2b. How often was the juice fortified with **Calcium**?

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

3. Over the past 12 months, how often did you drink **other 100% fruit juice** or **100% fruit juice mixtures** (such as apple, grape, pineapple, or others)?

- ○ NEVER (GO TO QUESTION 4)

○ 1 time per month or less	○ 1 time per day
○ 2-3 times per month	○ 2-3 times per day
○ 1-2 times per week	○ 4-5 times per day
○ 3-4 times per week	○ 6 or more times per day
○ 5-6 times per week	

Question 4 appears in the next column.

Over the past 12 months...

3a. Each time you drank **other fruit juice** or **fruit juice mixtures**, how much did you usually drink?

- ○ Less than 3/4 cup (6 ounces)
- ○ 3/4 to 1 1/2 cups (6 to 12 ounces)
- ○ More than 1 1/2 cups (12ounces)

4. How often did you drink other **fruit drinks** (such as cranberry cocktail, fruit punch, lemonade, or Kool-Aid, diet or regular)?

- ○ NEVER (GO TO QUESTION 5)

○ 1 time per month or less	○ 1 time per day
○ 2-3 times per month	○ 2-3 times per day
○ 1-2 times per week	○ 4-5 times per day
○ 3-4 times per week	○ 6 or more times per day
○ 5-6 times per week	

4a. Each time you drank **fruit drinks**, how much did you usually drink?

- ○ Less than 1 cup (8 ounces)
- ○ 1 to 2 cups (8 to 16 ounces)
- ○ More than 2 cups (16 ounces)

4b. How often were your fruit drinks **diet** or **sugar-free drinks**?

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

5. How often did you drink **milk as a beverage** NOT in coffee, NOT in cereal? (Please include chocolate milk and hot chocolate.)

- ○ NEVER (GO TO QUESTION 6)

○ 1 time per month or less	○ 1 time per day
○ 2-3 times per month	○ 2-3 times per day
○ 1-2 times per week	○ 4-5 times per day
○ 3-4 times per week	○ 6 or more times per day
○ 5-6 times per week	

5a. Each time you drank **milk as a beverage**, how much did you usually drink?

- ○ Less than 1 cup (8 ounces)
- ○ 1 to 1 1/2 cups (8 to 12 ounces)
- ○ More than 1 1/2cups (12 ounces)

Question 6 appears on the next page.

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5b. What kind of **milk** did you usually drink?

- ○ Whole milk
- ○ 2% fat milk
- ○ 1 % fat milk
- ○ Skim, nonfat, or 1/2 % fat milk
- ○ Soy milk
- ○ Rice milk
- ○ Other

6. How often did you drink **meal replacement**, **energy**, or **high-protein beverages** such as Instant Breakfast, Ensure, Slimfast, Boost or others?

- ○ NEVER (GO TO QUESTION 7)
- ○ 1 time per month or less
- ○ 2-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

6a. Each time you drank **meal replacement beverages**, how much did you usually drink?

- ○ Less than 1 cup (8 ounces)
- ○ 1 to 1 1/2 cups (8 to 12 ounces)
- ○ More than 1 1/2 cups (12 ounces)

7. Over the past 12 months, did you drink **soft drinks** or **pop**?

- ○ NO (GO TO QUESTION 8)
- ○ YES

7a. How often did you drink **soft drinks** or **pop** **IN THE SUMMER**?

- ○ NEVER
- ○ 1 time per month or less
- ○ 2-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

7b. How often did you drink **soft drinks** or **pop** **DURING THE REST OF THE YEAR**?

- ○ NEVER
- ○ 1 time per month or less
- ○ 2-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

Question 8 appears in the next column.

7c. Each time you drank **soft drinks** or **pop**, how much did you usually drink?

- ○ Less than 12 ounces or less than 1 can or bottle
- ○ 12 to 16 ounces or 1 can or bottle
- ○ More than 16 ounces or more than 1 can or bottle

7d. How often were these soft drinks or pop **diet** or **sugar-free**?

- ○ 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

7e. How often were these soft drinks or pop **caffeine-free**?

- ○ 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

8. Over the past 12 months, did you drink **beer**? (Please do not include non-alcoholic beer.)

- ○ NO (GO TO QUESTION 9)
- ○ YES

8a. How often did you drink **beer IN THE SUMMER**?

- ○ NEVER
- ○ 1 time per month or less
- ○ 2-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

8b. How often did you drink **beer DURING THE REST OF THE YEAR**?

- ○ NEVER
- ○ 1 time per month or less
- ○ 2-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

Question 9 appears on the next page.

8c. Each time you drank **beer**, how much did you usually drink?

- ○ Less than a 12-ounce can or bottle
- ○ 1 to 3 12-ounce cans or bottles
- ○ More than 3 12-ounce cans or bottles

9. How often did you drink **wine** or **wine coolers**?

- ○ NEVER (GO TO QUESTION 10)

- ○ 1 time per month or less
- ○ 2-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

9a. Each time you drank **wine** or **wine coolers**, how much did you usually drink?

- ○ Less than 5 ounces or less than 1 glass
- ○ 5 to 12 ounces or 1 to 2 glasses
- ○ More than 12 ounces or more than 2 glasses

10. How often did you drink **liquor** or **mixed drinks**?

- ○ NEVER (GO TO QUESTION 11)

- ○ 1 time per month or less
- ○ 2-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

10a. Each time you drank **liquor** or **mixed drinks**, how much did you usually drink?

- ○ Less than 1 shot of liquor
- ○ 1 to 3 shots of liquor
- ○ More than 3 shots of liquor

11. Over the past 12 months, did you eat **oatmeal**, **cream of wheat** or **other cooked cereal**?

- ○ NO (GO TO QUESTION 12)
- ○ YES

Question 11a appears at top of the next column.

Question 12 appears in the next column.

11a. How often did you eat **oatmeal, cream of wheat** or **other cooked cereal IN THE WINTER**?

- ○ NEVER

- ○ 1-6 times per winter
- ○ 7-11 times per winter
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

11b. How often did you eat oatmeal, **cream of wheat** or **other cooked cereal DURING THE REST OF THE YEAR**?

- ○ NEVER

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

11c. Each time you ate **oatmeal, cream of wheat** or **other cooked cereal** how much did you usually eat?

- ○ Less than 3/4 cups
- ○ 3/4 to 1 1/4 cups
- ○ More than 1 1/4 cups

12. How often did you eat **cold cereal**?

- ○ NEVER (GO TO QUESTION 13)

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

12a. Each time you ate **cold cereal**, how much did you usually eat?

- ○ Less than 1 cup
- ○ 1 to 2 1/2 cups
- ○ More than 2 1/2 cups

12b. How often was the cold cereal you ate **All Bran, Fiber One, 100% Bran,** or **Bran Buds**?

- ○ 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

Question 13 appears on the next page.

Over the <u>past 12 months</u>...

12c. How often was the cold cereal you ate **some other bran** or **fiber cereal** (such as Cheerios, Shredded Wheat, Raisin Bran, Bran Flakes, Grape Nuts, Granola or Mini-Wheats)?

- ○ 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

12d. How often was the cold cereal you ate any **other type of cold cereal** (such as Corn Flakes, Rice Krispies, Frosted Flakes, Special K, Froot Loops, Cap'n Crunch, or others)?

- ○ 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

12e. Was **milk** added to your cold cereal?

- ○ NO (GO TO QUESTION 13)
- ○ YES

12f. What kind of **milk** was usually added?

- ○ Whole milk
- ○ 2% fat milk
- ○ 1% fat milk
- ○ Skim, nonfat, or 1/2 % fat milk
- ○ Soy milk
- ○ Rice milk
- ○ Other

12g. Each time **milk was added to your cold cereal**, how much was usually added?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 cup
- ○ More than 1 cup

13. How often did you eat **applesauce**?

- ○ NEVER (GO TO QUESTION 14)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

Question 14 appears in the next column.

13a. Each time you ate **applesauce**, how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 cup
- ○ More than 1 cup

14. How often did you eat **apples**?

- ○ NEVER (GO TO QUESTION 15)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

14a. Each time you ate **apples**, how many did you usually eat?

- ○ Less than 1 apple
- ○ 1 apple
- ○ More than 1 apple

15. How often did you eat **pears** (fresh, canned, or frozen)?

- ○ NEVER (GO TO QUESTION 16)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

15a. Each time you ate **pears**, how many did you usually eat?

- ○ Less than 1 pear
- ○ 1 pear
- ○ More than 1 pear

16. How often did you eat **bananas**?

- ○ NEVER (GO TO QUESTION 17)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

Question 17 appears on the next page.

Over the past 12 months...

16a. Each time you ate **bananas**, how many did you usually eat?

- ○ Less than 1 banana
- ○ 1 banana
- ○ More than 1 banana

17. How often did you eat **dried fruit**, such as prunes or raisins (not including dried apricots)?

○ NEVER (GO TO QUESTION 18)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

17a. Each time you ate **dried fruit**, how much did you usually eat (not including dried apricots)?

- ○ Less than 2 tablespoons
- ○ 2 to 5 tablespoons
- ○ More than 5 tablespoons

18. Over the past 12 months, did you eat **peaches, nectarines** or **plums**?

○ NO (GO TO QUESTION 19)

○ YES

18a. How often did you eat **fresh peaches, nectarines,** or **plums** WHEN IN SEASON?

○ NEVER

○ 1-6 times per season	○ 2 times per week
○ 7-11 times per season	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

18b. How often did you eat **peaches, nectarines,** or **plums** (fresh, canned or frozen) **DURING THE REST OF THE YEAR**?

○ NEVER

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

Question 19 appears in the next column.

18c. Each time you ate **peaches, nectarines,** or **plums,** how much did you usually eat?

- ○ Less than 1 fruit or less than 1/2 cup
- ○ 1 to 2 fruits or 1/2 to 3/4 cup
- ○ More than 2 fruits or more than 3/4 cup

19. How often did you eat **grapes**?

○ NEVER (GO TO QUESTION 20)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

19a. Each time you ate **grapes**, how much did you usually eat?

- ○ Less than 1/2 cup or less than 10 grapes
- ○ 1/2 to 1 cup or 10 to 30 grapes
- ○ More than 1 cup or more than 30 grapes

20. Over the past 12 months, did you eat **cantaloupe**?

○ NO (GO TO QUESTION 21)

○ YES

20a. How often did you eat **fresh cantaloupe WHEN IN SEASON**?

○ NEVER

○ 1-6 times per season	○ 2 times per week
○ 7-11 times per season	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

20b. How often did you eat **fresh or frozen cantaloupe DURING THE REST OF THE YEAR** ?

○ NEVER

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

Question 21 appears on the next page.

Over the past 12 months...

20c. Each time you ate **cantaloupe,** how much did you usually eat?

