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Glycemic Load and Risk of Alzheimer's Disease: The Cache County Study on Memory, Health, and Aging

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GLYCEMIC LOAD AND RISK OF ALZHEIMER'S DISEASE:

THE CACHE COUNTY STUDY ON MEMORY,

HEALTH, AND AGING

by

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ABSTRACT

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by

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Carbohydrates are a major energy source for the human body and particularly glucose is the only energy source for the brain. Thus glucose metabolism is important to maintain normal brain function. Evidence showed insulin resistance and diabetes are associated with cognitive decline and a large amount of highly processed carbohydrate intake; in other words, a high glycemic load diet, which increases blood glucose faster and insulin demand, is associated with increased risk of insulin resistance and diabetes.

Based on this premise, the hypothesis that a high glycemic load (GL) diet increases the risk of incident Alzheimer's disease (AD) was examined among Cache County elderly people in Northern Utah. At the baseline survey, 3,831 participants 65 years of age or older completed a food frequency questionnaire (FFQ) and cognitive screening. Observation time to collect the data for incident AD was approximately 10 years. Incident AD was determined by final consensus conference after multi-steps of

screening. GL was calculated as the product of carbohydrate intake and glycemic index (GI) and adjusted for energy intake. FFQs from diabetics were considered to be invalid to assess dietary carbohydrates intake and excluded. The analysis was examined separately by gender.

The Cox proportional hazard regression model in survival analysis was used to relate GL to incident AD using a time variable with age of AD onset. There was no association in men but a negative association in women in the unadjusted model. Evidence of confounding by total kcal was apparent in women, particularly in the lowest GL group, which had the highest total kcal mean intake. Finally no association between GL and AD was found after adjustment for education, myocardial infarction (MI), stroke, Body Mass Index (BMI), physical activity, smoking, alcohol use, APOE ε-4 alleles, multi-vitamins use, total kcal, and controlling interaction between GL and total kcal.

The low GL group had unique characteristics in lifestyle factors, macro-nutrients intake, and pattern of food use. The inverse relationship between GL and total kcal may partly be explained by lifestyle factors, particularly alcohol intake. The characteristics of low GL group, current smokers, alcohol users, and their relationship and interaction between total kcal and risk of AD should be explored further.

(99 pages)

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects millions in the aging population. The prevalence of AD is estimated to increase three-fold in the United States and four-fold worldwide from current affected number by 2050 (1, 2). AD is the fifth leading cause of death in Americans age sixty five and older in 2005 and has appeared as the third leading cost of care in medical condition in the United States (1, 3). Sharply increasing number of AD patients indicates a growing socio-economic burden due to increasing number of functional dependence of aging populations, thus emphasis in strategies and efforts intended to maintain functional and cognitive health may be particularly important to prevent occurrences of dementia and AD.

The Cache County Study on Memory, Health, and Aging, established in 1994, is a prospective cohort study of prevalence and incidence of dementia and AD among 5,092 Cache County elderly people in Utah (3). The study has contributed to deepening and broadening the knowledge of AD in depth and breadth during four waves and three follow-up assessments. Dietary factors such as anti-oxidant vitamins from supplements and dietary intake and fruits and vegetables intake have been examined as modifiable risk factors that may reduce risk of AD in the study.

Dietary carbohydrate intake affects the brain energy metabolism and may be an important role in the pathology of AD. Substantial number of prospective cohort studies, two cross sectional studies, and one meta-analysis of clinical trials found the association between diabetes (4-8), insulin resistance (9-12), hyperinsulinemia (13-17), and increased risk of cognitive decline and AD. Evidences provided from clinical trials, large

prospective cohort studies, and population-based cross-sectional studies showed the association between high dietary intake pattern of carbohydrates that are rapidly absorbed from the gastrointestinal tract in term of glycemic index (GI) and glycemic load (GL) and increased risk of insulin resistance and type II diabetes (18-28). Based on these premises, the hypothesis that high glycemic load diet may increase the risk of AD is proposed. However, there was little study on this hypothesis and no association between GL and the risk of AD was found in a longitudinal cohort study (29).

Although supporting evidence from population studies are scant, the intent of this study is to examine the association between higher glycemic load and the risk of AD based on the following associations: association between glycemic index and glycemic load and insulin resistance and type II diabetes, and association between insulin resistance and type II diabetes and Alzheimer's disease.

REVIEW OF LITERATURE

Alzheimer's disease

Alzheimer's disease (AD) is not a normal part of aging but a progressive neurodegenerative brain disease in the elderly population (30). It is characterized by neuritic plaques from abnormally aggregated beta-amyloid peptide and intracellular neurofibrillary tangles (NFTs) from paired helical filaments of hyperphosphorylated microtubule-associated tau protein in the brain (30, 31). In 1907, Dr. Alois Alzheimer, a German neuropathlogist and psychiatrist, was the first to report findings of senile plaques and neurofibrillary tangles (31).

AD is the most common form of dementia accounting for 50 to 70 percent of the total dementia cases, begining with early signs including memory loss and subtle behavior changes (30). The symptoms of AD are not limited to memory loss and other cognitive deficits but extend to a wide range of challenges, such as impaired activities of daily life, depression, behavioral disturbances (30). Thus caring for AD patients becomes a physical, psychological, emotional, and financial burden on the family and caregivers along with the progression of the disease.

The mortality of AD had shown an increasing trend, particularly from 2000 to 2005, deaths from Alzheimer's disease increased by 44.7 percent, while the number one cause of death, heart disease, decreased by 8.6 percent and percentages in other cause of death, such as breast cancer, prostate cancer, and stroke tended to decrease (1). Approximately 5.2 million Americans were estimated to be affected by AD in 2008 (1). By 2050, the number of people of age 65 and over with AD will increase by almost three-fold ranging

from 11 million to 16 million if effective prevention or treatment are not available for the disease (1). The growing prevalence of AD along with increased life expectancy has appeared not only in the United States but also worldwide (1). Brookmeyer et al. estimated that the worldwide prevalence of AD was 26.6 million in 2006 and this number would increase fourfold, to 106.8 million in 2050 (about 1 in 85 persons) (32).

In the United States, direct and indirect costs of AD patients care, including Medicare, Medicaid, and business of caregiving, are projected to be more than $148 billion annually (1). The worldwide cost for dementia care including AD is estimated to $ 315 billion annually (33). This projected economic burden on medical cost along with substantially increasing prevalence of AD, indicates its impact on public health and imperative socioeconomic burden in near future. Therefore, it is crucial to study the pathology of AD and to find potential modifiable risk factors to reduce incidence of AD or to prevent cognitive impairment.

The risk of cognitive decline and AD, like other common chronic conditions, is influenced by multiple clustering factors, such as age over 65 years, genetics (APOE ε-4 gene), chronic condition of insulin resistance, type II diabetes, inflammation, oxidative stress, dietary factors, environmental factors (exposure to the exogenous substances, such as metals and pesticides), lifestyles, education levels, gender, and head trauma (34). Dietary factors are among modifiable risk factors and may play an important role in prevention or precipitation of cognitive decline and AD. Dietary factors, such as calorie restriction, homocysteine-related B-vitamins (vitamin B6, B12, folate), fatty acids including cholesterol, polyunsaturated fatty acids (PUFA), omega-3 fatty acids, docosahexaenoic acid (DHA) from fish linked to APOE ε-4 alleles, antioxidant nutrients

related to oxidative stress, flavonoids, and alcohol have been studied to find a way to reduce the risks of AD in prospective studies and clinical trials (34-38), but reports were inconsistent (36, 37).

The application of nutrition to the epidemiologic study, especially related to chronic diseases, is indeed complex because dietary components are highly interrelated to each other and people eat a mixed diet, not isolated foods or individual nutrients (39, 40). Thus, examining dietary patterns or food groups, which includes both macro- and micro-nutrients components, may capture the complexity of diet and be relevant in exploring the association between dietary factors and chronic diseases. The data from the Cache County on Memory, Health and Aging study by Wengreen et al. showed an example focusing on the relation between food groups and cognitive decline and dementia in which higher intakes of fruits and vegetables and consumption of fish at least once a week were associated with reduced risk of cognitive decline or dementia, particularly among ApoE4 non-carriers (41).

Mediterranean diet (MeDi) has received growing attention because of ecological and observational evidence of reduced risk for cardiovascular disease (CVD), certain forms of cancer, and overall mortality (25, 39). Recently the Washington Heights-Inwood Columbia Aging Project (WHICAP) study among 2258 community-based non-demented individuals, mean age of 77.2 years, by Scarmeas et al. showed that higher adherence to the MeDi is associated with reduced risk for AD (39). The characteristics of the MeDi, such as high intake of vegetables, legumes, fruits and cereals, olive oil, a moderate-high intake of fish, a low to moderate intake of dairy foods, a low intake of meat and poultry, and a regular but moderate amount of wine generally during the meals, seem to represent

many potentially beneficial dietary components for AD (35, 39).

But there are not many studies regarding the effect of dietary patterns on the risk of AD, thus with this perspective, diets low in GI and GL, which are characterized by more whole-grain foods, fruits and vegetables with high in fiber, vitamins, and minerals, may be good candidates dietary patterns to look into the reduced risk of AD.

Type II diabetes and Alzheimer's disease

Type II diabetes is the product of progressive abnormalities: insulin resistance, hyperinsulinemia, then pancreatic exhaustion as a result of the increased demand for insulin in early stage and is characterized by hyperglycemia at an advanced stage (27, 42-44). Type II diabetes mellitus is a pandemic public health problem; the global prevalence of diabetes in 2000 was estimated at 171 million; by the year 2030, almost twofold of that, about 366 million people, will be afflicted with diabetes (45, 46). The U.S. Centers of Disease Control and Prevention estimated that total prevalence of diabetes in the United States in 2005 was 20.8 million (7% of the population); 6.2 million people among diabetes were undiagnosed and about 10 million, half of these persons, are aged 60 years or older (47). It is indeed surprising that 6.2 million people, about one third of diabetes, are undiagnosed. Diabetes is the sixth-leading cause of death and it is the most common metabolic disorder that has been associated with various adverse health effects including heart failure, stroke, kidney failure, and cognitive impairment and AD (48, 49).

Criteria for the diagnosis of diabetes in non-pregnant adults are shown in Table 1 from the American Diabetes Association (ADA) (50). There are three ways to diagnose diabetes, and each must be confirmed on a subsequent day unless clear symptoms of

hyperglycemia are present (50). Although the 75g oral glucose tolerance test (OGTT) is more sensitive than fasting plasma glucose (FPG) to diagnose diabetes, the FPG test is preferred in practice because it is easy to use, costs less, and is more acceptable to patients than the OGTT test (50).

By ADA definition, impaired fasting glucose (IFG=fast plasma glucose 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l)) and impaired glucose tolerance (IGT= 2-h plasma glucose 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l))have been officially termed “pre-diabetes” and both categories, IFG and IGT, are risk factors for future diabetes and cardiovascular disease (50).

Type II diabetes has been associated with cognitive decline and AD in their pathogenesis and disease progress linked to underlying mechanism of insulin resistance (43, 49). First of all, Stewart et al. showed that type II diabetes elevated the risk of both vascular dementia and AD (51).

Table 1. Criteria for the diagnosis of diabetes (cited from ADA)

* Symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dl (11.1 mmol/l) Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
* FPG ≥126 mg/dl (7.0 mmol/L) Fasting is defined as no caloric intake for at least 8 hours
* 2-hour plasma glucose ≥ 200 mg/dl (11.1 mmol/L) during an OGTT OGTT test: glucose load containing 75 g anhydrous glucose dissolved in water

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test

In the early population-based prospective cohort study (the Rotterdam study) and later study in which 6,370 elderly people participated for 2.1 years, Ott et al. found that people with diabetes had almost a doubled risk of dementia and AD (relative risks with proportional hazard regression; both RR = 1.9) and more importantly patients receiving insulin treatment were at highest risk of dementia (RR = 4.3) (6, 52).

The Honolulu-Asia Aging Study conducted by Peila et al. with a population-based cohort of 2,574 Japanese-American men, found that diabetes was associated with total dementia, AD, and vascular dementia and the association between diabetes and AD was particularly strong among APOEe4 carriers (7). Another cohort study, in which 1,789 Latinos aged 60 and older participated during 1998-1999, showed that risk of dementia was nearly eight times higher in people with type II diabetes and stroke (53). The largest cohort, Nurses' Health Study, in which 18,999 women aged 70-81 years participated for 2 years, reported women with type II diabetes had increased odds of poor cognitive function and substantial cognitive decline (54). Arvanitakis et al. also found evidence among 824 older Catholic nuns, priests, and brothers (55).

However, the Canadian Study of Health and Aging by Mcknight et al. found contradicting result that no significant association existed between diabetes and AD, but significant with vascular impairment (56). Yamada et al. also had no significant finding in the Hiroshima Adult Health Study (57). In a historical prospective cohort study of Japanese-American men (n =3774) who were examined at ages 45 to 68 (1965 through 1968) and again at ages 71 to 93, (1991 through 1993) there has no relation of a 15-year or 25-year history of diabetes to AD (58), but a later study with the same sample mentioned above (the Honolulu-Asia Aging Study) showed patients with type II diabetes

had a significant association with AD (7).

Similarly, the early population-based study by Hassing et al. (59) found no association in AD with diabetes, but later longitudinal population-based study found that type II diabetes was associated with accelerated cognitive decline (60). Luchsinger et al. also produced conflicting results that had no significant diabetes-AD association among Blacks and Hispanics in their earlier study (5), but later studies showed that diabetes and current smoking were the strongest risk factors (4). The strong association between hyperinsulinemia and risk of AD among multiethnic elderly in Northern Manhattan was also found (13). Recently, Luchsinger et al. reported evidence of association between diabetes and higher risk of mild cognitive impairment (MCI) among same group, Northern Manhattan 1772 elderly people (61). Finally, in the Cache County Study on Memory, Health, and Aging, Charoonruk et al. found association of AD and type II diabetes in men (62).

To conclude, most longitudinal and population based cohort studies or cross-sectional studies have shown an increased risk of AD associated with diabetes and insulin resistance (hyperinsulinemia) even though some studies showed conflicting results. Furthermore, in several study groups, earlier findings weren't significant, but later follow-ups showed significant results. Therefore, a strong body of studies supports a notion that type II diabetes may increase risk of AD. However, special attention may be needed in large population studies because considerable large proportion of type II diabetes were undiagnosed due to dependence on self-report or medical record for the diagnosis of diabetes (63). Also, increasing interest on pre-diabetes stage, which is characterized by insulin resistance and hyperinsulinemia, has produced some evidence of

possibility that insulin resistance may independently associated with AD risk (63).

Insulin resistance and Alzheimer's disease

Insulin is a polypeptide consisting of alpha(α) and beta (ß) chain of 21 and 30 amino acids and is linked through a pair of disulfide bonds (64). It is synthesized from the ß cells in the pancreas by cleavage of a C-terminal 23-amino-acid sequence of porcine proinsulin, thus it is produced with C peptide which is its by-product and often used as a measure of insulin production (64). The half-life of insulin is about 5 minutes and it is normally degraded in the liver, kidney and muscles by insulin degrading enzyme (IDE), a thiol methalloprotease (42, 64).

Insulin is the only hormone that directly lowers blood glucose levels and plays the dominant role in the control of carbohydrate metabolism and also regulates fat and protein metabolism in many peripheral target tissues, such as hepatic cells, muscle cells, and adipose cells (64). For example, as the most important actions of insulin, insulin not only enhances the uptake of glucose in cells, where it is metabolized and stored as glycogen in the liver, but also stimulates protein synthesis in muscles as well as lipid synthesis in adiposities (64). Thus lack of insulin results in reversing action including lipolysis, ketogenesis, proteolysis due to unavailability of glucose and, ultimately, death (64). If excess insulin is prolonged, it may result in hypoglycemia with consequent brain failure and again, finally, death (64).

Other important actions of insulin are the effect on normal growth process and promotion of the full anabolic effect of growth hormone (64). Insulin is required for the action of growth hormone (GH) through its action on glucose uptake by muscle, and

provides the energy substrates necessary for protein synthesis and also its direct action on amino acid transport into the cells as well as RNA synthesis (64). For this reason, children with diabetes may experience dwarfism because insulin has an important role for the full anabolic effect of GH mainly in protein synthesis, and possibly due to the structural similarity of insulin, insulin-like-growth hormone-I (IGF-I), and their receptors (64).

Another important action of insulin is to maintain potassium (K^+) homeostasis by stimulating K^+ uptake by cells, thus hyperinsulinemia may cause hypokalemia (potassium level less than 3.5 mEq/L) (64). The effect on insulin in the brain is less well defined compared with the effects on peripheral tissues. Historically, the brain has been described as an insulin-insensitive tissue; however, recent views on insulin in the brain suggested that insulin has important roles in the central nervous system (CNS). Craft et al. and Gerozissis described that peripheral insulin from the pancreatic beta cells can be transported into (CNS) both via across blood-brain barrier (BBB) by saturable, insulin receptor-mediated transport process and the cerebrospinal fluid (CSF) reached through circumventricular regions which is deficient in BBB (63, 65, 66). Saturability of glucose transport through the BBB was discovered by Banks et al. who explained the nonlinear relationship between the concentrations of human insulin in brain and blood, so insulin enters the brain by a saturable transport system (67). There is a hypothesis of biosynthesis of insulin in the brain from some studies (66, 68), but it is still inconclusive (63). Raising of the peripheral insulin concentration increases insulin concentration in brain and CSF, while chronic periphery hyperinsulinaemia down-regulates BBB insulin receptors thereby reducing insulin transport into the brain resulting in brain-insulin

deficiency (12, 63, 69)

Insulin receptors (IR) are highly concentrated in several specific brain regions including the choroid plexus, olfactory bulb, piryform cortex, amygdaloid nucleus, hippocampus, hypothalamic nucleus, and cerebellar cortex that control fundamental behaviors such as food intake, reproduction, and cognition (42, 63, 66, 70).

Glucose transport (GLUT) is mediated by 13 members of GLUTs family and expressed in specific cells and tissues; GLUT 1, 2, and 3 have been known to be not regulated by insulin, but GLUT 4 and 8 are insulin-sensitive transporters which increase glucose uptake 10- to 40-fold within minutes by translocation into membrane through insulin signaling cascade (42). GLUTs in CNS are mediated by mainly GLUT 1, 3, 4 and 8; GLUT 1 and 3 are widespread in the brain; but insulin-sensitive GLUT 4 and 8 are selectively distributed in the brain, such as in the hippocampus and hypothalamus, indicating the effect of insulin in selective brain regions supporting memory (42, 71, 72).

Craft has studied brain aging and described the role of insulin in the brain in her review paper which reported that insulin enhances memory with optimal plasma insulin levels of 10-20 μU/ml and sufficient glucose (69). This notion is supported by both animal (intracerebroventricular administration of insulin in rodents) and human (intravenous and intranasal insulin administration) studies which memory is facilitated by administration of insulin (11, 73). Insulin-modulated glucose utilization affects levels of neurotransmitters, such as acetylcholine and noreepiniphrine, that play important roles in cognition and long-term potentiation (LTP) of memory (12, 66, 69). Insulin also promotes rapid delivery of N-methyl-D-aspartate receptors to the cell membrane by exocytosis to modulate membrane potentials and neuronal firing/LTP in hippocampus (74, 75).

Gerozissis described insulin as a neuromodulator involved in neurotransmitter release and also as a regulator for food intake behavior and energy homeostasis related to body weight in hypothalamus (66, 76). Zhao examined the role of insulin and insulin receptor in learning and memory through molecular mechanism associated with cognitive function and aging (68). Insulin and insulin receptor modify neurotransmitter release processes at various types of presynaptic terminals and modulate the activities of both excitatory and inhibitory postsynaptic receptors (68). They also explained molecular mechanism of insulin and insulin receptor activities in the brain that insulin and insulin receptors participate in regulation of learning and memory through activation of specific pathways such as shc, Grb-r/SOS, Ras/Raf, MEK/MAP kinases, IRS1, PI3 kinase, and protein kinase C in the formation of long-term memory formation (68).

Another role of insulin and IGF-1, which has similar molecular structures, in Aß clearance is that insulin increases Aß secretion by trafficking intracellular Aß from the Golgi to the plasma membrane and then IGF-1 enhances the transport of Aß carrier proteins (albumin and transthyretin) into the brain (77, 78).

Therefore, peripheral insulin hormone has an important role in blood glucose homeostasis, the regulation of macronutrient metabolism, normal growth and development, and potassium (K^+) homeostasis. In the brain, insulin is involved in memory, cognitive process with selective distribution of insulin, its receptors, and transporters, energy balance, and food intake behavior (12, 71, 75). Furthermore, insulin has an important role in Aß metabolism that increases Aß secretion and decreases the intracellular levels of Aß via intracellular trafficking mechanism (78).

Insulin resistance is a diminished ability of cells to respond to the action of insulin

in transporting glucose from the bloodstream into muscle and other tissues and is a pre-diabetes condition that appeared in 41 million people ages 40 – 74 (about 40% of US adult) in 2000 data from the U.S. Department of Health and Human Services (79). Reaven described “the insulin resistance syndrome” with a broad range of physiological abnormality rooted to insulin resistance as listed in Table 2 (80).

From a molecular perspective, mechanism of insulin resistance can be divided into three categories; receptor, pre-receptor, and post-receptor insulin resistance (64). The majority of insulin resistance can be explained by the mechanism of the post-receptor insulin resistance due to the failure of signaling of insulin’s action by some intracellular effectors (64). Petersen et al. proposed a plausible mechanism of this post-receptor insulin resistance via the defects in insulin-stimulated muscle glycogen synthesis and increased intracellular lipid accumulation in muscle and liver tissue (48).

Their mechanism is that increasing plasma fatty acid levels raises intracellular lipid metabolites, such as fatty acyl CoAs and diacylglycerol, which in turn activate protein kinase C (PKC), thus leading to defects in insulin signaling through phosphorylation of insulin receptor substrate (IRS)-1 (48).