- ○ Less than 1/4 melon or less than 1/2 cup
- ○ 1/4 melon or 1/2 to 1 cup
- ○ More than 1/4 melon or more than 1 cup

21. Over the past 12 months, did you eat **melon, other than cantaloupe** (such as watermelon or honeydew)?

- ○ NO (GO TO QUESTION 22)
- ○ YES

21a. How often did you eat **fresh melon, other than cantaloupe** (such as watermelon or honeydew) **WHEN IN SEASON**?

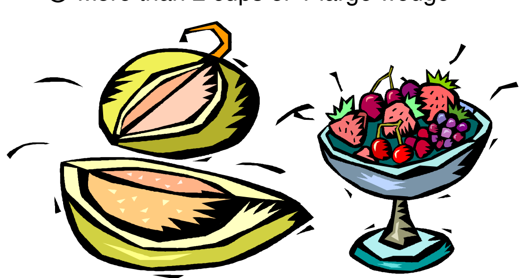
- ○ NEVER
- ○ 1-6 times per season
- ○ 7-11 times per season
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

21b. How often did you eat **fresh** or **frozen melon, other than cantaloupe, DURING THE REST OF THE YEAR** ?

- ○ NEVER
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

21c. Each time you ate **melon other than cantaloupe,** how much did you usually eat?

- ○ Less than 1/2 cup or 1 small wedge
- ○ 1/2 to 2 cups or 1 medium wedge
- ○ More than 2 cups or 1 large wedge



Question 22 appears in the next column.

22. Over the past 12 months, did you eat **strawberries**?

- ○ NO (GO TO QUESTION 23)
- ○ YES

22a. How often did you eat **fresh strawberries WHEN IN SEASON**?

- ○ NEVER
- ○ 1-6 times per season
- ○ 7-11 times per season
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

22b. How often did you eat **fresh or frozen strawberries, DURING THE REST OF THE YEAR** ?

- ○ NEVER
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

22c. Each time you ate **strawberries,** how much did you usually eat?

- ○ Less than 1/4 cup or less than 3 berries
- ○ 1/4 to 3/4 cup or 3 to 8 berries
- ○ More than 3/4 cup or more than 8 berries

23. Over the past 12 months, did you eat **oranges, tangerines,** or **tangelos**?

- ○ NO (GO TO QUESTION 24)
- ○ YES

23a. How often did you eat **oranges, tangerines,** or **tangelos WHEN IN SEASON**?

- ○ NEVER
- ○ 1-6 times per season
- ○ 7-11 times per season
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

Question 24 appears on the next page.

23b. How often did you eat **oranges, tangerines,** or **tangelos** (fresh or canned) **DURING THE REST OF THE YEAR** ?

○ NEVER

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

23c. Each time you ate **oranges, tangerines,** or **tangelos,** how many did you usually eat?

○ Less than 1 fruit
○ 1 fruit
○ More than 1 fruit

24. Over the past 12 months, did you eat **grapefruit**?

○ NO (GO TO QUESTION 25)
○ YES

24a. How often did you eat **fresh grapefruit WHEN IN SEASON**?

○ NEVER

○ 1-6 times per season
○ 7-11 times per season
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

24b. How often did you eat **grapefruit** (fresh or canned) **DURING THE REST OF THE YEAR**?

○ NEVER

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

24c. Each time you ate **grapefruit,** how much did you usually eat?

○ Less than 1/2 grapefruit
○ 1/2 grapefruit
○ More than 1/2 grapefruit

Question 25 appears in the next column.

25. How often did you eat **other kinds of fruit**?

○ NEVER (GO TO QUESTION 26)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

25a. Each time you ate **other kinds of fruit,** how much did you usually eat?

○ Less than 1/4 cup
○ 1/4 to 3/4 cup
○ More than 3/4 cup

26. How often did you eat **COOKED greens** (such as spinach, chard, or kale)?

○ NEVER (GO TO QUESTION 27)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

26a. Each time you ate **COOKED greens,** how much did you usually eat?

○ Less than 1/2 cup
○ 1/2 to 1 cup
○ More than 1 cup

27. How often did you eat **RAW greens** (such as spinach, chard, or kale)? *(We will ask about lettuce later.)*

○ NEVER (GO TO QUESTION 28)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

27a. Each time you ate **RAW greens,** how much did you usually eat?

○ Less than 1/2 cup
○ 1/2 to 1 cup
○ More than 1 cup

Question 28 appears on the next page.

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Over the past 12 months...

28. How often did you eat **coleslaw**?

- ○ NEVER (GO TO QUESTION 29)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

28a. Each time you ate **coleslaw,** how much did you usually eat?

- ○ Less than 1/4 cup
- ○ 1/4 to 3/4 cup
- ○ More than 3/4 cup

29. How often did you eat **sauerkraut** or **cabbage** (other than coleslaw)?

- ○ NEVER (GO TO QUESTION 30)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

29a. Each time you ate **cabbage** or **sauerkraut,** how much did you usually eat?

- ○ Less than 1/4 cup
- ○ 1/4 to 1 cup
- ○ More than 1 cup

30. How often did you eat **carrots** (fresh, canned, or frozen)?

- ○ NEVER (GO TO QUESTION 31)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

30a. Each time you ate **carrots,** how much did you usually eat?

- ○ Less than 1/4 cup or less than 2 baby carrots
- ○ 1/4 to 1/2 cup or 2 to 5 baby carrots
- ○ More than 1/2 cup or more than 5 baby carrots

Question 31 appears in the next column.

31. How often did you eat **string beans** or **green beans** (fresh, canned, or frozen)?

- ○ NEVER (GO TO QUESTION 32)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

31a. **Each time you ate string beans** or **green beans,** how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 cup
- ○ More than 1 cup

32. How often did you eat **peas** (fresh, canned or frozen)?

- ○ NEVER (GO TO QUESTION 33)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

32a. Each time you ate **peas,** how much did you usually eat?

- ○ Less than 1/4 cup
- ○ 1/4 to 3/4 cup
- ○ More than 3/4 cup

33. Over the past 12 months, did you eat **corn**?

- ○ NO (GO TO QUESTION 34)
- ○ YES

33a. How often did you eat **fresh corn WHEN IN SEASON**?

- ○ NEVER

○ 1-6 times per season	○ 2 times per week
○ 7-11 times per season	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

Question 34 appears on the next page.

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Over the past 12 months...

33b. How often did you eat **corn** (fresh, canned, or frozen) **DURING THE REST OF THE YEAR**?

○ NEVER

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

33c. Each time you ate **corn,** how much did you usually eat?

○ Less than 1 ear or less than 1/2 cup
○ 1 ear or 1/2 to 1 cup
○ More than 1 ear or more than 1 cup

34. Over the past 12 months how often did you eat **broccoli** (fresh or frozen)?

○ NEVER (GO TO QUESTION 35)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

34a. Each time you ate **broccoli,** how much did you usually eat?

○ Less than 1/4 cup
○ 1/4 to 1 cup
○ More than 1 cup

35. How often did you eat **cauliflower** or **brussels sprouts** (fresh or frozen)?

○ NEVER (GO TO QUESTION 36)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

35a. Each time you ate **cauliflower** or **brussels sprouts,** how much did you usually eat?

○ Less than 1/4cup
○ 1/4 to 1/2 cup
○ More than 1/2 cup

Question 36 appears in the next column.

36. How often did you eat **mixed vegetables**?

○ NEVER (GO TO QUESTION 37)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

36a. Each time you ate **mixed vegetables,** how much did you usually eat?

○ Less than 1/2 cup
○ 1/2 to 1 cup
○ More than 1 cup

37. How often did you eat **onions**?

○ NEVER (GO TO QUESTION 38)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

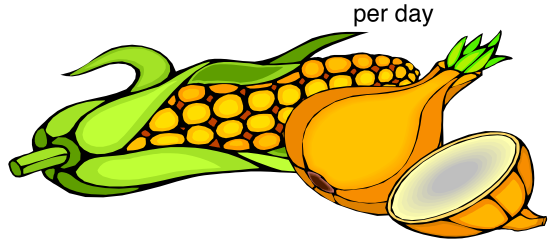
37a. Each time you ate **onions,** how much did you usually eat?

○ Less than 1 slice or less than 1 tablespoon
○ 1 slice or 1 to 4 tablespoons
○ More than 1 slice or more than 4 tablespoons

38. Now think about all the **cooked vegetables** you ate in the past 12 months and how they were prepared. How often were your vegetables **COOKED WITH** some sort of **fat**, including oil spray? *(Please do not include potatoes.)*

○ NEVER (GO TO QUESTION 39)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day



Question 39 appears on the next page.

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Over the past 12 months...

38a. Which fats were usually added to your vegetables **DURING COOKING**? *(Please do not include potatoes. **Mark as many as apply.**)*

- ○ Margarine (including low-fat)
- ○ Butter (including low-fat)
- ○ Lard, or bacon fat
- ○ Olive oil
- ○ Corn oil
- ○ Canola or rapeseed oil
- ○ Oil spray, such as Pam or others
- ○ Other kinds of oils
- ○ None of the above

39. Now, thinking again about all the **cooked vegetables** you ate in the past 12 months, how often was some sort of fat, sauce, or dressing added **AFTER COOKING OR AT THE TABLE**? *(Please do not include potatoes.)*

- ○ NEVER (GO TO QUESTION 40)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 times per day
- ○ 3 or more times per day

39a. Which fats, sauces, or dressings were usually added **AFTER COOKING OR AT THE TABLE**? *(Please do not include potatoes. **Mark as many as apply.**)*

- ○ Margarine (including low-fat)
- ○ Butter (including low-fat)
- ○ Lard, or bacon fat
- ○ Salad dressing
- ○ Cheese sauce
- ○ White sauce
- ○ Other

39b. If margarine, butter, lard, fatback, or bacon fat was added to your cooked vegetables **AFTER COOKING OR AT THE TABLE,** how much did you usually add?

- ○ Did not usually add these
- ○ Less than 1 teaspoon
- ○ 1 to 3 teaspoons
- ○ More than 3 teaspoons

39c. If salad dressing, cheese sauce, or white sauce was added to your cooked vegetables **AFTER COOKING OR AT THE TABLE,** how much did you usually add?

- ○ Did not usually add these
- ○ Less than 1 tablespoon
- ○ 1 to 3 tablespoons
- ○ More than 3 tablespoons

Question 40 appears in the next column.

40. Over the past 12 months how often did you eat **sweet peppers** (green, red, or yellow)?

- ○ NEVER (GO TO QUESTION 41)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

40a. Each time you ate **sweet peppers,** how much did you usually eat?

- ○ Less than 1/8 pepper
- ○ 1/8 to 1/4 pepper
- ○ More than 1/4 pepper

41. Over the past 12 months did you eat **fresh tomatoes** (including those in salads)?

- ○ NO (GO TO QUESTION 42)
- ○ YES

41a. How often did you eat **fresh tomatoes** (including those in salads) **WHEN IN SEASON**?

- ○ NEVER
- ○ 1-6 times per season
- ○ 7-11 times per season
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

41b. How often did you eat **fresh tomatoes** (including those in salads) **DURING THE REST OF THE YEAR**?