Blunted insulin-stimulated IRS-1 tyrosine phosphorylation by increasing PKC activity reduces phosphatidylinositol (PI) 3-kinase activity, which plays an essential role in insulin-stimulated glucose transport activity (GLUT 4), thereby resulting in reduced insulin-stimulated muscle-glycogen synthesis and increased plasma blood glucose levels (48). Thus increased intracellular lipid metabolites trigger the insulin resistance through the mechanism described above and this intracellular fat-induced insulin resistance mechanism is especially important.

Table 2. Abnormalities related to insulin resistance
and hyperinsulinemia (cited from Reaven (80))

* Some degree of glucose intolerance Impaired fasting glucose Impaired glucose tolerance
* Dyslipidemia ↑ Triglycerides ↓ HDL-C ↓ LDL-particle diameter (small, dense LDL particles) ↑ Postprandial accumulation of triglyceride-rich lipoproteins
* Endothelial dysfunction ↑ Mononuclear cell adhesion ↑ Plasma concentration of cellular adhesion molecules ↑ Plasma concentration of asymmetric dimethylarginine ↓ Endothelial-dependent vasodilatation
* Procoagulant factors ↑ Plasminogen activator inhibitor-1 ↑ Fibrinogen
* Hemodynamic changes ↑ Sympathetic nervous system activity ↑ Renal sodium retention
* Markers of inflammation ↑ C-reactive protein, white blood cell count, etc.
* Abnormal uric acid metabolism ↑ Plasma uric acid concentration ↓ Renal uric acid clearance
* Increased testosterone secretion (ovary)
* Sleep-disordered breathing

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein.

Morino and Petersen et al. linked this intracellular fat-induced insulin resistance mechanism to mitochondrial dysfunction through magnetic resonance spectroscopy studies in healthy lean elderly subjects and healthy lean insulin-resistant offspring of parents with type II diabetes (45). They hypothesized that reduced mitochondrial function may predispose these individuals to intramyocellular lipid accumulation and insulin resistance (45). They assessed mitochondrial oxidative phosphorylation activity in the healthy lean elderly people and observed about 40% reduction in rates of this activity which is associated with increased intramyocellular and intrahepatic lipid content (45). For the Insulin-resistance offspring of patients with type II diabetes, their inherited condition causes a reduction in mitochondrial content in skeletal muscle by 38%, which in turn reduced rates of mitochondrial oxidative phosphorylation predisposing them to intramyocellular lipid accumulation by about 80% increase in its lipid content (45).

In conclusion, molecular mechanisms in peripheral insulin resistance underscore the role of intracellular content of lipid in liver and skeletal muscle rather than absolute quantity of body fat. Obviously, insulin resistance occurs often in obese people because excess of caloric intake leads to fat accumulation not only in adipocytes, but also in muscle and liver cells. It also may occur in healthy and lean elderly people who acquired age-associated decline in mitochondrial function or inherited insulin-resistant offspring of parents with type II diabetes who have inherited reduction in mitochondrial density via mitochondrial dysfunction mechanism (45, 48).

Petersen et al. provided evidence supporting the hypothesis described above as skeletal muscle insulin resistance mechanism from their recent human study (81). They reported the pattern of energy distribution derived from two high-carbohydrate meals in

young, lean, insulin-resistant individuals compared with young, lean, insulin-sensitive individuals (81). Their finding was that net muscle glycogen synthesis was reduced by about 60% in young, lean, insulin-resistant subjects compared to controls; on the contrary, hepatic de novo lipogenesis and hepatic triglyceride synthesis were both increased by greater than two fold in the insulin-resistant subjects, consequently resulting in increased plasma triglyceride concentration by 60% and decreased plasma high-density lipoprotein (HDL) concentration by 20% (81). The result indicates that insulin resistance in skeletal muscle can promote atherogenic dyslipidimia by changing the pattern of ingested carbohydrate away from skeletal muscle glycogen synthesis into hepatic de novo lipogenesis (81).

Insulin resistance has a well known role in the metabolic syndrome, also known as the insulin resistance syndrome or syndrome X, which is a cluster of symptoms that include central obesity (men: waist circumference > 40 inches, women: waist circumference> 35nches), hyperglycemia (fasting glucose ≥ 110, < 126 mg/dl) , hypertension (blood pressure ≥ 130/80 mm Hg), dyslipidaemia (triglycerides ≥ 150 mg/dl) , and low-HDL level (men < 40 mg/dl, women < 50 mg/dl) (80). The metabolic syndrome is estimated to affect more than 50 million Americans and approximately half of all Americans are predisposed to it (81). This cluster of metabolic anormalities have been linked to an increase in the risk of chronic diseases including CVD, CHD, type II diabetes, and AD.

Watson and Craft et al. have intensively studied the role of insulin resistance particularly in the pathogenesis of AD. They explained that in the periphery, the most direct effects of insulin resistance are compensatory hyperinsulinemia and hyperglycemia

whereas in the CNS, insulin resistance may alter glucose metabolism in selective brain regions, as there is a unique distribution of insulin receptors and insulin-sensitive GLUTs in the hippocampus and adjoining medial temporal cortex (12, 42, 71, 72). Craft emphasized an important consequence of insulin resistance syndrome and reduced insulin transport into the brain, which causes brain insulin deficiency (12). Finally this insufficient insulin concentration in the brain compromises beneficial roles of insulin in CNS, thereby increases the risk of age-related memory impairment and AD (12). Other studies from Craft et al. have provided evidence for the association between insulin resistance and risk of cognitive impairment and AD. At first, in their 18 months longitudinal controlled clinical trial, they examined the effect of hyperglycemia on hormone levels, metabolite levels, and memory performance in 22 subjects with very mild and mild probable dementia of the Alzheimer type (DAT) and in 12 normal elderly adults (82). Subjects were tested in 3 plasma glucose conditions (fasting baseline, 175 mg/dl, and 225 mg/dl) at initial and 18-month follow-up sessions. For the initial session, adults with very mild DAT showed memory facilitation and elevations in plasma insulin in the 225-mg/dl glucose condition relative to baseline, and then at follow-up, very mild DAT patients whose dementia had progressed showed significant decreases in insulin and hyperglycemic memory facilitation (82). This finding suggested that glucoregulatory abnormalities may contribute to the pathophysiology of DAT (82).

The following study explored whether memory improvement is due to a secondary elevation in plasma insulin levels, independent of hyperglycemia (83). They found that raising plasma insulin through intravenous infusion while keeping plasma glucose at a fasting baseline level produced striking memory enhancement for patients with DAT (83).

This finding proposed that neuroendocrine factors (insulin, insulin receptors, and insulin-mediate glucose utilization) play an important role in the pathophysiology of DAT (83).

Their continued clinical trial examined the effects of hyperinsulinemia acutely in older adults and in patients with AD using a hyperisulinemic-euglycemic clam. They found that normal older adults had a memory facilitation in plasma insulin levels of 10-20 μU/ml (optimal levels in normal physiological condition) with low-doses of insulin administration, while AD patients with insulin resistance needed higher insulin doses achieving levels of 60-85 μU/ml to facilitate memory (84). They also found interesting results in the subgroup of AD patients with insulin resistance came from mainly non-APOE ε-4 carriers indicating that insulin resistance may play an important role in pathogenesis of AD and may independently associated with increased risk of AD (84).

Another clinical trial by Craft et al. with insulin treatment in 16 healthy older adults (mean age 68.7 years) examined insulin effects on CSF Aß42 levels (85). The result was that insulin infusion facilitated memory, however it increased CSF Aß42 levels particularly in older subjects and such memory facilitation was attenuated in the subjects with the greatest increase in CSF Aß42 levels (85). This study is consistent with role of insulin on Aß metabolism which increases CSF Aß levels by facilitating intracellular Aß trafficking to the membrane suggested by Gasparini et al. and implicating abnormal insulin metabolism in the pathophysiology of AD.

Fishel and the Craft laboratory studied the effects of peripheral hyperinsulinemia on inflammation in the CNS through a similar experimental design with previous Aß and hyperinsulinemia study (86). Sixteen healthy older adults (mean age 68.2 years) received insulin infusion achieving plasma typical insulin resistance levels (>20 uU/mL) for 105

minutes and measured both plasma and CSF levels of inflammatory markers, cytokines (IL-1ß, IL-6, TNF-α, and F2-isoprostane (CSF only)) and Aß42. The result was that insulin increased CSF levels of F2-isoprostane and cytokines (both P<.01), as well as plasma and CSF levels of Abeta42 (both P<.05). These synchronous hyperinsulinemia-induced increases in Aß42 and inflammation markers in the CNS may increase the risk of AD (86).

Craft et al. proposed a model that their main hypothesis, in which insulin resistance and hyperinsulinemia contribute to the pathogenesis of AD, was linked to obesity through free fatty acids (FFAs) (87). Their mechanism is that peripheral insulin resistance and hyperinsulinemia increase peripheral FFA levels, which in turn elevate inflammatory agents in both periphery and CNS, reduce activity of insulin degrading enzyme, consequently inhibit peripheral Aß uptake and clearance, thereby increasing plasma Aß levels and elevate Aß transport into the brain (12, 87). This chain of effects is exacerbated by age and obesity (12, 87). Their cumulated experimental studies, based on the association between insulin resistance and AD, seemed to be integrated into this model.

Craft pointed out the possibility that insulin resistance independent of diabetes or APOE ε-4 gene may increase the risk of AD (63) and population-based cross-sectional studies have provided evidence for this association.

Kalmijn et al. from the Netherlands studied the cross-sectional association of cognitive function with hyperinsulinemia, impaired glucose tolerance (IGT), and diabetes in 462 men aged 69 to 89 years (88). They found that diabetes as well as non-diabetic subjects with IGT and hyperinsulinemia had impaired cognitive function as measured by the Mini-Mental State Examination (MMSE) (88). Another cross-sectional study of 980

people aged 69 to 78 (349 men, 631 women) from eastern Finland by Kuusisto et al. measured the insulin resistance syndrome and diagnosis of AD and found that in 532 non-diabetic subjects without the APOE ε-4 allele, hyperinsulinemia was associated with an increased risk for Alzheimer's disease (prevalence of disease 7.5% v 1.4% in normoinsulinemic subjects, P = 0.0004) whereas in the 228 with the APOEe4, hyperinsulinemia had no effect on the risk of disease (7.0% v 7.1%, respectively) (17). This study suggested that insulin resistance syndrome is associated with Alzheimer's disease independently of APOEε-4 phenotype (17). Furthermore, a recent population-based cohort study conducted by Luchsinger et al explored the association between hyperinsulinemia and risk of AD (13). 683 elderly people without dementia from northern Manhattan were followed-up for 3.7 years and the result was that the risk of AD doubled in the 39% of the sample with hyperinsulinemia (hazard ratio (HR) = 2.1; 95% CI: 1.5, 2.9) and was highest in people without diabetes indicating that higher insulin levels were related to the risk of dementia and particularly the cases with diabetes with highest HR was noticeable finding which adds a strong evidence of independent association between insulin resistance and AD (13, 63).

In addition, the population-based cohort study (1990-1991) of 959 elderly subjects from eastern Finland on the association of metabolic syndrome with AD by Vanhanen et al. provides more evidence for the independent association (89). They found that metabolic syndrome was significantly associated with AD in multivariate logistic regression analysis (OR = 2.46; 95% CI 1.27 to 4.78) and also this significant association appeared in people without diabetes (OR = 3.26; 95% CI 1.45 to 7.27) (89).