- ○ NEVER
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

41c. Each time you ate **fresh tomatoes,** how much did you usually eat?

- ○ Less than 1/4 tomato
- ○ 1/4 to 1/2 tomato
- ○ More than 1/2 tomato

Question 42 appears on the next page.

Over the past 12 months...

42. How often did you eat **lettuce salads** (with or without other vegetables)?

- ○ NEVER (GO TO QUESTION 43)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

42a. Each time you ate **lettuce salads,** how much did you usually eat?

- ○ Less than 1/4 cup
- ○ 1/4 to 1 1/4 cups
- ○ More than 1 1/4 cups

43. How often did you eat **salad dressing** (including low-fat) on salads?

- ○ NEVER (GO TO QUESTION 44)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

43a. Each time you ate **salad dressing** on salads, how much did you usually eat?

- ○ Less than 2 tablespoons
- ○ 2 to 4 tablespoons
- ○ More than 4 tablespoons

44. How often did you eat **sweet potatoes** or **yams**?

- ○ NEVER (GO TO QUESTION 45)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

44a. Each time you ate **sweet potatoes** or **yams,** how much did you usually eat?

- ○ 1 small potato or less than 1/4 cup
- ○ 1 medium potato or 1/4 to 3/4 cup
- ○ 1 large potato or more than 3/4 cup

Question 45 appears in the next column.

45. How often did you eat **French fries, home fries, hash browned potatoes,** or **tater tots**?

- ○ NEVER (GO TO QUESTION 46)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

45a. Each time you ate **French fries, home fries, hash browned potatoes,** or **tater tots** how much did you usually eat?

- ○ Less than 10 fries or less than 1/2 cup
- ○ 10 to 25 fries or 1/2 to 1 cup
- ○ More than 25 fries or more than 1 cup

46. How often did you eat **potato salad**?

- ○ NEVER (GO TO QUESTION 47)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

46a. Each time you ate **potato salad,** how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 cup
- ○ More than 1 cup

47. How often did you eat **baked, boiled,** or **mashed potatoes**?

- ○ NEVER (GO TO QUESTION 48)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

47a. Each time you ate **baked, boiled,** or **mashed potatoes,** how much did you usually eat?

- ○ 1 small potato or less than 1/2 cup
- ○ 1 medium potato or 1/2 to 1 cup
- ○ 1 large potato or more than 1 cup

Question 48 appears on the next page.

Over the <u>past 12 months</u>...

47b. How often was **sour cream** (including low-fat) added to your potatoes, **EITHER IN COOKING OR AT THE TABLE**?

- ○ Almost never or never (GO TO QUESTION 47d)
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

47c. Each time **sour cream** was added to your potatoes, how much was usually added?

- ○ Less than 1 tablespoon
- ○ 1 to 3 tablespoons
- ○ More than 3 tablespoons

47d. How often was **margarine** (including low-fat) added to your potatoes, **EITHER IN COOKING OR AT THE TABLE**?

- ○ 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

47e. How often was **butter** (including low-fat) added to your potatoes, **EITHER IN COOKING OR AT THE TABLE**?

- ○ 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

47f. Each time **margarine** or **butter** was added to your potatoes, how much was usually added?

- ○ Never added
- ○ Less than 1 teaspoon
- ○ 1 to 3 teaspoons
- ○ More than 3 teaspoons

47g. How often was **cheese** or **cheese sauce** added to your potatoes, **EITHER IN COOKING OR AT THE TABLE**?

- ○ Almost never or never (GO TO QUESTION 48)
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

Question 48 appears in the next column.

47h. Each time **cheese or cheese sauce** was added to your potatoes, how much was usually added?

- ○ Less than 1 tablespoon
- ○ 1 to 3 tablespoons
- ○ More than 3 tablespoons

48. How often did you eat **salsa**?

- ○ NEVER (GO TO QUESTION 49)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

48a. Each time you ate **salsa,** how much did you usually eat?

- ○ Less than 1 tablespoon
- ○ 1 to 5 tablespoons
- ○ More than 5 tablespoons

49. How often did you eat **ketchup**?

- ○ NEVER (GO TO QUESTION 50)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

49a. Each time you ate **ketchup,** how much did you usually eat?

- ○ Less than 1 teaspoon
- ○ 1 to 6 teaspoons
- ○ More than 6 teaspoons

50. How often did you eat **stuffing, dressing,** or **dumplings**?

- ○ NEVER (GO TO QUESTION 51)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

50a. Each time you ate **stuffing, dressing,** or **dumplings,** how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 cup
- ○ More than 1 cup

Question 51 appears on the next page.

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Over the past 12 months...

51. How often did you eat **chili**?

- ○ NEVER (GO TO QUESTION 52)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

51a. Each time you ate **chili,** how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 3/4 cups
- ○ More than 1 3/4 cups

52. How often did you eat **Mexican foods** (such as tacos, tostados, burritos, tamales, fajitas, enchiladas, quesadillas, and chimichangas)?

- ○ NEVER (GO TO QUESTION 53)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

52a. Each time you ate **Mexican foods,** how much did you usually eat?

- ○ Less than 1 taco, burrito, etc.
- ○ 1 to 2 tacos, burritos, etc.
- ○ More than 2 tacos, burritos, etc.

53. How often did you eat **cooked dried beans** (such as baked beans, pintos, kidney, blackeyed peas, lima, lentils, soybeans, or refried beans)? *(Please don't include bean soups or chili.)*

- ○ NEVER (GO TO QUESTION 54)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

53a. Each time you ate **beans,** how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 cup
- ○ More than 1 cup

Question 54 appears in the next column.

53b. How often were the beans you ate **refried beans, beans prepared with any type of fat,** or **with meat added**?

- ○ 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

54. How often did you eat **other kinds of vegetables**?

- ○ NEVER (GO TO QUESTION 55)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

54a. Each time you ate **other kinds of vegetables,** how much did you usually eat?

- ○ Less than 1/4cup
- ○ 1/4 to 1/2 cup
- ○ More than 1/2 cup

55. How often did you eat **rice** or **other cooked grains** (such as bulgur, cracked wheat, or millet)?

- ○ NEVER (GO TO QUESTION 56)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

55a. Each time you ate **rice** or **other cooked grains,** how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 1/2 cups
- ○ More than 1 1/2 cups

55b. How often was **butter, margarine,** or **oil** added to your rice **IN COOKING OR AT THE TABLE**?

- ○ 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

Question 56 appears on the next page.

Over the <u>past 12 months</u>...

56. How often did you eat **pancakes, waffles,** or **French toast**?

- ○ NEVER (GO TO QUESTION 57)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

56a. Each time you ate **pancakes, waffles,** or **French toast,** how much did you usually eat?

- ○ Less than 1 medium piece
- ○ 1 to 3 medium pieces
- ○ More than 3 medium pieces

56b. How often was **margarine** (including low-fat) added to your pancakes, waffles, or French toast, **AFTER COOKING OR AT THE TABLE**?

- ○ 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

56c. How often was **butter** (including low-fat) added to your pancakes, waffles, or French toast, **AFTER COOKING OR AT THE TABLE**?

- ○ 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

56d. Each time **margarine** or **butter** was added to your pancakes, waffles or French toast, how much was usually added?

- ○ Never added
- ○ Less than 1 teaspoon
- ○ 1 to 3 teaspoons
- ○ More than 3 teaspoons

56e. How often was **syrup** added to your pancakes, waffles, or French toast?

- ○ Almost never or never *(GO TO QUESTION 57)*
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

Question 57 appears in the next column.

56f. Each time **syrup** was added to your pancakes, waffles, or French toast, how much was usually added?

- ○ Less than 1 tablespoon
- ○ 1 to 4 tablespoons
- ○ More than 4 tablespoons

57. How often did you eat **lasagna, stuffed shells, stuffed manicotti, ravioli,** or **tortellini**? (Please do not include spaghetti or other pasta.)

- ○ NEVER (GO TO QUESTION 58)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

57a. Each time you ate **lasagna, stuffed shells, stuffed manicotti, ravioli,** or **tortellini,** how much did you usually eat?

- ○ Less than 1 cup
- ○ 1 to 2 cups
- ○ More than 2 cups

58. How often did you eat **macaroni and cheese**?

- ○ NEVER (GO TO QUESTION 59)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

58a. Each time you ate **macaroni and cheese**, how much did you usually eat?

- ○ Less than 1 cup
- ○ 1 to 1 1/2 cups
- ○ More than 1 1/2 cups

59. How often did you eat **pasta salad** or **macaroni salad?**

- ○ NEVER (GO TO QUESTION 60)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

Question 60 appears on the next page.

59a. Each time you ate **pasta salad** or **macaroni salad,** how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 cup
- ○ More than 1 cup

60. Other than the pastas listed in Questions 57, 58, and 59, how often did you eat **pasta, spaghetti,** or **other noodles?**

○ NEVER (GO TO QUESTION 61)

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

60a. Each time you ate **pasta, spaghetti,** or **other noodles,** how much did you usually eat?

- ○ Less than 1 cup
- ○ 1 to 3 cups
- ○ More than 3 cups

60b. How often did you eat your pasta, spaghetti, or other noodles with **tomato sauce** or **spaghetti sauce made WITH meat**?

- ○ 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

60c. How often did you eat your pasta, spaghetti, or other noodles with **tomato sauce** or **spaghetti sauce made WITHOUT meat**?

- ○ 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

60d. How often did you eat your pasta, spaghetti, or other noodles with **margarine, butter, oil,** or **cream sauce**?

- ○ 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

Question 61 appears in the next column.

61. How often did you eat **bagels** or **English muffins**?

○ NEVER (GO TO INTRODUCTION TO QUESTION 62)

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

61a. Each time you ate **bagels** or **English muffins,** how much did you usually eat?

- ○ Less than 1 bagel or English muffin
- ○ 1 bagel or English muffin
- ○ More than 1 bagel or English muffin

61b. How often was **margarine** (including low-fat) added to your bagels or English muffins?

- ○ 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

61c. How often was **butter** (including low-fat) added to your bagels or English muffins?

- ○ 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

61d. Each time **margarine** or **butter** was added to your bagels or English muffins, how much was usually added?

- ○ Never added
- ○ Less than 1 teaspoon
- ○ 1 to 2 teaspoons
- ○ More than 2 teaspoons

61e. How often was **cream cheese** (including low-fat**)** added to your bagels or English muffins?

- ○ Almost never or never (GO TO INTRODUCTION TO QUESTION 62)
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

Question 62 appears on the next page.

Over the past 12 months...

61f. Each time **cream cheese** was added to your bagels or English muffins, how much was usually added?

- ○ Less than 1 tablespoon
- ○ 1 to 2 tablespoons
- ○ More than 2 tablespoons

The next questions ask about your intake of breads other than bagels or English muffins. First, we will ask about bread you ate as part of sandwiches only. Then we will ask about all other bread you ate.

62. How often did you eat **breads** or **rolls AS PART OF SANDWICHES** (including burger and hot dog rolls)?

- ○ NEVER (GO TO QUESTION 63)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

62a. Each time you ate **breads** or **rolls AS PART OF SANDWICHES,** how much did you usually eat?

- ○ 1 slice or 1/2 roll
- ○ 2 slices or 1 roll
- ○ More than 2 slices or more than 1 roll

62b. How often were the breads or rolls that you used for your sandwiches **white bread** (including burger and hot dog rolls)?

- ○ 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

62c. How often was **mayonnaise** or **mayonnaise-type dressing** (including low-fat) added to your sandwich breads or rolls?

- ○ Almost never or never (GO TO QUESTION 62e)
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

Question 62e appears in the next column.

Question 63 appears in the next column.

62d. Each time **mayonnaise** or **mayonnaise-type dressing** was added to your sandwich breads or rolls, how much was usually added?

- ○ Less than 1 teaspoon
- ○ 1 to 3 teaspoons
- ○ More than 3 teaspoons

62e. How often was **margarine** (including low-fat) added to your sandwich bread or rolls?

- ○ 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

62f. How often was **butter** (including low-fat) added to your sandwich breads or rolls?

- ○ 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

62g. Each time **margarine** or **butter** was added to your sandwich breads or rolls, how much was usually added?

- ○ Never added
- ○ Less than 1 teaspoon
- ○ 1 to 2 teaspoons
- ○ More than 2 teaspoons

63. How often did you eat **breads** or **dinner rolls NOT AS PART OF SANDWICHES** ?

- ○ NEVER (GO TO QUESTION 64)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

63a. Each time you ate **breads** or **dinner rolls NOT AS PART OF SANDWICHES,** how much did you usually eat?

- ○ 1 slice or 1 dinner roll
- ○ 2 slices or 2 dinner rolls
- ○ More than 2 slices or 2 dinner rolls

Question 64 appears on the next page.

Over the past 12 months...

63b. How often were the breads or rolls you ate **white bread**?

- ○ 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

63c. How often was **margarine** (including low-fat) added to your breads or rolls?

- ○ 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

63d. How often was **butter** (including low-fat) added to your breads or rolls?

- ○ 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

63e. Each time **margarine** or **butter** was added to your breads or rolls, how much was usually added?

- ○ Never added
- ○ Less than 1 teaspoon
- ○ 1 to 2 teaspoons
- ○ More than 2 teaspoons

63f. How often was **cream cheese** (including low-fat) added to your breads or rolls?

- ○ Almost never or never *(GO TO QUESTION 64)*
- ○ About 1/4 of the time
- ○ About 1/2 of the time
- ○ About 3/4 of the time
- ○ Almost always or always

63g. Each time **cream cheese** was added to your breads or rolls, how much was usually added?

- ○ Less than 1 tablespoon
- ○ 1 to 2 tablespoons
- ○ More than 2 tablespoons

Question 64 appears in the next column.

64. How often did you eat **jam, jelly,** or **honey** on bagels, muffins, bread, rolls, or crackers?

○ NEVER (GO TO QUESTION 65)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

64a. Each time you ate **jam, jelly** or **honey,** how much did you usually eat?

- ○ Less than 1 teaspoon
- ○ 1 to 3 teaspoons
- ○ More than 3 teaspoons

65. How often did you eat **peanut butter** or **other nut butter**?

○ NEVER (GO TO QUESTION 66)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

65a. Each time you ate **peanut butter** or **other nut butter,** how much did you usually eat?

- ○ Less than 1 tablespoon
- ○ 1 to 2 tablespoons
- ○ More than 2 tablespoons

66. How often did you eat **roast beef** or **steak IN SANDWICHES**?

○ NEVER (GO TO QUESTION 67)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

66a. Each time you ate **roast beef** or **steak IN SANDWICHES,** how much did you usually eat?

- ○ Less than 1 slice or less than 2 ounces
- ○ 1 to 2 slices or 2 to 4 ounces
- ○ More than 2 slices or more than 4 ounces

Question 67 appears on the next page.

67. How often did you eat **turkey** or **chicken COLD CUTS** (such as loaf, luncheon meat, turkey ham, turkey salami, or turkey pastrami)? *(We will ask about other turkey or chicken later.)*

○ NEVER (GO TO QUESTION 68)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

67a. Each time you ate **turkey,** or **chicken COLD CUTS,** how much did you usually eat?

○ Less than 1 slice
○ 1 to 3 slices
○ More than 3 slices

68. How often did you eat **luncheon** or **deli-style ham**? *(We will ask about other ham later.)*

○ NEVER (GO TO QUESTION 69)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

68a. Each time you ate **luncheon** or **deli-style ham,** how much did you usually eat?

○ Less than 1 slice
○ 1 to 3 slices
○ More than 3 slices

68b. How often was the luncheon or deli-style ham you ate **light, low-fat,** or **fat-free**?

○ 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

Question 69 appears in the next column.

69. How often did you eat **other cold cuts** or **luncheon meats** (such as bologna, salami, corned beef, pastrami, or others, including low-fat)? *(Please do not include ham, turkey, or chicken cold cuts.)*

○ NEVER (GO TO QUESTION 70)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

69a. Each time you ate **other cold cuts** or **luncheon meats,** how much did you usually eat?

○ Less than 1 slice
○ 1 to 3 slices
○ More than 3 slices

69b. How often were the other cold cuts or luncheon meats you ate **light, low-fat,** or **fat-free**? *(Please do not include ham, turkey, or chicken cold cuts.)*

○ 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

70. How often did you eat **canned tuna** *(including in salads, sandwiches, or casseroles)?*

○ NEVER (GO TO QUESTION 71)

○ 1-6 times per year
○ 7-11 times per year
○ 1 time per month
○ 2-3 times per month
○ 1 time per week
○ 2 times per week
○ 3-4 times per week
○ 5-6 times per week
○ 1 time per day
○ 2 or more times per day

70a. Each time you ate **canned tuna,** how much did you usually eat?

○ Less than 1/4 cup or less than 2 ounces
○ 1/4 to 1/2 cup or 2 to 3 ounces
○ More than 1/2 cup or more than 3 ounces

70b. How often was the canned tuna you ate **water-packed tuna**?

○ 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

Question 71 appears on the next page.

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70c. How often was the canned tuna you ate **prepared with mayonnaise** or **other dressing** (including low-fat)?

- ○ 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

71. How often did you eat **GROUND chicken or turkey**? *(We will ask about other chicken and turkey later.)*

○ NEVER (GO TO QUESTION 72)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

71a. Each time you ate **GROUND chicken** or **turkey,** how much did you usually eat?

- ○ Less than 2 ounces or less than 1/2 cup
- ○ 2 to 4 ounces or 1/2 to 1 cup
- ○ More than 4 ounces or more than 1 cup

72. How often did you eat **beef hamburgers** or **cheeseburgers**?

○ NEVER (GO TO QUESTION 73)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

72a. Each time you ate **beef hamburgers** or **cheeseburgers,** how much did you usually eat?

- ○ Less than 1 patty or less than 2 ounces
- ○ 1 patty or 2 to 4 ounces
- ○ More than 1 patty or more than 4 ounces

72b. How often were the beef hamburgers or cheeseburgers you ate made with **lean ground beef**?

- ○ 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

Question 73 appears in the next column.

73. How often did you eat **ground beef in mixtures** (such as meatballs, casseroles, chili, or meatloaf)?

○ NEVER (GO TO QUESTION 74)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

73a. Each time you ate **ground beef in mixtures,** how much did you usually eat?

- ○ Less than 3 ounces or less than 1/2 cup
- ○ 3 to 8 ounces or 1/2 to 1 cup
- ○ More than 8 ounces or more than 1 cup

74. How often did you eat **hot dogs or frankfurters**? *(Please do not include sausages or vegetarian hot dogs.)*

○ NEVER (GO TO QUESTION 75)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

74a. Each time you ate **hot dogs** or **frankfurters,** how many did you usually eat?

- ○ Less than 1 hot dog
- ○ 1 to 2 hot dogs
- ○ More than 2 hot dogs

74b. How often were the hot dogs or frankfurters you ate **light** or **low-fat hot dogs**?

- ○ 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

Question 75 appears on the next page.

75. How often did you eat beef mixtures such as **beef stew, beef pot pie, beef and noodles,** or **beef and vegetables**?

- ○ NEVER (GO TO QUESTION 76)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

75a. Each time you ate **beef stew, beef pot pie, beef and noodles,** or **beef and vegetables,** how much did you usually eat?

- ○ Less than 1 cup
- ○ 1 to 2 cups
- ○ More than 2 cups

76. How often did you eat **roast beef** or **pot roast**? *(Please do not include roast beef or pot roast in sandwiches.)*

- ○ NEVER (GO TO QUESTION 77)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

76a. Each time you ate **roast beef** or **pot roast,** (including in mixtures) how much did you usually eat?

- ○ Less than 2 ounces
- ○ 2 to 5 ounces
- ○ More than 5 ounces

77. How often did you eat **steak** (beef)? *(Do not include steak in sandwiches.)*

- ○ NEVER (GO TO QUESTION 78)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

77a. Each time you ate **steak** (beef), how much did you usually eat?

- ○ Less than 3 ounces
- ○ 3 to 7 ounces
- ○ More than 7 ounces

Question 78 appears in the next column.

77b. How often was the steak you ate **lean steak**?

- ○ 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

78. How often did you eat **pork** or **beef spareribs**?

- ○ NEVER (GO TO QUESTION 79)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

78a. Each time you ate **pork** or **beef spareribs**, how much did you usually eat?

- ○ Less than 4 ribs
- ○ 4 to 12 ribs
- ○ More than 12 ribs

79. How often did you eat **roast turkey, turkey cutlets,** or **turkey nuggets** (including in sandwiches)?

- ○ NEVER (GO TO QUESTION 80)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

79a. Each time you ate **roast turkey, turkey cutlets,** or **turkey nuggets**, how much did you usually eat? *(Please note: 4-8 turkey nuggets=3 ounces.)*

- ○ Less than 2 ounces
- ○ 2 to 4 ounces
- ○ More than 4 ounces

80. How often did you eat **chicken** as part of **salads, sandwiches, casseroles, stews,** or **other mixtures**?

- ○ NEVER (GO TO QUESTION 81)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

Question 81 appears on the next page.

Over the past 12 months...

80a. Each time you ate **chicken** as part of **salads, sandwiches, casseroles, stews,** or **other mixtures**, how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 1/2 cups
- ○ More than 1 1/2 cups

81. How often did you eat **baked, broiled, roasted, stewed,** or **fried chicken** (including nuggets)? *(Please do not include chicken in mixtures.)*

- ○ NEVER (GO TO QUESTION 82)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

81a. Each time you ate **baked, broiled, roasted, stewed,** or **fried chicken** (including nuggets), how much did you usually eat?