In summary, insulin resistance may increase the risk of age-related memory

impairment and AD through possible mechanisms mentioned above and many evidences from population-based studies give the possibility of its independent association to AD among non-diabetes.

The role of glycemic index/ glycemic load in insulin resistance and type II diabetes

Carbohydrates have been traditionally classified as 'simple carbohydrates' or 'complex carbohydrates' based on their chemical structure (the length of sugar compound chain) (90). Simple carbohydrates that have one or two sugar molecule (mono or disaccharides) such as fruit sugar (fructose), corn sugar (glucose), and table sugar (sucrose), which are considered as 'bad carbohydrates' whereas complex carbohydrates that are considered 'good carbohydrates' include any sugar molecules that have more than three linked sugar compounds (polysaccharides) (90).

However, most digestible carbohydrates can be converted into glucose to be used as an energy source for the body. Therefore, the judgment of carbohydrate as 'good' or 'bad' by old assumption is ambiguous because it does not explain how different types of carbohydrates physiologically affect plasma glucose and insulin responses, thereby, implicating health effects. For this reason, GI was proposed in 1981 by Jenkins et al to classify carbohydrate-containing foods according to their postprandial glycemic effect which has a basic idea that food sources of carbohydrate vary greatly in their rate of absorption and physiological effects on blood glucose and insulin concentrations (27, 91).

GI is defined as an index of the postprandial glucose response of a food, compared with a reference, usually glucose or white bread (92). It represents the incremental area under the curve of blood glucose produced by a standard amount of carbohydrate in a

food (test food), usually 50g, relative to the incremental area produced by the same amount of carbohydrate from standard source (reference food), usually white bread or glucose as shown in Figure 1 and the formula for GI calculation is as follows: (27, 92) GI = (Blood glucose area under the curve (AUC) of test food/ blood glucose AUC of referenced food) x 100 (92).

It is determined by feeding 10 or more healthy people a portion of the food containing 50 grams of digestible carbohydrate after an overnight fast and then finger-prick blood samples are taken at 15-30 minute intervals to measure the effect on their blood glucose levels over the next two hours so that for each person, the area under their two-hour blood glucose response (glucose AUC) for the test food is measured (93).

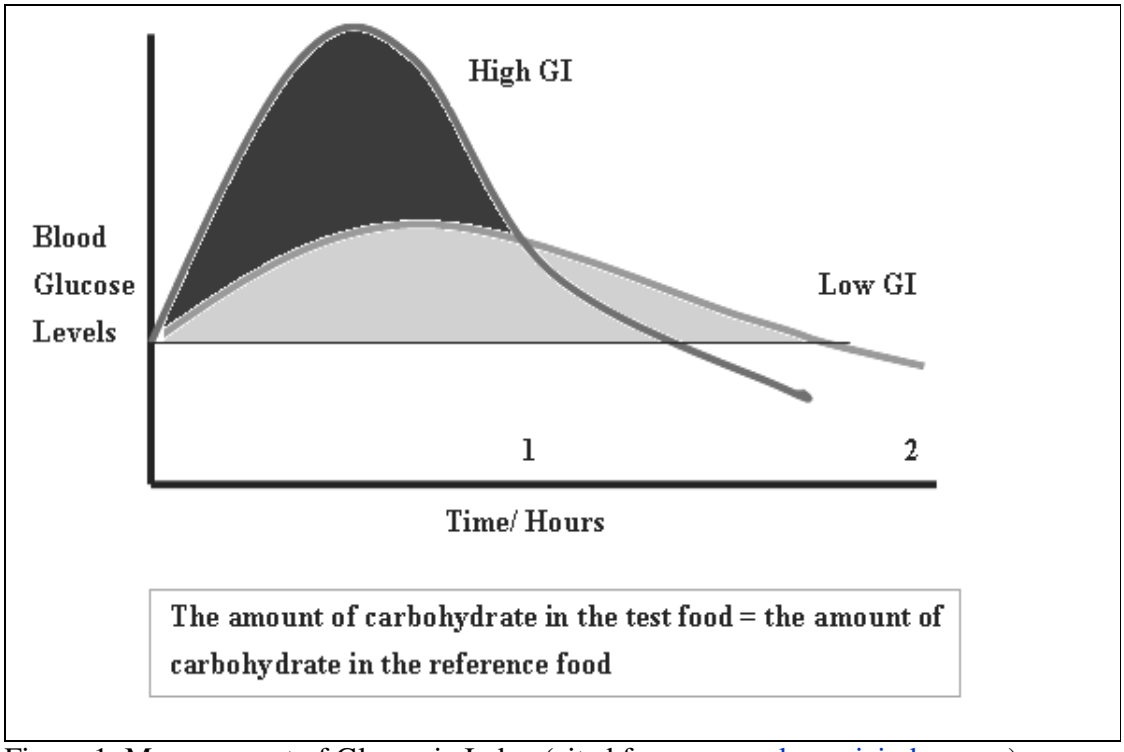

Figure 1. Measurement of Glycemic Index (cited from www.glycemicindex.com)

On the other hand, the same 10 people consume an equal-carbohydrate portion of glucose sugar (the reference food) and their two-hour blood glucose response is also measured and then a GI value (% ranking) for the test food is then calculated for each person by dividing their glucose AUC for the test food by their glucose AUC for the reference food and then multiplying by 100. The final GI value for the test food is the average GI value for the 10 people (93).

GI is a ranking of carbohydrates on a scale from 0 to 100 according to the extent to which they raise blood glucose levels after intake of carbohydrate-containing foods. Foods with a high GI (greater than 70) indicate that they are rapidly digested and absorbed and result in a marked increase in blood glucose levels. On the contrary, low-GI foods (less than 55) are slowly digested and produce gradual rises in blood glucose and insulin levels.

Augustin et al. described the factors that may affect GI values, as follows: ratio of amylase to amylopectin present in the raw food (more amylopectin, higher GI), the type of monosaccharide components (glucose ↑ or fructose ↓), the amount and type of dietary fiber (increasing soluble fiber, decreasing GI), cooking and food processing, particle size (more processing, increasing GI), ripeness, α-Amylase inhibitors such as phytic acid, lectins, and tannins (↓ GI), and the presence of large amounts of fat or protein (↓ GI) (94).

Assessment of carbohydrate quality using glucose as the reference was made with international Table that contained more than 500 foods was produced by Foster-Powell and Brand-Miller et al. at the University of Sydney in 1995 and then it was revised and compiled to " International Tables of Glycemic Index and Glycemic Load Values: 2002" which was containing nearly 1300 data entries representing more than 750 different types

of foods (91).

2002 version of GI table contained mainly carbohydrate foods that were classified into twenty two food groups (91). There were no GI values in the table for foods containing little or no carbohydrate such as meat, fish, eggs, avocados, cheese, and salad vegetables because clinical determination of GI is required a person to consume a serving of food containing at least twenty five to fifty gram of carbohydrate (95).

Glycemic load (GL) was first introduced in 1997 by Willett et al. at Harvard School of Public Health and is defined as a measure that incorporates both the quantity and quality of dietary carbohydrate (27, 92). GL is calculated by multiplying the amount of carbohydrate by its glycemic index and the formula is as follows (27, 92):
GL = (GI of individual food x g carbohydrate per serving of food)/ 100 (92).

Each unit of dietary GL represents the equivalent of one gram of carbohydrate from white bread or glucose (96). Physiological implication of GL is that the GI is more important when carbohydrate intake is high (27). Dietary glycemic load can be estimated as the sum of the glycemic loads of all carbohydrate foods consumed during a day (27, 97). Brand-Miller et al. validated the concept of GL with the clinical trial in lean young adults (97) and Galgani et al. showed GL was useful in predicting the acute impact on blood glucose and insulin response within mixed meals (98).

There have been existing continuous criticisms on the glycemic index concept such as GI values in the mixed meals (difference in GI value will be lost in mixed meal due to the effects of protein and fat contents). It is less practical application to people due to its difficult concept and potential dietary restriction, and issue on beneficial foods with high GI (99).

Kendall et al. and Willett et al. addressed these issues. For the first issue on GI values in the mixed meals, the study results from Wolever et al. and Bornet et al. have shown that fat and protein did not affect the relative differences between carbohydrate-containing foods (27, 99-101). Willett et al. explained the way of calculation in the total GI from mixed foods as a weighted average of the GI values of the individual foods, with the weights corresponding to each food's carbohydrate content (27).

In the recent study, Wolever et al. ascertained their finding with the use of crossover design in both Sydney and Toronto and concluded that GI was a significant determinant of the glycemic effect of mixed meals in normal subjects and GI explained approximately 90% of the variation in the mean glycemic response, with protein and fat having negligible effects (28).

For the second issue, Kendall et al. answered that GI might simply be used as a tool for selecting better quality starchy foods (99). For the last issue, some foods, such carrots have been condemned because they have a high GI, but maybe, this issue can be explained with GL concept from Willett et al.

The glucose and insulin responses depend on both the quantity and quality of the carbohydrate and GL represents both of these components of carbohydrates, thus even though carrots have high glycemic index, GL of carrots is very low because they have small amount of carbohydrate implicating little impact on blood glucose (27, 99). In general, low calorie foods such as fruits and vegetables that have high GI tend to have no significant effect on blood glucose levels and they also have high levels of beneficial factors such as fiber, vitamins, and minerals (99). Therefore, GI may be a useful tool for selecting better quality starchy foods and GL may be more relevant to apply the concept

of GI to whole mixed meals and overall diet.

GI and GL have been related to chronic diseases such as insulin resistance, type II diabetes, coronary heart disease (CHD), obesity, colon cancer, and breast cancer (94). Because GI was driven by the effects of carbohydrate-containing foods on blood glucose and insulin concentration, GI and GL have been associated with insulin resistance but not all, type II diabetes, and metabolic syndrome in clinical trials, large prospective cohort studies, and population-based cross-sectional studies.

Epidemiological evidences from Nurses' Health Study and Health Professional study by the same group, Salmeron et al. showed a significant association between GI expressed as GL and risk of diabetes that diets with a high glycemic load and a low cereal fiber content increased risk of diabetes in both men and women (18, 19).

In the other cohort study, Meyer et al. followed 35,988 women who completed the same dietary questionnaire used in the Nurses' Health Study for 6 years and found that total carbohydrates intake, GI, GL, fruits & vegetables were not associated with risk of diabetes whereas whole-grain intake and cereal fiber were inversely associated with diabetes (102). In response to this finding, Willett pointed out the lack of association with GI or GL in Meyer's study may have been related in part to use of a single measure of dietary intake and self-reported diabetes without confirmatory information (27).

The relation between whole-grain consumption and the risk of type II diabetes among women in the Nurses' Health Study was examined by Liu et al. who has collaborated with the Harvard study group and the results were that women in the top quintile of whole-grain intake (median: 2.7servings/d) had a 27% lower risk of diabetes than did those in the lowest quintile (median: 0.13 serving/d) and the ratio of refined to

whole grains was significantly associated with risk of diabetes (103). Follow-up study of 42,898 men from the Health Professionals reported the same confirmative results with Lie by Fung et al who again involved in the same study group (21).