- ○ Less than 2 drumsticks or wings, 1 breast or thigh, or less than 4 nuggets
- ○ 2 drumsticks or wings, 1 breast or thigh, or 4 to 8 nuggets
- ○ More than 2 drumsticks or wings, 1 breast or thigh, or more than 8 nuggets

81b. How often was the chicken you ate **fried chicken** (including deep fried) or **chicken nuggets**?

- ○ 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

81c. How often was the chicken you ate **WHITE meat**?

- ○ 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

81d. How often did you eat chicken **WITH skin**?

- ○ 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

Question 82 appears in the next column.

82. How often did you eat **baked ham** or **ham steak**?

- ○ NEVER (GO TO QUESTION 83)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

82a. Each time you ate **baked ham** or **ham steak**, how much did you usually eat?

- ○ Less than 1 ounce
- ○ 1 to 3 ounces
- ○ More than 3 ounces

83. How often did you eat **pork** (including chops, roasts, and in mixed dishes)? *(Please do not include ham, ham steak, or sausage.)*

- ○ NEVER (GO TO QUESTION 84)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

83a. Each time you ate **pork**, how much did you usually eat?

- ○ Less than 2 ounces or less than 1 chop
- ○ 2 or 5 ounces or 1 chop
- ○ More than 5 ounces or more than 1 chop

84. How often did you eat **gravy** on meat, chicken, potatoes, rice, etc?

- ○ NEVER (GO TO QUESTION 85)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

84a. Each time you ate **gravy** on meat, chicken, potatoes, or rice, etc., how much did you usually eat?

- ○ Less than 1/8 cup
- ○ 1/8 to 1/2 cup
- ○ More than 1/2 cup

Question 85 appears on the next page.

Over the past 12 months...

85. How often did you eat **liver** (all kinds) or **liverwurst**?

- ○ NEVER (GO TO QUESTION 86)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

85a. Each time you ate **liver** or **liverwurst**, how much did you usually eat?

- ○ Less than 1 ounce
- ○ 1 to 4 ounces
- ○ More than 4 ounces

86. How often did you eat **bacon** (including low-fat)?

- ○ NEVER (GO TO QUESTION 87)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

86a. Each time you ate **bacon**, how much did you usually eat?

- ○ Fewer than 2 slices
- ○ 2 to 3 slices
- ○ More than 3 slices

86b. How often was the bacon you ate **light, low-fat,** or **lean bacon**?

- ○ 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

87. How often did you eat **sausage** (including low-fat)?

- ○ NEVER (GO TO QUESTION 88)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

Question 88 appears in the next column.

87a. Each time you ate **sausage**, how much did you usually eat?

- ○ Fewer than 1 patty or 2 links
- ○ 1 to 3 patties or 2 to 5 links
- ○ More than 3 patties or 5 links

87b. How often was the sausage you ate **light, low-fat,** or **lean sausage**?

- ○ 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

88. How often did you eat **fish sticks** or **fried fish** (including fried seafood or shellfish)?

- ○ NEVER (GO TO QUESTION 89)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

88a. Each time you ate **fish sticks** or **fried fish**, how much did you usually eat?

- ○ Less than 2 ounces or less than 1 fillet
- ○ 2 to 7 ounces or 1 fillet
- ○ More than 7 ounces or more than 1 fillet

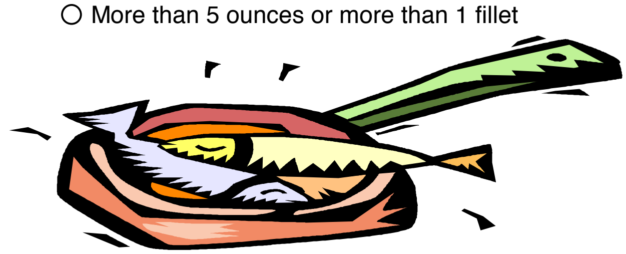
89. How often did you eat **fish** or **seafood that was NOT FRIED** (including shellfish)?

- ○ NEVER (GO TO THE INTRODUCTION TO QUESTION 90)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

89a. Each time you ate **fish** or **seafood that was not fried**, how much did you usually eat?

- ○ Less than 2 ounces or less than 1 fillet
- ○ 2 to 5 ounces or 1 fillet
- ○ More than 5 ounces or more than 1 fillet



Question 90 appears on the next page

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Now think about all the meat, poultry, and fish you ate in the past 12 months and how they were prepared.

90. How often was **oil, butter, margarine,** or **other fat used to FRY, SAUTE, BASTE, OR MARINATE** any meat, poultry, or fish you ate? *(Please do not include deep frying.)*

- ○ NEVER (GO TO QUESTION 91)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

90a. Which of the following **fats** were regularly used to prepare your meat, poultry, or fish? ***(Mark all that apply.)***

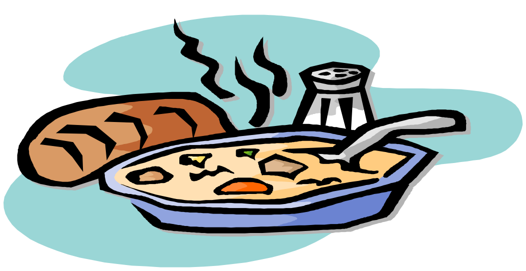
- ○ Margarine (including low-fat)
- ○ Butter (including low-fat)
- ○ Lard, fatback, or bacon fat
- ○ Olive oil
- ○ Corn oil
- ○ Canola or rapeseed oil
- ○ Oil spray, such as Pam or others
- ○ Other kinds of oils
- ○ None of the above

91. How often did you eat **tofu, soya burgers,** or **soy meat-substitutes**?

- ○ NEVER (GO TO QUESTION 92)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

91a. Each time you ate **tofu, soy burgers, or soy meat-substitutes,** how much did you usually eat?

- ○ Less than 1/4 cup or less than 2 ounces
- ○ 1/4 to 1/2 cup or 2 to 4 ounces
- ○ More than 1/2 cup or more than 4 ounces



Question 92 appears in the next column.

92. Over the past 12 months, did you eat **soups**?

- ○ NO (GO TO QUESTION 93)
- ○ YES

92a. How often did you eat **soup DURING THE WINTER**?

- ○ NEVER
- ○ 1-6 times per winter
- ○ 7-11 times per winter
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

92b. How often did you eat **soup DURING THE REST OF THE YEAR**?

- ○ NEVER
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

92c. Each time you ate **soup,** how much did you usually eat?

- ○ Less than 1 cup
- ○ 1 to 2 cups
- ○ More than 2 cups

92d. How often were the soups you ate **bean soups**?

- ○ 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

92e. How often were the soups you ate **cream soups** (including chowders)?

- ○ 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

Question 93 appears on the next page.

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Over the past 12 months...

92f. How often were the soups you ate **tomato** or **vegetable soups**?

- ○ 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

92g. How often were the soups you ate **broth soups** (including chicken) **with** or **without noodles** or **rice**?

- ○ 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

93. How often did you eat **pizza**?

○ NEVER (GO TO QUESTION 94)

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

93a. Each time you ate **pizza,** how much did you usually eat?

- ○ Less than 1 slice or less than 1 mini pizza
- ○ 1 to 3 slices or 1 mini pizza
- ○ More than 3 slices or more than 1 mini pizza

93b. How often did you eat pizza with **pepperoni, sausage,** or **other meat**?

- ○ 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

94. How often did you eat **crackers**?

○ NEVER (GO TO QUESTION 95)

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

Question 95 appears in the next column.

94a. Each time you ate **crackers,** how much did you usually eat?

- ○ Fewer than 4 crackers
- ○ 4 to 10 crackers
- ○ More than 10 crackers

95. How often did you eat **corn bread** or **corn muffins**?

○ NEVER (GO TO QUESTION 96)

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

95a. Each time you ate **corn bread** or **corn muffins,** how much did you usually eat?

- ○ Less than 1 piece or muffin
- ○ 1 to 2 pieces or muffins
- ○ More than 2 pieces or muffins

96. How often did you eat **baking powder biscuits**?

○ NEVER (GO TO QUESTION 97)

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

96a. Each time you ate **baking powder biscuits,** how many did you usually eat?

- ○ Fewer than 1 biscuit
- ○ 1 to 2 biscuits
- ○ More than 2 biscuits

97. How often did you eat **potato chips, tortilla chips,** or **corn chips** (including low-fat, fat-free, or low-salt)?

○ NEVER (GO TO QUESTION 98)

- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

Question 98 appears on the next page

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97a. Each time you ate **potato chips, tortilla chips,** or **corn chips,** how much did you usually eat?

- ○ Fewer than 10 chips or less than 1 cup
- ○ 10 to 25 chips or 1 to 2 cups
- ○ More than 25 chips or more than 2 cups

97b. How often were the chips you ate **low-fat,** or **fat-free chips**?

- ○ 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

98. How often did you eat **popcorn** (including low-fat)?

○ NEVER (GO TO QUESTION 99)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

98a. Each time you ate **popcorn,** how much did you usually eat?

- ○ Less than 2 cups, popped
- ○ 2 to 5 cups, popped
- ○ More than 5 cups, popped

99. How often did you eat **pretzels**?

○ NEVER (GO TO QUESTION 100)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

99a. Each time you ate **pretzels,** how many did you usually eat?

- ○ Fewer than 5 average twists
- ○ 5 to 20 average twists
- ○ More than 20 average twists

Question 100 appears in the next column.

100. How often did you eat **peanuts, walnuts, seeds,** or **other nuts**?

○ NEVER (GO TO QUESTION 101)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

100a. Each time you ate **peanuts, walnuts, seeds,** or **other nuts,** how much did you usually eat?

- ○ Less than 1/4 cup
- ○ 1/4 to 1/2 cup
- ○ More than 1/2 cup

101. How often did you eat **energy, high-protein,** or **breakfast bars** such as **Power Bars, Balance, Clif, Boost** or **others**?

○ NEVER (GO TO QUESTION 102)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

101a. Each time you ate **energy, high-protein,** or **breakfast bars,** how much did you usually eat?

- ○ Less than 1 bar
- ○ 1 bar
- ○ More than 1 bar

102. How often did you eat **yogurt** (NOT including frozen yogurt)?

○ NEVER (GO TO QUESTION 103)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

102a. Each time you ate **yogurt,** how much did you usually eat?

- ○ Less than 1/2 cup or less than 1 container
- ○ 1/2 to 1 cup or 1 container
- ○ More than 1 cup or more than 1 container

Question 103 appears on the next page.

103. How often did you eat **cottage cheese** (including low-fat)?

- ○ NEVER (GO TO QUESTION 104)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

103a. Each time you ate **cottage cheese,** how much did you usually eat?

- ○ Less than 1/4 cup
- ○ 1/4 to 1 cup
- ○ More than 1 cup

104. How often did you eat **cheese** (including low-fat; including on cheeseburgers or in sandwiches or subs)?

- ○ NEVER (GO TO QUESTION 105)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

104a. Each time you ate **cheese,** how much did you usually eat?

- ○ Less than 1/2 ounce or less than 1 slice
- ○ 1/2 to 1 1/2 ounces or 1 slice
- ○ More than 1 1/2 ounces or more than 1 slice

104b. How often was the cheese you ate **light** or **low-fat cheese**?

- ○ 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

104c. How often was the **cheese** you ate **fat-free cheese**?

- ○ 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

Question 105 appears in the next column.

105. How often did you eat **frozen yogurt, sorbet,** or **ices** (including low-fat or fat-free)?

- ○ NEVER (GO TO QUESTION 106)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

105a. Each time you ate **frozen yogurt, sorbet,** or **ices,** how much did you usually eat?

- ○ Less than 1/2 cup or less than 1 scoop
- ○ 1/2 to 1 cup or 1 to 2 scoops
- ○ More than 1 cup or more than 2 scoops

106. How often did you eat **ice cream, ice cream bars,** or **sherbet** (including low-fat or fat-free)?

- ○ NEVER (GO TO QUESTION 107)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

106a. Each time you ate **ice cream, ice cream bars, or sherbet,** how much did you usually eat?

- ○ Less than 1/2 cup or less than 1 scoop
- ○ 1/2 to 1 1/2 cups or 1 to 2 scoops
- ○ More than 1 1/2 cups or more than 2 scoops

106b. How often was the ice cream you ate **light, low-fat,** or **fat-free ice cream** or **sherbet**?

- ○ 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

107. How often did you eat **cake** (including low-fat or fat-free)?

- ○ NEVER (GO TO QUESTION 108)

○ 1-6 times per year	○ 2 times per week
○ 7-11 times per year	○ 3-4 times per week
○ 1 time per month	○ 5-6 times per week
○ 2-3 times per month	○ 1 time per day
○ 1 time per week	○ 2 or more times per day

Question 108 appears on the next page.

107a. Each time you ate **cake,** how much did you usually eat?

- ○ Less than 1 medium piece
- ○ 1 medium piece
- ○ More than 1 medium piece

107b. How often was the cake you ate **light, low-fat,** or **fat-free cake**?

- ○ 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

108. How often did you eat **cookies** or **brownies** (including low-fat or fat-free)?

- ○ NEVER (GO TO QUESTION 109)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

108a. Each time you ate **cookies** or **brownies,** how much did you usually eat?

- ○ Less than 2 cookies or 1 small brownie
- ○ 2 to 4 cookies or 1 medium brownie
- ○ More than 4 cookies or 1 large brownie

108b. How often were the cookies or brownies you ate **light, low-fat,** or **fat-free cookies or brownies**?

- ○ 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

109. How often did you eat **doughnuts, sweet rolls, Danish,** or **pop tarts**?

- ○ NEVER (GO TO QUESTION 110)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

Question 110 appears in the next column.

109a. Each time you ate **doughnuts, sweet rolls, Danish,** or **pop tarts,** how much did you usually eat?

- ○ Less than 1 piece
- ○ 1 to 2 pieces
- ○ More than 2 pieces

110. How often did you eat **sweet muffins** or **dessert breads** (including low-fat or fat-free)?

- ○ NEVER (GO TO QUESTION 111)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

110a. Each time you ate **sweet muffins** or **dessert breads,** how much did you usually eat?

- ○ Less than 1 medium piece
- ○ 1 medium piece
- ○ More than 1 medium piece

110b. How often were the sweet muffins or dessert breads you ate **light, low-fat,** or **fat-free sweet muffins** or **dessert breads**?

- ○ 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

111. How often did you eat **fruit crisp, cobbler,** or **strudel**?

- ○ NEVER (GO TO QUESTION 112)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

111a. Each time you ate **fruit crisp, cobbler, or strudel,** how much did you usually eat?

- ○ Less than 1/2 cup
- ○ 1/2 to 1 cup
- ○ More than 1 cup

Question 112 appears on the next page.

Over the past 12 months...

112. How often did you eat **pie**?

- ○ NEVER (GO TO QUESTION 113)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

112a. Each time you ate **pie,** how much did you usually eat?

- ○ Less than 1/8 of a pie
- ○ About 1/8 of a pie
- ○ More than 1/8 of a pie

The next four questions ask about the kinds of pie you ate. Please read all four questions before answering.

112b. How often were the pies you ate **fruit pie** (such as apple, blueberry, others)?

- ○ 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

112c. How often were the pies you ate **cream, pudding, custard,** or **meringue pie**?

- ○ 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

112d. How often was the pie you ate **pumpkin pie**?

- ○ 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

112e. How often was the pie you ate **pecan pie**?

- ○ 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

Question 113 appears in the next column.

113. How often did you eat **chocolate**?

- ○ NEVER (GO TO QUESTION 114)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

113a. Each time you ate **chocolate,** how much did you usually eat?

- ○ Less than 1 average bar or less than 1 ounce
- ○ 1 average bar or 1 to 2 ounces
- ○ More than 1 average bar or more than 2 ounces

114. How often did you eat **other candy**?

- ○ NEVER (GO TO QUESTION 115)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

114a. Each time you ate **other candy,** how much did you usually eat?

- ○ Fewer than 2 pieces
- ○ 2 to 9 pieces
- ○ More than 9 pieces

115. How often did you eat **eggs, egg whites,** or **egg substitutes** (NOT including eggs in baked goods and desserts)? *(Please include eggs in salads, quiche, and souffles.)*

- ○ NEVER (GO TO QUESTION 116)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

115a. Each time you ate **eggs,** how many did you usually eat?

- ○ 1 egg
- ○ 2 eggs
- ○ 3 or more eggs

Question 116 appears on the next page.

Over the past 12 months...

115b. How often were the eggs you ate **egg substitutes**?

- ○ 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

115c. How often were the eggs you ate **egg whites only**?

- ○ 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

115d. How often were the eggs you ate **regular whole eggs**?

- ○ 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

115e. How often were the eggs you ate **cooked in oil, butter, or margarine**?

- ○ 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

115f. How often were the eggs you ate part of **egg salad**?

- ○ 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

116. How many cups of **coffee**, caffeinated or decaffeinated, did you drink?

○ NONE (GO TO QUESTION 117)

○ Less than 1 cup per month	○ 5-6 cups per week
○ 1-3 cups per month	○ 1 cup per day
○ 1 cup per week	○ 2-3 cups per day
○ 2-4 cups per week	○ 4-5 cups per day
	○ 6 or more cups per day

116a. How often was the coffee you drank **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

Question 117 appears in the next column.

117. How many glasses of **ICED tea**, caffeinated or decaffeinated, did you drink?

○ NONE (GO TO QUESTION 118)

○ Less than 1 cup per month	○ 5-6 cups per week
○ 1-3 cups per month	○ 1 cup per day
○ 1 cup per week	○ 2-3 cups per day
○ 2-4 cups per week	○ 4-5 cups per day
	○ 6 or more cups per day

117a. How often was the iced tea you drank **decaffeinated** or **herbal tea**?

- ○ 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

118. How many cups of **HOT tea**, caffeinated or decaffeinated, did you drink?

○ NONE (GO TO QUESTION 119)

○ Less than 1 cup per month	○ 5-6 cups per week
○ 1-3 cups per month	○ 1 cup per day
○ 1 cup per week	○ 2-3 cups per day
○ 2-4 cups per week	○ 4-5 cups per day
	○ 6 or more cups per day

118a. How often was the hot tea you drank **decaffeinated** or **herbal tea**?

- ○ 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

119. How often did you add **sugar** or **honey** to your coffee or tea?

○ NEVER (GO TO QUESTION 120)

○ Less than 1 time per month	○ 5-6 times per week
○ 1-3 times per month	○ 1 time per day
○ 1 time per week	○ 2-3 times per day
○ 2-4 times per week	○ 4-5 times per day
	○ 6 or more times per day

119a. Each time **sugar** or **honey** was added to your coffee or tea**,** how much was usually added?

- ○ Less than 1 teaspoon
- ○ 1 to 3 teaspoons
- ○ More than 3 teaspoons

Question 120 appears on the next page.

Over the past 12 months...

120. How often did you add **artificial sweetener** to your coffee or tea?

- ○ NEVER (GO TO QUESTION 121)
- ○ Less than 1 time per month
- ○ 1-3 times per month
- ○ 1 time per week
- ○ 2-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

120a. What kind of **artificial sweetener** do you usually use?

- ○ Equal or aspartame
- ○ Sweet N Low or saccharin
- ○ Splenda

121. How often was **non-dairy creamer** added to your coffee or tea?

- ○ NEVER (GO TO QUESTION 122)
- ○ Less than 1 time per month
- ○ 1-3 times per month
- ○ 1 time per week
- ○ 2-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

121a. Each time **non-dairy creamer** was added to your coffee or tea, how much was usually added?

- ○ Less than 1 teaspoon
- ○ 1 to 3 teaspoons
- ○ More than 3 teaspoons

121b. What kind of **non-dairy creamer** did you usually use?

- ○ Regular powdered
- ○ Low-fat or fat-free powdered
- ○ Regular liquid
- ○ Low-fat or fat-free liquid

122. How often was **cream** or **half and half** added to your coffee or tea?

- ○ NEVER (GO TO QUESTION 123)
- ○ Less than 1 time per month
- ○ 1-3 times per month
- ○ 1 time per week
- ○ 2-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

Question 123 appears in the next column.

122a. Each time **cream** or **half and half** was added to your coffee or tea, how much was usually added?

- ○ Less than 1 tablespoon
- ○ 1 to 2 tablespoons
- ○ More than 2 tablespoons

123. How often was **milk** added to your coffee or tea?

- ○ NEVER (GO TO QUESTION 124)
- ○ Less than 1 time per month
- ○ 1-3 times per month
- ○ 1 time per week
- ○ 2-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2-3 times per day
- ○ 4-5 times per day
- ○ 6 or more times per day

123a. Each time **milk** was added to your coffee or tea, how much was usually added?

- ○ Less than 1 tablespoon
- ○ 1 to 3 tablespoons
- ○ More than 3 tablespoons

123b. What kind of **milk** was usually added to your coffee or tea?

- ○ Whole milk
- ○ 2% fat milk
- ○ 1 % fat milk
- ○ Skim, nonfat, or 1/2% milk
- ○ Evaporated or condensed (canned) milk
- ○ Soy milk
- ○ Rice milk
- ○ Other

124. How often was **sugar** or **honey** added to foods you ate? (Please do not include sugar in coffee, tea, other beverages, or baked goods).

- ○ NEVER (GO TO INTRODUCTION TO QUESTION 125)
- ○ 1-6 times per year
- ○ 7-11 times per year
- ○ 1 time per month
- ○ 2-3 times per month
- ○ 1 time per week
- ○ 2 times per week
- ○ 3-4 times per week
- ○ 5-6 times per week
- ○ 1 time per day
- ○ 2 or more times per day

124a. Each time **sugar** or **honey** was added to foods you ate, how much was usually added?