The Nurses' Health Study II by Schulze et al. examined the association between GI, GL, and dietary fiber and the risk of type II diabetes in a large cohort of young women and they found that GI was significantly associated with an increased risk of diabetes and cereal fiber intake was associated with a decreased risk of diabetes but GL was no significant association (26).

In the other cohort study, McKeown et al. examined the cross-sectional association between whole- or refined-grain foods and several metabolic markers of disease risk in their early Framingham Offspring Study and found that increased intakes of whole grains was inversely associated with reduced metabolic risk factors (104) and then their follow-up study explored the associations between carbohydrate-related dietary factors including total dietary carbohydrate, fiber, whole- and refined-grain foods, GI, and GL, insulin resistance, and the prevalence of the metabolic syndrome in 2,834 subjects at the fifth examination (1991-1995) (23). Their results were continuum of similar results that whole-grain intake, largely attributed to the cereal fiber, was inversely associated with Homeostasis model assessment of insulin resistance (HOMA-IR) and a lower prevalence of the metabolic syndrome but GI was appeared as an opposite result (23). Sahyoun et al. from the same cohort study examined the same cross-sectional association in older adults aged 60-98 years and the results showed a significant inverse association between whole-grain intake and metabolic syndrome and mortality from CVD (24).

An interesting cross-sectional study from Japan examined the cross-sectional

association between GI and GL and several metabolic risk factors including BMI, fasting triacylglycerol, fasting blood glucose, and glycated hemoglobin in healthy Japanese women with traditional dietary habits (105). They found that GI was positively associated with BMI, fasting blood glucose, and glycated hemoglobin while GL was independently negatively associated with HDL and positively associated with fasting triacylglycerol and glucose (105). Negative correlation between GL and HDL was a noticeable finding, but it was a snap-shot observation from Japanese female farmers, therefore further long-term observation may be needed.

With the stream of whole grains study, cross-sectional study of Jenson et al. examined the association between whole grains, bran, and germ in relation to homocystein and markers of glycemic control, lipids, and inflammation among healthy sub-samples (n = 938) from the Health Professionals Follow-up Study and the Nurses' Health Study II and found that whole grains intake was inversely associated with homocystein, total cholesterol, the most strongly with glycemic control, but not associated with markers of inflammation (106).

However, Qi et al. found a significant association between whole grains, GI, and GL and plasma biomarkers of inflammation among 902 diabetic women in the same study group, the Nurses' Health Study (107). In a meta-analysis of randomized controlled trials, Brand-Miller et al. searched 14 studies comprising 356 subjects and all were parallel experimental design of 12 days' to 12 months' duration with modification of at least two meals per day (108). The result was that low-GI diets reduced Hemoglobin A1c by 43% indicating the effect of low-GI diets was small but clinically useful for the glycemic control in patients with diabetes (108). Table 3 summarized population-based

prospective and cross-sectional studies and one meta-analysis of clinical trials.

Table 3. Reports from prospective cohort & cross-sectional studies examining the relationship between dietary glycemic index & glycemic load and chronic diseases

Reference	Study design	N	Disease state	Difference in parameter	Association RR or OR	Note
Salmeron, 1997 (18)	Cohort (6 yrs) in men	42759	Type 2 diabetes	Quintiles in GI	GI, RR 1.37 (1.02-1.83) Comb, RR 2.17 (1.04-4.54)	Significance for 5th quintile of GI after adjusting fiber Highly significant in combination of GL & fiber
Salmeron, 1997 (19)	Cohort (6 yrs) in women	65173	Type 2 diabetes	Quintiles in GI	RR 1.37 (1.09-1.71)	Significance for 5th quintile of GI after adjusting fiber
Liu, 2000 (103)	Cohort (10 yrs) in women	75521	Diabetes	Quintiles in whole grains	RR 0.62 for whole grains RR 1.31 for refined grains	More significance in women BMI > 25
Fung , 2000 (21)	Prospective cohort (≥12 yrs) in men	42898	Type 2 diabetes	Quintiles in whole-grain intake	RR 0.57 (0.48-0.69)	Significance for 5th quintile of whole-grain intake after adjusting age; inverse association-can be modified by BMI
Schulze, 2004 (26)	Prospective cohort (for 8 yrs) in young women	91249	Type 2 diabetes	Quintiles in GI, GL, fiber	RR GI 1.59(1.21-2.10)/fiber 0.64 (0.48-0.86)	GI – significant positive Fiber – inverse assoc. GL – no significant (RR; 1, 1.31, 1.20, 1.14, and 1.33, p=0.21)
Mckeown, 2004 (104)	Framingham offspring cohort (1991-95)	2834	Insulin resistance & metabolic syndrome	Quintiles in GI, GL, whole-grain, fiber	OR; cereal fiber 0.62 whole-grain 0.67, GI 1.41	Significance for 5th quintile of GI, whole-grain, largely from cereal fiber. Whole-grain intake↓ HOMA-IR & metabolic syndrome
Sahyoun, 2006 (24)	Cohort (1981-1984) in older adult	535	Metabolic syndrome, CVD, mortality from CVD	Quartiles in whole-grain	whole-grain OR 0.46 for metabolic RR 0.48 for CVD mortality	Significance for 4th quartile of whole-grain intake & refined grains
Murakami, 2006 (105)	Cross-sectional study in Japanese women	1354	Type 2 diabetes & CVD			GI & GL are independently correlated with several metabolic risk factors (GL inversely associated with HDL)
Jenson, 2006 (106)	Cross-sectional study	938	Diabetes, inflammation, IHD	Quintiles in homocystein, plasma markers		Whole grain diet lower risk of diabetes, heart disease, but not inflammation
Qi, 2006 (107)	Cohort in women	902	Diabetes inflammation	Quintiles in GI		Whole grains and low GI diet reduce the risk of systemic inflammation in type 2 diabetes women
Brand-Miller, 2003 (108)	Meta-analysis of randomized controlled trials	356 (14 trials)	Diabetes		HbA1c ↓ 40% by low GI diet	The use of Low GI diet to improve glycemic control in practice – the effect was samall, but useful in clinical setting.

There were also contradicting findings that did not support the hypothesis that a high-GI leads to diabetes. In the Iowa Women's Health Study by Meyer et al. (102) and the Atherosclerosis Risk in Communities Study by Stevens et al. (109), neither GI nor GL showed any association with diabetes risk.

In conclusion, although a few studies have reported contradicting findings, substantial evidence from population-based cohort studies has accumulated showing that the long-term consumption of high GI and GL diet can adversely affect metabolism and health (110). Cordain et al pointed out that chronic exposure in hyperglycemia and hyperinsulinemia induced by high GL diet may promote insulin resistance and the metabolic syndrome (110).

Link between glycemic index / glycemic load and Alzheimer's disease via its role in insulin resistance and type II diabetes

Diabetes and insulin resistance (hyperinsulinemia) have been associated with an increased risk of AD in clinical experiments, population-based cross-sectional study or cohort study, as well as animal studies. Dietary intake of foods containing carbohydrates that are rapidly absorbed from the gastrointestinal tract thereby increase blood glucose levels and affect insulin concentrations in terms of high in GI and GL have been associated with an increased risk of type II diabetes and metabolic syndrome through insulin resistance and hyperinsulinemia.

Syllogistically the hypothesis that GI and GL may be associated with risk of AD via insulin resistance can be made. The growing body of study has related nutrients to cognitive decline and AD through epidemiological studies, particularly focusing on

individual dietary nutrients such as homocystein-related B vitamins (folate, vitamin B6,12), antioxidants (vitamin E, C, carotenoids, flavonoids, enzymatic cofactors), dietary lipids (poly-, mono-unsaturated fat, and DHA (mainly fish), EHA) (35). However, there has been little invested in the research for this association between GI & GL and AD.

Only two studies were found: one large cohort and one small clinical trial, but they had a conflicting result. In the clinical trial, Greenwood et al. examined the impact of acute carbohydrate consumption on memory impairment among 19 adults with type II diabetes and they found that poorer glycemic control is associated with lower performance on tests of declarative memory and acute ingestion of high GI foods further contributed to the underlying memory impairment (111). Contrary, in the cohort study, Luchshinger et al. explored the relation of GL with AD risk among 939 elderly people without dementia for 6.3 years, but the result was that higher risk of AD was associated with only total calories, not GL (37).

Prospective cohort studies from the Cache County Study on Memory, Health and Aging, CHAP study, Kame project, and WHICAP study focused on the relation between food groups or dietary patterns and cognitive decline and dementia (37). Not all (CHAP study found no fruit-cognitive change association), but the results from three large prospective cohort studies provided evidence for the inverse association between fruits, vegetables and fish intake and risk of AD or MeDi diet and risk of AD (39, 41). Interestingly, carbohydrate foods of inversely associated with risk of AD and the carbohydrate components in diet (MeDi) are both mutual in low or medium GI/GL foods.

GI & GL have been used as a tool to measure physiological effect of carbohydrates intake related to insulin resistance and DM. Insulin resistance and type II diabetes have

been linked with increased risk of AD with substantial evidences. However association between AD and insulin resistance or AD and type II diabetes were not always provided from prospective cohort studies and clinical trials. Similarly, with existing controversies and much debate among researchers, the findings of association between GI/ GL and insulin resistance and DM have been outnumbered non-significant ones. Based on this premise, GI/GL can be linked to the risk of AD and a hypothesis that low GI & GL diet is associated with reduced risk of AD can be established. If the finding of this research provides evidence of hypothesized association, dietary GI/GL may contribute an important role in preventing or delaying cognitive impairment and AD.

RESEARCH OBJECTIVE

The objective of this study is to find a possible relationship between dietary glycemic load intake and Alzheimer's disease based on the premise as follows: association between high glycemic index and glycemic load and the risk of insulin resistance and type II diabetes, and association between insulin resistance and type II diabetes and the risk of Alzheimer's disease. Therefore, the hypothesis to be tested is that high glycemic load diet is associated with increased risk of incident Alzheimer's disease.

SUBJECTS AND METHODS

Study participants

The Cache County Study on Memory, Health and Aging is a population-based, prospective cohort study of the prevalence and incidence of dementia and Alzheimer's disease (AD) among the Cache County elderly people of Northern Utah, was established in 1994, and has been funded by the United States National Institute on Aging (3, 41). The study has been collaborated with Duke University at the beginning, John Hopkins University, Harvard University, the University of Washington, Brigham Young University, and the University of Utah later (3).

There were 5,092 participants (ninety percent) among 5,677 Cache County residents aged sixty five years or older (mean age, 74.9 years for men and 76.5 years for women) at the baseline examination (3, 41, 62) . Approximately 90 percent of elderly Cache County people are members of The Church of Jesus Christ of Latter-day Saints (LDS or Mormon) (3). Their religion forbids smoking, drinking alcohol, and caffeinated drink such as tea and coffee. This life style may contribute to the health effects thereby a long-life span. Because of a long-life span compared to other states, rates of AD are projected to rise 127 percent by 2025 (3).

The participants completed the baseline interview regarding demographic characteristics, medical history, occupational history, family history of dementia, diet, smoking, alcohol use, and other lifestyle factors between 1995 and 1996 (3, 41). The APOE ε-4 alleles genotyping was examined by a cheek-swab DNA sample from the participants (41).