- ○ Less than 1 teaspoon
- ○ 1 to 3 teaspoons
- ○ More than 3 teaspoons

Question 125 appears on the next page.

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The following questions are about the kinds of margarine, mayonnaise, sour cream, cream cheese, and salad dressing that you eat. If possible, please check the labels of these foods to help you answer.

125. Over the <u>past 12 months,</u> did you eat **margarine**?

- ○ NO (GO TO QUESTION 126)
- ○ YES

125a. How often was the margarine you ate **regular-fat margarine** (stick or tub)?

- ○ 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

125b. How often was the margarine you ate **light** or **low-fat margarine** (stick or tub)?

- ○ 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

125c. How often was the margarine you ate **fat-free margarine**?

- ○ 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

126. Over the <u>past 12 months,</u> did you eat **butter**?

- ○ NO (GO TO QUESTION 127)
- ○ YES

126a. How often was the butter you ate **light** or **low-fat** butter)?

- ○ 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

Question 127 appears in the next column.

127. Over the <u>past 12 months,</u> did you eat **mayonnaise** or **mayonnaise-type dressing**?

- ○ NO (GO TO QUESTION 128)
- ○ YES

127a. How often was the mayonnaise you ate **regular-fat mayonnaise**?

- ○ 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

127b. How often was the mayonnaise you ate **light** or **low-fat mayonnaise**?

- ○ 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

127c. How often was the mayonnaise you ate **fat-free mayonnaise**?

- ○ 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

128. Over the <u>past 12 months</u>, did you eat **sour cream**?

- ○ NO (GO TO QUESTION 129)
- ○ YES

128a. How often was the sour cream you ate **regular-fat sour cream**?

- ○ 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

128b. How often was the sour cream you ate **light, low-fat** or **fat-free sour cream**?

- ○ 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

Question 129 appears on the next page.

Over the past 12 months...

129. Over the past 12 months, did you eat **cream cheese**?

- ○ NO (GO TO QUESTION 130)
- ○ YES

129a. How often was the cream cheese you ate **regular-fat cream cheese**?

- ○ 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

129b. How often was the cream cheese you ate **light, low-fat** or **fat-free cream cheese**?

- ○ 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

130. Over the past 12 months, did you eat **salad dressing**?

- ○ NO (GO TO INTRODUCTION TO QUESTION 131)
- ○ YES

130a. How often was the salad dressing you ate **regular-fat salad dressing** (including oil and vinegar dressing)?

- ○ 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

130b. How often was the salad dressing you ate **light** or **low-fat salad dressing**?

- ○ 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

130c. How often was the salad dressing you ate **fat-free salad dressing**?

- ○ 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

Question 131 appears in the next column.

The following two questions ask you to summarize your usual intake of vegetables and fruits. Please do not include salads, potatoes, or juices.

131. Over the past 12 months, how many servings of **vegetables** (not including salad or potatoes) did you eat per week or per day?

- ○ Less than 1 per week
- ○ 1-2 per week
- ○ 3-4 per week
- ○ 5-6 per week
- ○ 1 per day
- ○ 2 per day
- ○ 3 per day
- ○ 4 per day
- ○ 5 or more per day

132. Over the past 12 months, how many servings of **fruit** (not including juices) did you eat per week or per day?

- ○ Less than 1 per week
- ○ 1-2 per week
- ○ 3-4 per week
- ○ 5-6 per week
- ○ 1 per day
- ○ 2 per day
- ○ 3 per day
- ○ 4 per day
- ○ 5 or more per day

133. Over the past month, which of the following foods did you eat **AT LEAST THREE TIMES?** ***(Mark as many as apply.)***

- ○ Avocado, guacamole
- ○ Cheesecake
- ○ Chocolate, fudge, or butterscotch toppings or syrups
- ○ Chow mein noodles
- ○ Croissants
- ○ Dried apricots
- ○ Egg rolls
- ○ Granola bars
- ○ Hot peppers
- ○ Jello, gelatin
- ○ Milkshakes or ice-cream sodas
- ○ Olives
- ○ Oysters
- ○ Pickles or pickled vegetables or fruit
- ○ Plantains
- ○ Pork neckbones, hock, head, feet
- ○ Pudding or custard
- ○ Veal, venison, lamb
- ○ Whipped cream, regular
- ○ Whipped cream, substitute
- ○ NONE

134. For all of the past 12 months, have you followed any type of **vegetarian diet**?

- ○ NO (GO TO INTRODUCTION TO QUESTION 135)
- ○ YES

134a. Which of the following food did you **TOTALLY EXCLUDE** from your diet? *(Mark all that apply.)*

- ○ Meat (beef, pork, lamb, etc.)
- ○ Poultry (chicken, turkey, duck)
- ○ Fish and seafood
- ○ Eggs
- ○ Dairy products (milk, cheese, etc.)

Question 135 appears in the next column.

The next questions are about your use of fiber supplements or vitamin pills.

135. Over the <u>past 12 months</u>, did you take any of the following types of **fiber** or **fiber supplements** on a regular basis (more than once per week for at least 6 of the last 12 months)? ***(Mark all that apply.)***

- ○ NO, didn't take any fiber supplements on a regular basis (GO TO QUESTION 136)
- ○ YES, psyllium products (such as Metamucil, Prodiem, Correctol)
- ○ YES, Bran (such as wheat bran, oat bran, or bran wafers)

136. Over the <u>past 12 months</u>, did you take any **multivitamins,** such as One-a-Day-, or Centrum-type multivitamins (as pills, liquids, or packets)?

- ○ NO (GO TO INTRODUCTION TO QUESTION 138)
- ○ YES

137. How often did you take **<u>One-a-Day-, or Centrum-type</u>** multivitamins?

- ○ Less than 1 day per month
- ○ 1-3 days per month
- ○ 1-3 days per week
- ○ 4-6 days per week
- ○ Every day

137a. Does your **multivitamin** usually contain **minerals** (such as iron, zinc, etc.)?

- ○ NO
- ○ YES
- ○ Don't know

137b. For how many years have you taken **multivitamins**?

- ○ Less than 1 year
- ○ 1-4 years
- ○ 5-9 years
- ○ 10 or more years

Question 138 appears in the next column.

These last questions are about the vitamins, minerals, or herbal supplements you took that are <u>NOT</u> part of a One-a-Day- or Centrum-type of multivitamin. Please include vitamins taken as part of an antioxidant supplement.

138. How often did you take **Beta-carotene (NOT** as part of a multivitamin in Question 137)?

- ○ NEVER (GO TO QUESTION 139)
- ○ Less than 1 day per month
- ○ 1-3 days per month
- ○ 1-3 days per week
- ○ 4-6 days per week
- ○ Every day

138a. When you took **Beta-carotene**, about how much did you take in one day?

- ○ Less than 10,000 IU
- ○ 10,000 -14,999 IU
- ○ 15,000 - 19,999 IU
- ○ 20,000 - 24,999 IU
- ○ 25,000 IU or more
- ○ Don't know

138b. For how many years have you taken **Beta-carotene**?

- ○ Less than 1 year
- ○ 1-4 years
- ○ 5-9 years
- ○ 10 or more years

139. How often did you take **Vitamin A** (**NOT** as part of a multivitamin in Question 137)?

- ○ NEVER (GO TO QUESTION 140)
- ○ Less than 1 day per month
- ○ 1-3 days per month
- ○ 1-3 days per week
- ○ 4-6 days per week
- ○ Every day

139a. When you took **Vitamin A**, about how much did you take in one day?

- ○ Less than 8,000 IU
- ○ 8,000 - 9,999 IU
- ○ 10,000 - 14,999 IU
- ○ 15,000 - 24,999 IU
- ○ 25,000 IU or more
- ○ Don't know

Question 140 appears on the next page.

139b. For how many years have you taken **Vitamin A**?

- ○ Less than 1 year
- ○ 1-4 years
- ○ 5-9 years
- ○ 10 or more years

140. How often did you take **Vitamin C (NOT** as part of a multivitamin in Question 137)?

- ○ NEVER (GO TO QUESTION 141)
- ○ Less than 1 day per month
- ○ 1-3 days per month
- ○ 1-3 days per week
- ○ 4-6 days per week
- ○ Every day

140a. When you took **Vitamin C**, about how much did you take in one day?

- ○ Less than 500 mg
- ○ 500-999 mg
- ○ 1,000-1,499 mg
- ○ 1,500-1,999 mg
- ○ 2,000 mg or more
- ○ Don't know

140b. For how many years have you taken **Vitamin C**?

- ○ Less than 1 year
- ○ 1-4 years
- ○ 5-9 years
- ○ 10 or more years

141. How often did you take **Vitamin E (NOT** as part of a multivitamin in Question 137)?

- ○ NEVER (GO TO QUESTION 142)
- ○ Less than 1 day per month
- ○ 1-3 days per month
- ○ 1-3 days per week
- ○ 4-6 days per week
- ○ Every day

Question 142 appears in the next column.

141a. When you took **Vitamin E**, about how much did you take in one day?

- ○ Less than 400 IU
- ○ 400-799 IU
- ○ 800-999 IU
- ○ 1,000 IU or more
- ○ Don't know

141b. For how many years have you taken **Vitamin E**?

- ○ Less than 1 year
- ○ 1 - 4 years
- ○ 5 - 9 years
- ○ 10 or more years

142. How often did you take **Calcium supplements** or **Calcium containing antacids (NOT** as part of a multi vitamin in Question 137)?

- ○ NEVER (GO TO QUESTION 143)
- ○ Less than 1 day per month
- ○ 1-3 days per month
- ○ 1-3 days per week
- ○ 4-6 days per week
- ○ Every day

142a. When you took **Calcium supplements** or **Calcium containing antacids**, about how much elemental calcium did you take in one day? *(If possible, please check label for elemental calcium.)*

- ○ Less than 500 mg
- ○ 500-599 mg
- ○ 600-999mg
- ○ 1,000 mg or more
- ○ Don't know

142b. For how many years have you taken **Calcium supplements** or **calcium-containing antacids** ?

- ○ Less than 1 year
- ○ 1 - 4 years
- ○ 5 - 9 years
- ○ 10 or more years

Question 143 appears on the next page.

Over the past 12 months...

143. How often did you take **Vitamin D** on its own or as part of a calcium supplement **(NOT** as part of a multivitamin in Question 137)?

- ○ NEVER (GO TO QUESTION 144)
- ○ Less than 1 day per month
- ○ 1-3 days per month
- ○ 1-3 days per week
- ○ 4-6 days per week
- ○ Every day

143a. When you took **Vitamin D**, about how much did you take in one day?