Demographic characteristics of participants including age, gender, body max index (BMI = Weight in kg/ (Height in meter)^2), diabetes, myocardial infarction (MI), stroke, education, physical activity (indicator of moderate physical activity), smoking, alcohol use, and APOE ε-4 genotype obtained from the baseline interview were used as non-dietary covariates in this data analysis.

Diagnosis of dementia and Alzheimer's disease

Cognitive screening was assessed in the baseline interview (1995) and four follow-up screenings were conducted during 1996-1997 (Telephone) 1998-1999 (Wave 2), 2002-2003 (Wave 3), and 2006-2007 (Wave 4) (3, 62). The Modified Mini-mental State Examination (3MS) was used to assess cognitive function and to screen for dementia (41). If participants scored below a sensory adjusted cut-point at any time points of screening, then all suspicious cases of dementia went on the sequential multi-stage screening to diagnose prevalence and incidence of dementia and AD. Final clinical diagnoses for dementia and AD were appointed by consensus conferences including geropsychiatrists, neuropsychologists, a neurologist, and a neuroscientist (3). Incidence of AD was measured as new cases of AD during the time period of wave 2, wave 3, and wave 4 among participant without dementia and AD at the baseline. The data for the incident of AD we used was collected after the baseline screening to the time point somewhere between wave 3 and wave 4.

Diet assessment

At the baseline examination, 3831 dietary Food Frequency Questionnaires (FFQ) were collected among 5,092 participants because 355 people who were scored below the

cutoff for the 3MS at the baseline cognitive screening were not received FFQ and 3,831 people among remaining 4,737 participants returned the FFQ. Of those, 3,634 persons remained after excluding 197 persons who reported implausible dietary data (daily calorie intake less than 500 kcal and more than 5000 kcal), diagnosed as an additional prevalent dementia after clinical assessment, and two persons who did not participate the baseline dementia screening (41). The final sample data of 3634 participants including 1,564 men and 2,070 women from the baseline examination were used to estimate usual dietary intake of carbohydrates in terms of GI and GL and other macro-nutrients characteristics.

Assessment of usual daily dietary intake was examined with self-reported a 142 food item Food Frequency Questionnaire (FFQ) as shown in Appendix. FFQ used in the Cache County Study was based on the semi quantitative FFQ developed by the Nurses' Health Study (NHS). The reproducibility of the NHS FFQ was evaluated among 38,121 elderly women aged from fifty five to sixty nine years in the Iowa Woman's Health Study by Munger et al. (41, 112).

The FFQ we used had 142 food items and a specified portion size for each food item (e.g., 8oz. of skim milk). Some food items with ambiguous portion size or without portion size were referred to the nutritional professionals and the registered dietitian (RD). There were nine possible responses ranging from "NONE OR LESS THAN 1 PER MO." to "6 PER DAY." Nutrient values for all food items in the baseline FFQ were derived from the ESHA program, 1997 version.

Glycemic Index Table and a web site maintained by Sydney University were used as primary sources to assign GI values to foods (91, 93). There are two GI values: one for

glucose referenced and one for white bread referenced for each food. This study used glucose referenced GI value. If food items were not in the GI tables, the method to determine GI values for those food items were referred to the methodology created by Flood et al. Their article published in 2006 described nine-steps of an algorithm linking GI values to foods, but this study set the seven steps based on their methods (Figure 2) (95).

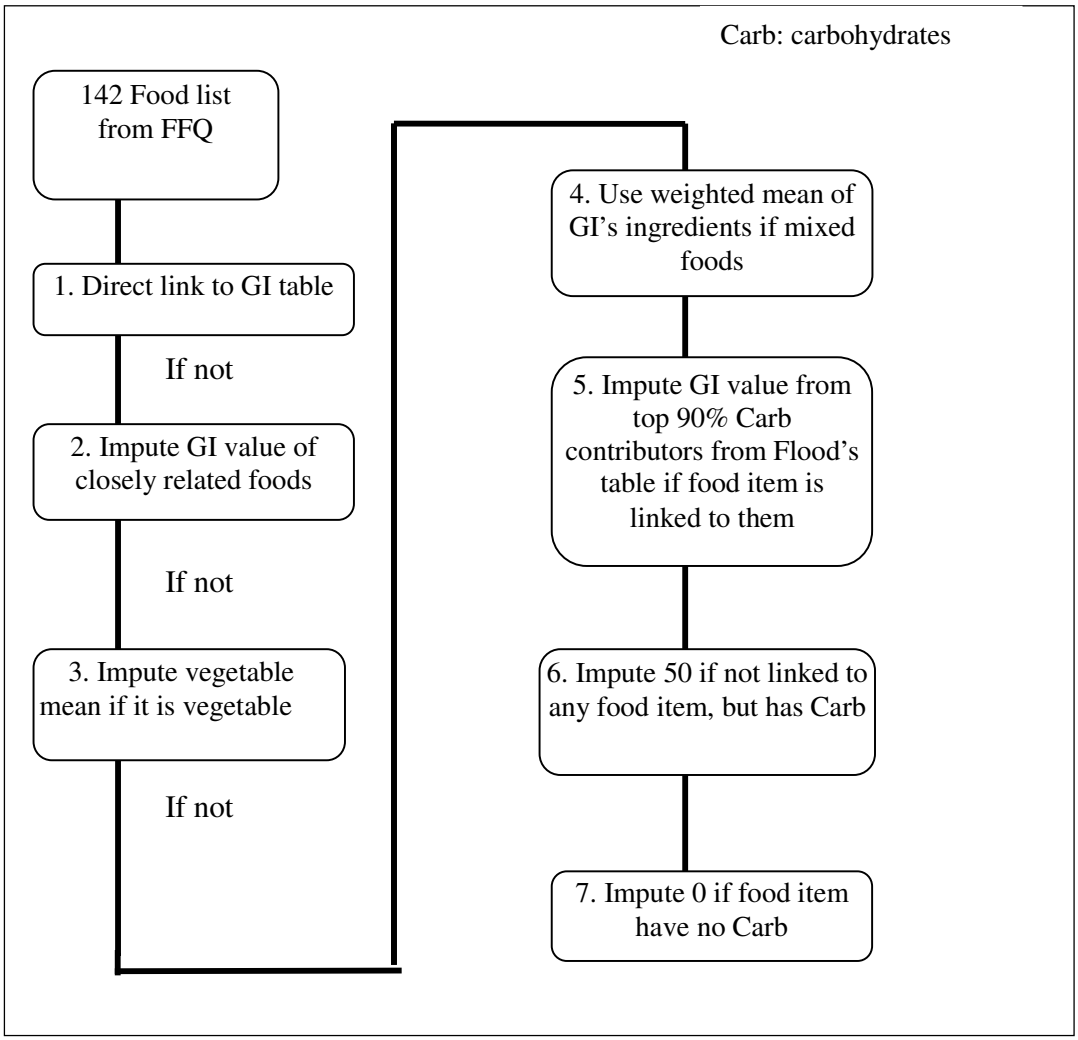

Figure 2. Seven steps of algorithm in linking GI values (cited from Flood, 2006 (95))

The ESHA program had a nutrient database per 100 grams of food, so the gram of carbohydrate for each food item (Carb) was calculated as follows: CHO = (total gram of each food/ a portion on FFQ x carbohydrate content per 100 gram of each food from ESHA data base)÷100. Other nutrients for each food item per portion were calculated by the same way. And then, nutrient intakes were computed by multiplying the frequency response by the nutrient content of the specified portion sizes.

A separate table for the Ready to Eat Cold Cereal (RTECC) was made because RTECC had a great variety in types as well as in amounts of carbohydrates. RETCC table contained 62 different types of cereal list and nutrient values were also derived from the 1997 version of ESHA program. GI value for each cereal was assigned from the Glycemic Index Table and if there is no GI value for certain type of cereal, the GI value of the cereal with closed amounts in carbohydrate, fiber, and sugar content was given. And then this table was merged into the original Food table.

Finally two tables, food table including nutrients content of 142 food item per 100g as well as GI value for the each food item and data base input file which had total gram of carbohydrates of 142 food items consumed by participants per day, were prepared to calculate total glycemic load (GL) per day (dietary GL intake per day). We used the FoodCalc program written by Jasper Lauritsen to make cross these tables and to calculate total dietary GL intake for 3634 participants (113).

GL for each food item in each participant was calculated by multiplying the final grams of carbohydrate from the carbohydrate content for each portion of food times the average number of servings of that food per day by the food's GI value. Total dietary GL for each participant then was produced by summing the GL scores over all food items.

Statistical methods

Statistical analyses were conducted with SPSS 15.0 for Window software program. Descriptive statistic analysis was used to see normality of the distribution of total glycemic load (GL), the demographic and nutrient characteristics of participants, and correlations of GL with other dietary variables at the baseline. The demographic, clinical, and dietary characteristics were crossed by gender and then demographic and clinical characteristics were crossed by kcal adjusted GL quintiles separately in gender. Energy adjusted GL was calculated as follows:

Kcal adjusted GL = (total GL/total kcal) x 1000 = GL/1000kcal

We analyzed most of data separately by gender because men and women had very different characteristics in many aspects.

Continuous variables such as age (years), BMI, total kcals, total carbohydrates (g), total fiber (g), total sugar (g), total protein (g), and total fat (g) were compared using one-way ANOVA test, and categorical variables such as dementia (all dementia types, 0/1 indicator), gender, education (< high school or > high school), diabetes (yes or no), smoking (yes or no), alcohol use (yes or no), APOE ε-4 alleles (0 – 2 copies), and moderate physical activity (3 levels: everyday or 2-6 times per week, 1-4 times per week, and rare) were compared using chi-squared test.

Distribution of diabetes crossed GL quintiles stratified by gender as well as distribution of dementia among diabetes was examined to look at whether diabetes is a confounding factor or not. Distribution of dementia among GL quintiles stratified by gender and diabetes was also examined to look at the association between diabetes, dementia, and GL. And then, the same test was conducted after exclusion of 464 diabetes

cases by assuming diabetes as a confounder. Finally the same procedure, but with different GL categories (dichotomy): the first group for the first quintile and the second group for the upper groups (Quintiles 2-5), was conducted to examine the association between dietary lower GL intake and the risk of dementia.

Survival analysis: Cox proportional hazards regression models were used in univariate and multivariate analyses exploring the relation of GL with AD. The time to event variable represents time from the baseline dietary assessment to incident AD. We used a time variable with the time of age onset. Persons who were lost to follow-up or did not develop dementia were censored at the last time of follow up (code = 0). Persons who developed dementias coded according to the type of dementia (1 = pure AD, 2 = primary VaD with secondary AD, 3 = VaD: vascular dementia, and 4 = other types of dementia). Estimated hazard ratios (HRs) for AD with the dichotomy of GL using the lower group (the first quintile group, 20%) as the reference was used to compare with upper groups (quintile 2 – 5, 80%).

The study used the univariate and multivariate analyses for two models: one (I) for the raw model and one (II) adjusted for covariates including education, MI, stroke, BMI, physical activity, smoking, alcohol, APOE ε-4 alleles, and multi-vitamins use. Genders were split before running Cox hazard regression models. To detect confounding factors among nutritious factors, at first, Cox hazard regression was used to compare hazard ratio between nutritious factors and incident AD and an adjustment technique was used and the results from adjusted estimate were compared to the crude result.

RESULTS

Frequency distribution in the histogram from the descriptive analysis of glycemic load (GL) showed right skewness in Figure 3. After adjusted energy, the distribution of GL became normal (skewness = 0.096) as shown in Figure 4.

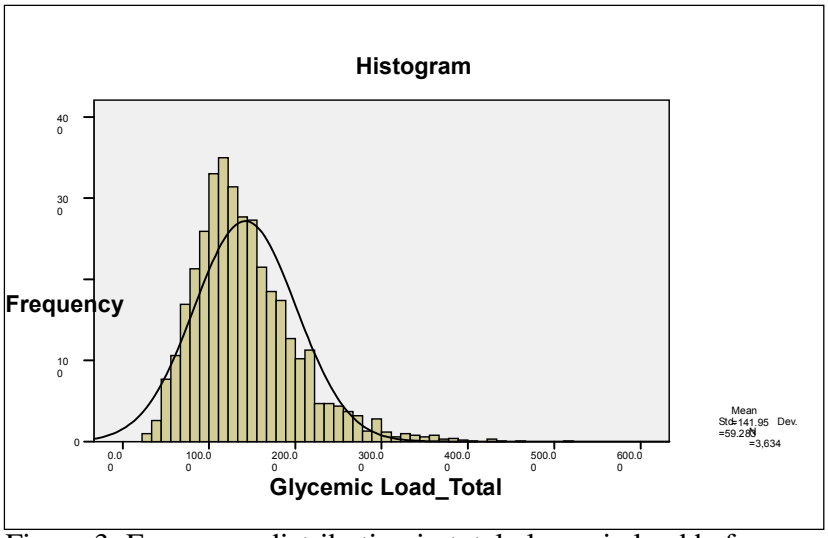

Figure 3. Frequency distribution in total glycemic load before energy adjustment

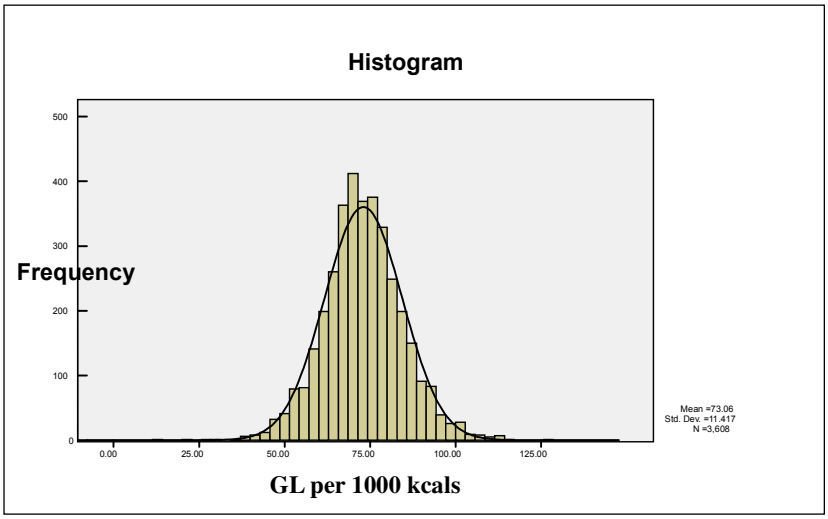

Figure 4. Frequency distribution in total glycemic load after energy adjustment

Table 4 includes overall demographic and clinical characteristics of valid participants at baseline by gender before energy adjustment. Of the total participants, approximately 57 percent were female and mean age for men and women was 74.2 years and 75.0 years. Mean BMI for men and women were 26.4 and 26.1 which both belong to over-weight category (BMI $\geq$ 25: over-weight, BMI $\geq$ 30: obese). There is no gender difference in mean BMI. The majority of participants had attained at least a high school education or higher (81.5 percent for men and 86.6 percent for women) and more women were educated at the level of high school or greater. Seventy-two percent of men and 65.5 percent of women had a moderate physical activity every day or two to six times per week, so more men were appeared physically active. Over 90 percent of women reported never having smoked cigarettes and consumed alcohol, but men reported that over 70 percent never drank alcohol and over 60 percent never smoked cigarettes. Self-reported diabetes was 14 percent for men and 12 percent for women. Additional characteristics of participant by gender are listed in Table 4.

Table 5 includes characteristics of dietary and macro-nutrients obtained from the baseline FFQ. Mean total GL per day for men and women were 147 (SD = 60.1) and 138 (SD = 58.3). Energy adjusted GL was 72.1 (SD = 11.4) for men and 73.8 (SD = 11.4) for women. Mean total GL intake was greater in men, but it was greater in women after energy adjustment. Mean total kcals for men and women were 2048 (SD = 785.6) kcals and 1882 (SD = 763.9) kcals. Other characteristics such as carbohydrate, fiber, sugar, protein, fat, and use of multi-vitamins are listed in Table 5. Noticeable thing is overall macro-nutrients mean intake was higher in men but fiber mean intake was the same in both men and women.

Table 4. Demographic and clinical characteristics of baseline in the Cache County Study on Memory, Health, and Aging by gender [1]

Characteristics		Male (n = 1564)	Female (n = 2070)
Total glycemic load**		147.2 ± 60.1[2]	138.0 ± 58.3
Glycemic load/1000 kcals**		72.1 ± 11.4	73.8 ± 11.4
Age**		74.2 ± 6.5	75.0 ± 6.8
BMI (kg/m^2)*		26.4 ± 3.9	26.1 ± 4.8
Dementia (%)[3]	Yes	8.1	9.3
	No	91.9	90.7
Diabetes (%)*	Yes	14.0	12.0
	No	86.0	88.0
MI (%)**	Yes	17.5	8.8
	No	82.5	91.2
Stroke (%)	Probable	3.7	3.0
	Uncertain	0.8	0.5
	No	95.6	96.4
Education (%)**			
	> High School	81.5	86.6
	< High School	18.5	13.4
Physical Activity (%) **			
	Everyday or 2-6x/week	76.2	65.5
	1-4 times/ month	12.8	17.5
	Rare	11.0	17.0
Smoking (%) **	Never	65.2	93.1
	Former	31.5	5.5
	Current	3.3	1.4
Use Alcohol (%) **	Never	72.7	92.5
	Former	20.8	5.1
	Current	6.5	2.3
APOE ε-4 alelles	0 copy	67.7	69.2
	1 copy	29.2	29.0
	2 copies	3.1	1.9

[1] Distribution of demographic and clinical covariates of baseline population by gender

[2] Mean ± standard deviation (SD)

** Significant difference between geder, $p < 0.000$

* Significant difference between geder, $p < 0.05$

[3] Dementia = Incident dementia between wave 3 and 4, not prevalent dementia

Table 5. Dietary and macro-nutrients characteristics of baseline in the Cache County Study on Memory, Health, and Aging by gender [1]

Dietary Characteristics	Male (n = 1564)	Female (n = 2070)
Total kcals*	2048.8 ± 785.6[2]	1882 ± 763.9
Total carbohydrates*	268.3 ± 106.0	255.1 ± 106.8
Total fiber	19.0 ± 9.2	19.6 ± 10.2
Total sugar*	136.8 ± 63.1	129.3 ± 63.5
Total protein*	87.8 ± 35.6	82.9 ± 37.1
Total fat*	74.0 ± 34.9	64.2 ± 31.9
Total glycemic load*	147.2 ± 60.1	138.0 ± 58.3
Glycemic load/1000 kcals*	72.1 ± 11.4	73.8 ± 11.4
Use Multi-Vitamins (%)*		
Yes	38.6	45.8
No	61.4	54.2

[1] Distribution of dietary covariates of baseline population by gender
[2] Mean ± stan between gender, p < standard deviation (SD), all macro-nutrients are in gram
* Significant difference 0.000 except Total fiaber (p=0.07)

The range of correlations was greatly changed between GL and other dietary characteristics after energy adjustment, but GL was still correlated with carbohydrates and sugar intake, moderately correlated with fiber, and negatively correlated with protein and fat intake in Table 6 and Table 7. Correlation between energy (kcals) and other macro-nutrients ranging from 0.45 to 0.90 were not significantly changed after energy adjustment.

Table 8 and Table 9 separately show the demographic and clinical characteristics among energy adjusted GL quintiles by gender. In men, GL was significantly associated ($p<0.000$) with diabetes, smoking, and alcohol use, and moderately associated ($p<0.05$) with education and physical activity. Other covariates including age, BMI, dementia, MI, stroke, and APOE ε-4 alleles were not associated with GL. In women, GL was significantly associated with diabetes, and alcohol use, moderately associated with age,

BMI, and smoking, not associated with other covariates.

Table 6. Correlations of glycemic load (GL) with other dietary variables

	GL	Kcals	Protein	Carb	Fiber	Sugar	Fat
GL	1						
Kcals	.919(**)	1					
Protein	.683(**)	.869(**)	1				
Carbohydrates	.984(**)	.927(**)	.718(**)	1			
Fiber	.698(**)	.687(**)	.612(**)	.779(**)	1		
Sugar	.865(**)	.792(**)	.580(**)	.902(**)	.676(**)	1	
Fat	.728(**)	.908(**)	.779(**)	.713(**)	.454(**)	.561(**)	1

** Correlation is significant at the 0.01 level (2-tailed). Carb=carbohydrates

Table 7.Correlations of energy-adjusted glycemic load with other dietary variables

	GL	Kcals	Protein	Carb	Fiber	Sugar	Fat
GL	1						
Kcals	-.092(**)	1					
Protein	-.349(**)	.868(**)	1				
Carbohydrates	.220(**)	.927(**)	.713(**)	1			
Fiber	.086(**)	.693(**)	.616(**)	.779(**)	1		
Sugar	.241(**)	.789(**)	.570(**)	.898(**)	.664(**)	1	
Fat	-.327(**)	.907(**)	.779(**)	.712(**)	.463(**)	.562(**)	1

** Correlation is significant at the 0.01 level (2-tailed). Carb=carbohydrates

In current alcohol users in both men and women, percentage of people in current use was notably decreased with increasing quintiles. On the other hand, never user showed opposite direction in Table 8 and Table 9. A similar trend was appeared in the current smokers particularly in men. In short, current alcohol user and smoker had the lowest GL intake in both genders.

Table 10 and Table 11 show diabetes as a confounder in the relation between GL and AD through diabetes distribution among GL quintiles and dementia rates among diabetes. The percentage of diabetes in the lowest quintile (Q1) over the highest quintile

(Q2) was almost two times in men (21% vs. 13.6%) and greater than two times in women (18.4% vs. 8.2%) in Table 10. Among non-diabetics, overall percentage increased with ascending GL quintiles. People with diabetes had a higher percentage of dementia compared to non-diabetes in Table 11. Our previous finding in the Cache County study showed that diabetes at the baseline was associated with 4 times greater risk for developing incident AD among men (RR=4.05, 95% CI:1.84-8.65) than non-diabetics, but not in women from the data of W2 observation (62). Thus, this result indicated that diabetes is problematic factor to estimate people's usual carbohydrate intake as well as to examine the association between GL and AD.