- ○ Less than 125 IU
- ○ 125-249 IU
- ○ 250-399 IU
- ○ 400 IU or more
- ○ Don't know

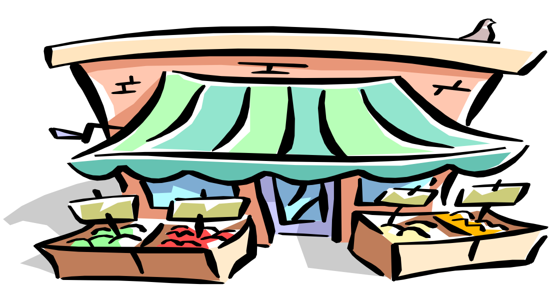
143b. For how many years have you taken **Vitamin D**?

- ○ Less than 1 year
- ○ 1 - 4 years
- ○ 5 - 9 years
- ○ 10 or more years

These last two questions ask about other supplements you took more than once per week.

144. Please mark any of the following **single supplements** you took more than once per week (**NOT** as part of a multivitamin):

- ○ B-6
- ○ B-Complex
- ○ Brewer's yeast
- ○ Cod liver oil
- ○ Coenzyme Q
- ○ Fish oil (Omega-3 fatty acids)
- ○ Folic acid/folate
- ○ Glucosamine
- ○ Hydroxytryptophan (HTP)
- ○ Iron
- ○ Niacin
- ○ Selenium
- ○ Zinc



145. Please mark any of the following **herbal** or **botanical supplements** you took more than once per week:

- ○ Aloe Vera
- ○ Astragalus
- ○ Bilberry
- ○ Cascara sagrada
- ○ Cat's claw
- ○ Cayenne
- ○ Cranberry
- ○ Dong Kuai (Tangkwei)
- ○ Echinacea
- ○ Evening primrose oil
- ○ Feverfew
- ○ Garlic
- ○ Ginger
- ○ Ginko biloba
- ○ Ginseng (American or Asian)
- ○ Goldenseal
- ○ Grapeseed extract
- ○ Kava, kava
- ○ Milk thistle
- ○ Saw palmetto
- ○ Siberian ginseng
- ○ St. John's wort
- ○ Valerian
- ○ Other

146. Is there anything else you eat at least once a month? Please write name of food, frequency and amount.

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Thank you very much for completing this questionnaire!

Before sending the questionnaire back to us, please check that you did not accidentally skip any pages.

Appendix B: Lifetime Total Physical Activity Questionnaire

I. PHYSICAL ACTIVITY HABITS

This section will be about your physical activity patterns over your lifetime. Specifically, I will be asking you about your *<u>occupational, household and recreational activities</u>*.

I1. OCCUPATIONAL & VOLUNTEER ACTIVITIES

Starting with your occupational activities, please tell me what jobs (paid or volunteer) you have done for at least ***8 hours per week for 4 months*** *of the year (****128 hours*** *total per year or* ***2.5 hours*** *per week per year) over your lifetime starting with your first job.*

Please tell me about each job that you had. I need to know how old you were when you started and stopped working at each job and the number of months per year, days per week, hours per day that you worked at each job. Finally, I need to know what kind of physical effort you had for each job. Please choose one intensity level from the list on this separate page that defines each level.

LIFETIME RECORD OF OCCUPATIONAL & VOLUNTEER ACTIVITIES

No. of Rows _____

No	**Job Title**	**Description of Occupational Activity**	**Age Started**	**Age Ended**	**No. of Mos/ Yr**	**No. of Days/ Wk.**	**Time/Day Hrs.**	**Mins.**	**Intensity of Activity (1,2,3,4)**	**Did you ever walk, bike, rollerblade, or run to this job?**	**Which ones did you normally do?** (*Check all that apply.*)	**No. of Mos/ Yr**	**No. of Days/ Wk**	**Time/Day Hrs.**	**Mins.**	**Intensity of Activity (1,2,3,4)**
1										[1]O yes [2]O no (**next job**) [97]O Ref (**next job**) [99]O DK (**next job**)	[1]O walk [2]O bike [3]O rollerblade [4]O run [5]O other_____ [97]O Ref (**next job**) [99]O DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
2										[1]O yes [2]O no (**next job**) [97]O Ref (**next job**) [99]O DK (**next job**)	[1]O walk [2]O bike [3]O rollerblade [4]O run [5]O other_____ [97]O Ref (**next job**) [99]O DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	

No	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr	No. of Days/ Wk.	Time/Day Hrs.	Mins.	Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr	No. of Days/ Wk	Time/Day Hrs.	Mins.	Intensity of Activity (1,2,3,4)
3										[1]O yes [2]O no (**next job**) [97]O Ref (**next job**) [99]O DK (**next job**)	[1]O walk [2]O bike [3]O rollerblade [4]O run [5]O other_____ [97]O Ref (**next job**) [99]O DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
4										[1]O yes [2]O no (**next job**) [97]O Ref (**next job**) [99]O DK (**next job**)	[1]O walk [2]O bike [3]O rollerblade [4]O run [5]O other_____ [97]O Ref (**next job**) [99]O DK (**next job**)	………. …….. ………. …….	……….. ……….. ……….	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
5										[1]O yes [2]O no (**next job**) [97]O Ref (**next job**) [99]O DK (**next job**)	[1]O walk [2]O bike [3]O rollerblade [4]O run [5]O other_____ [97]O Ref (**next job**) [99]O DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
6										[1]O yes [2]O no (**next job**) [97]O Ref (**next job**) [99]O DK (**next job**)	[1]O walk [2]O bike [3]O rollerblade [4]O run [5]O other_____ [97]O Ref (**next job**) [99]O DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
7										[1]O yes [2]O no (**next job**) [97]O Ref (**next job**) [99]O DK (**next job**)	[1]O walk [2]O bike [3]O rollerblade [4]O run [5]O other_____ [97]O Ref (**next job**) [99]O DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	

No	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr	No. of Days/ Wk.	Time/Day Hrs.	Mins.	Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr	No. of Days/ Wk	Time/Day Hrs.	Mins.	Intensity of Activity (1,2,3,4)
8										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	....	....	....	....	
9										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	....	....	....	....	
10										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	....	....	....	....	
11										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	....	....	....	....	
12										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	....	....	....	....	

No	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr	No. of Days/ Wk.	Time/Day Hrs.	Mins.	Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr	No. of Days/ Wk	Time/Day Hrs.	Mins.	Intensity of Activity (1,2,3,4)
13										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	………. …….. ………. …….	………. ………. ………. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
14										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	………. …….. ………. …….	………. ………. ………. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
15										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	………. …….. ………. …….	………. ………. ………. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
16										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	………. …….. ………. …….	………. ………. ………. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
17										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	………. …….. ………. …….	………. ………. ………. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
18										[1]○ yes [2]○ no (**next job**) [97]○ Ref (**next job**) [99]○ DK (**next job**)	[1]○ walk [2]○ bike [3]○ rollerblade [4]○ run [5]○ other_____ [97]○ Ref (**next job**) [99]○ DK (**next job**)	………. …….. ………. …….	………. ………. ………. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	

No	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr	No. of Days/ Wk.	Time/Day Hrs.	Mins.	Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr	No. of Days/ Wk	Time/Day Hrs.	Mins.	Intensity of Activity (1,2,3,4)
19										[1] ○ yes [2] ○ no (**next job**) [97] ○ Ref (**next job**) [99] ○ DK (**next job**)	[1] ○ walk [2] ○ bike [3] ○ rollerblade [4] ○ run [5] ○ other_____ [97] ○ Ref (**next job**) [99] ○ DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
20										[1] ○ yes [2] ○ no (**next job**) [97] ○ Ref (**next job**) [99] ○ DK (**next job**)	[1] ○ walk [2] ○ bike [3] ○ rollerblade [4] ○ run [5] ○ other_____ [97] ○ Ref (**next job**) [99] ○ DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
21										[1] ○ yes [2] ○ no (**next job**) [97] ○ Ref (**next job**) [99] ○ DK (**next job**)	[1] ○ walk [2] ○ bike [3] ○ rollerblade [4] ○ run [5] ○ other_____ [97] ○ Ref (**next job**) [99] ○ DK (**next job**)	………. …….. ………. …….	……….. ………. ……….. …	……. ……. ……. ……. …….	……. ……. ……. ……. …….	
22																
23																
24																

No	Job Title	Description of Occupational Activity	Age Started	Age Ended	No. of Mos/ Yr	No. of Days/ Wk.	Time/Day		Intensity of Activity (1,2,3,4)	Did you ever walk, bike, rollerblade, or run to this job?	Which ones did you normally do? (*Check all that apply.*)	No. of Mos/ Yr	No. of Days/ Wk	Time/Day		Intensity of Activity (1,2,3,4)
							Hrs.	Mins.						Hrs.	Mins.	
25																
26																
27																
28																
29																
30																

I2. HOUSEHOLD ACTIVITIES

Now I am going to ask you to tell me about your patterns of household and gardening activities over your lifetime. Again, we will start with your past activity and then continue up to your reference year. Please include only those activities that you have done at least 7 ***hours per week 4 months*** *of the year (****112 hours*** *total per year or* ***2.15 hours*** *per week per year).*

It may help you to consider what a typical day or week was for you. Then think about how many hours of household, gardening, yard work or do-it-yourself jobs around your home that you did in a typical day or week. For seasonal activities, such as gardening, you can report those separately from all other household activities that are done all year. Seated activities (such as sewing or paying bills) are not included. ***Childcare*** *and* ***housework*** *are included.*

LIFETIME RECORD OF HOUSEHOLD ACTIVITIES

No. of Rows ____

No.	Age Started	Age Ended	Number of Months/Yr.	Number of Days/Wk.	Time per day Hrs. Mins		Hours per day spent in activities that were in category: 2	3	4
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									

No.	Age Started	Age Ended	Number of Months/Yr.	Number of Days/Wk.	Time per day Hrs. Mins		Hours per day spent in activities that were in category: 2	3	4
13									
14									
15									
16									
17									
18									
19									
20									
21									
22									
23									
24									
25									
26									
27									
28									
29									

I3. EXERCISE & SPORTS ACTIVITIES

Now I would like to know all your exercise or sports activities that you did during your lifetime starting with your childhood and continuing to your reference year. Please report the activities that you have done at least ***2 hours per week for 4 months*** *of the year (**32 hours** total per year or **40 minutes** per week per year).*

Please tell us what exercise and sports activities you have done at least ***10 times during your lifetime****. Besides sports and exercise, we are also interested in knowing whether you* ***walked, biked, ran or rollerbladed to school****. If you have done this, please report all the information as for the other sports activities. Please begin by telling me the activities that you did during your school years including your physical education (**gym**) classes.*

LIFETIME RECORD OF EXERCISE & SPORTS ACTIVITIES

No. of Rows ____

No.	Description of Exercise/Sports Activity	Code	Age Started	Age Ended	Frequency of Activity				Time per Activity		Intensity of Activity (2,3,4)
					Day	Week	Month	Year	Hrs.	Mins.	
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											

No.	Description of Exercise/Sports Activity	Code	Age Started	Age Ended	Frequency of Activity				Time per Activity		Intensity of Activity (2,3,4)
					Day	Week	Month	Year	Hrs.	Mins.	
13											
14											
15											
16											
17											
18											
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