Diabetes was tested by cross-tabulating dementia distribution among GL quintiles by gender and diabetes status because the observed association between GL and dementia (no association in Table 8 and 9) may be affected by diabetes (changing their diet as diet treatment). The effect of diabetes may also be appeared differently between male and female. As depicted in Table 12, percentage of dementia in the fifth quintile was appeared twice of the percentage of the first quintile in non-diabetic men featuring like a dose and response-effect; however women had a U-shape in the distribution of percentage of dementia among GL quintiles in non-diabetics. There might be a possibility association of dementia related to GL in non-diabetic men, but p-value was not significant (p-value < 0.05).

Because of possible dose- response effect shown in non-diabetic men in Table 12, we had an additional test by grouping GL quintiles into a dichotomy: the first quintile (Q1, 20%) versus upper level quintiles (80%, Q2 – Q5). The result showed that dementia was significantly associated with GL in non-diabetic men (p = 0.019) in Table 13.

Table 8. Demographic and clinical characteristics among energy-adjusted glycemic load quintiles in men

Characteristics	Glycemic Load Quintiles				
	1 (n=352)	2 (n=327)	3 (n=306)	4 (n=295)	5 (n=284)
Glycemic Load	57.2 ±.6.1	67.3 ± 1.7	72.8 ± 1.6	78.3 ± 1.8	88.7± 6.2
Age	73.6 ± 6.4	74.0 ± 6.6	74.6 ± 6.7	74.3 ± 6.2	74.7 ± 6.7
BMI (kg/m^2)	26.9 ± 4.4	26.4 ± 3.5	26.2 ± 4.0	26.2 ± 3.4	26.2 ± 3.9
Dementia (%) Yes	6.0	7.0	8.8	10.2	8.8
No	94	93	91.2	89.8	91.2
Education (%)*					
> High School	79.5	81	76.5	87.8	83.5
< High School	20.5	19.0	23.5	12.2	16.5
Physical Activity (%) *					
Everyday or 2- 6x/week	69.8	76.6	82.2	77.6	75.4
1-4 times/ month	16.1	14	8.3	14.1	11
Rare	14.1	9.3	9.6	8.3	13.5
Diabetes (%) ** Yes	21.0	9.5	11.9	13.1	13.6
No	79.0	90.5	88.1	86.9	86.4
MI (%) Yes	14.0	16.0	16.8	20.8	21.1
No	86.0	84.0	83.2	79.2	78.9
Stroke (%)					
Probable	5.5	4.9	2.0	2.4	2.9
Uncertain	1.2	0.3	1.0	1.0	0.4
No	93.3	94.8	97.0	96.5	96.7
Smoking (%) **					
Never	54.0	64.2	70.0	72.2	68.1
Former	37.4	32.1	29.0	26.8	30.8
Current	8.6	3.7	1.0	1.0	1.1
Use Alcohol (%) **					
Never	61.5	70.2	74.3	81.2	79.0
Former	21.7	22.4	21.4	17.5	20.6
Current	16.8	7.4	4.3	1.4	0.4
APOE ε-4 alelles 0copy	67.7	71.6	70.8	63.5	64.5
1 copy	30.0	26.0	27.2	31.1	31.9
2 copies	2.3	2.4	2.0	5.5	3.5

* $p<0.05$, ** $p<0.000$, Mean ± SD (all such values)
Physical Activity is moderate activity

Table 9. Demographic and clinical characteristics among energy-adjusted glycemic load quintiles in women

Characteristics		Glycemic Load Quintiles				
		1 (n=374)	2 (n=400)	3 (n=422)	4 (n=432)	5 (n=442)
Glycemic Load range		57.8 ±.6.2	67.6± 1.6	72.7± 1.6	78.5± 1.8	89.5 ± 6.7
Age *		74.4 ± 6.7	74.7 ± 6.7	75.1 ± 6.6	74.5 ± 6.6	76.2 ± 7.0
BMI (kg/m^2) *		26.5 ± 5.1	26.1 ± 5.0	26.2 ± 4.6	26.1 ± 4.8	25.4 ± 4.6
Dementia (%)	Yes	12.3	8.5	6.9	9.0	10.0
	No	87.7	91.5	93.1	91.0	90.0
Education (%)						
	> High School	84.8	87.8	86.7	86.3	87.3
	< High School	15.2	12.3	13.3	13.7	12.7
Physical Activity (%)						
Everyday or 2-6x/week		65.5	61.4	70.9	66.9	62.8
1-4 times/ month		16.6	20.2	16.0	15.1	19.4
Rare		18.0	18.4	13.1	18.0	17.8
Diabetes (%) **						
	Yes	18.4	12.0	11.2	10.9	8.2
	No	81.6	88.0	88.8	89.1	91.8
MI (%)	Yes	10.3	8.0	8.2	9.3	8.5
	No	89.7	92.0	91.8	90.7	91.5
Stroke (%)	Probable	2.7	2.3	3.6	4.2	2.3
	Uncertain	0.8	0.0	0.7	0.2	0.9
	No	96.5	97.7	95.6	95.6	96.8
Smoking (%) *	Never	90.1	91.0	94.0	93.5	96.1
	Former	8.0	6.0	4.8	5.6	3.6
	Current	1.9	3.0	1.2	0.9	0.2
Use Alcohol (%) **						
	Never	88.5	91.0	92.6	93.5	96.4
	Former	7.2	5.0	4.5	6.0	3.2
	Current	4.3	4.0	2.9	0.5	0.5
APOEε−4alelles (%)	0copy	68.5	70.7	65.2	68.9	72.5
	1 copy	30.5	28.3	31.9	28.3	26.1
	2 copies	1.1	1.0	2.9	2.8	1.4

* p<0.05, ** p<0.000, mean ± SD (all such values)

Physical Activity is moderate activities.

Table 10. Diabetes distribution among glycemic load quintiles[1]
stratified by gender

Gender	Diabetes	Glycemic Load Quintiles 1	2	3	4	5	Total
Male**	Total Count	348.0	326.0	303.0	289.0	280.0	1546
	No (%)	79.0	90.5	88.1	86.9	86.4	
	Yes (%)	**21.0**	**9.5**	**11.9**	**13.1**	**13.6**	
Female**	Total Count	374.0	399.0	418.0	430.0	441.0	2062
	No (%)	81.6	88.0	88.8	89.1	91.8	
	Yes (%)	**18.4**	**12.0**	**11.2**	**10.9**	**8.2**	

[1] Energy adjusted glycemic load, ** $p < 0.000$

Table 11. Dementia distribution among diabetes stratified by gender

		Diabetes	Non-diabetes
Male	Dementia (%)	**10.35**	**6.5**
	Non dementia (%)	89.65	94.5
Female	Dementia (%)	**11.2**	**10.25**
	Non dementia (%)	88.8	89.75

Table 12. Distribution of dementia among kcal adjusted
glycemic load quintiles by gender and diabetes

Gender	Diabetes	Dementia (%)	Quintiles of Kcal-adjusted Glycemic Load 1 (n=726)	2 (n=721)	3 (n=728)	4 (n=727)	5 (n=726)
Male	No Diabetes	Non-Dementia	95.6	92.2	91.4	90.8	90.9
(n=1564)		Dementia	**4.4**	**7.8**	**8.6**	**9.2**	**9.1**
	Diabetes	Non-Dementia	87.7	100	88.9	86.8	92.1
	(n=216,14%)	Dementia	12.3	0.0	11.1	13.2	7.9
Female	No Diabetes	Non-Dementia	88.2	91.7	93.3	90.9	89.6
(n=2070)		Dementia	11.8	8.3	6.7	9.1	10.4
	Diabetes	Non-Dementia	85.5	89.6	91.5	93.6	94.4
	(n=247, 12%)	Dementia	14.5	10.4	8.5	6.4	5.6

All p-values were not significant

Table 13. Dementia distribution comparison across gender stratified by diabetes among energy adjusted GL quintile 1 vs. quintile 2 - 5

Gender	Diabetes	Dementia (%)	GL Quintile 1 vs. GL Quintile 2 - 5		p-value[1]
			Q1 (n=722)	Q2 - Q5 (n=2912)	
Male (n=1564)	Non-Diabetes	Non-Dementia	95.6	91.4	
		***Dementia**	**4.4**	**8.6**	**0.019**
	Diabetes (n=216,14%)	Non-Dementia	87.7	91.6	
		Dementia	12.3	8.4	0.356
Female (n=2070)	Non-Diabetes	Non-Dementia	88.2	91.3	
		Dementia	11.8	8.7	0.085
	Diabetes (n=247,12%)	Non-Dementia	85.5	92.1	
		Dementia	14.5	7.9	0.115

p-value [1] = Pearson Chi-Square 2-sided p-value
* significant, if p-value < 0.05

Therefore, we considered diabetes as a confounding factor in association between GL and dementia because diabetes was associated with GL in both genders and with incident AD in men. Furthermore, Using FFQ from diabetics was not appropriate to measure usual dietary carbohydrate intake because diabetic patients changed their diet to treat the disease. Thus, 464 diabetics from the valid FFQ (n=3,634) were excluded and remained 3,170. After exclusion of diabetes, Table 14 shows the significant positive association (p=0.014) between GL and dementia in men, not for women (p=0.087).

Cox proportional hazards regression models were used to explore the relation of GL with pure incident AD. Overall, 273 (8.6%) participants among 3,170 participants experienced development of incident dementia; AD developed in 180 (5.7% of sample population, 65.9% of total dementia) of these people during about 10 years observation.

In Model I, energy adjusted GL categorized as dichotomy: upper 80% higher GL

group vs. 20% lowest GL group using the first quintile group as a reference was not associated with incident AD in men (HR for AD =1.33; 95% CI: 0.63, 2.81; p = 0.456) while inversely associated with incident AD in women (HR for AD = 0.62; 95% CI: 0.4, 0.95; p = 0.027) (Table 15).

Table 14. Dementia dstribution cmparison across gnder
by eergy adjusted GL qintile 1 vs. quintile 2 - 5
after eclusion of diabetes (n=464)

Gender		**GL Quintile 1 vs. GL Quintile 2 - 5**		
	Dementia	**Q1**	**Q2 - Q5**	**p-value[1]**
Male	Count	279	1068	
(n=1348)	No Dementia (%)	95.7	91.3	
	Dementia (%)*	**4.3**	**8.7**	**0.014**
Female	Count	305	1518	
(n=1823)	No Dementia (%)	88.2	91.3	
	Dementia (%)	11.8	8.7	0.087

p-value [1] = Pearson Chi-Square 2-sided p-value
* significant, if p-value < 0.05

Table 15. Cox proportional hazard models for AD by GL

			GL Q2-5 vs. Q1	
Model	At Risk, n	AD (%)	HR (95% CI)	*p* value
I[1]			1 (reference)	
Male	1346	58 (4.3)	1.33 (0.63-2.81)	0.456
Female	1820	122 (6.7)	0.62 (0.40-0.95)	0.027
II[2]			1 (reference)	
Male	1245	56 (4.2)	1.10 (0.5-2.39)	0.817
Female	1632	106 (5.8)	0.54(0.34-0.85)	0.007

[1] is unadjusted raw model
[2] is adjusted for education, MI, stroke, BMI, physical activity, smoking, alcohol use, APOE ε-4 alleles, and multi-vitamins use
GL = Glycemic Load; HR = Hazard ratio; CI = Confidence interval
AD = Alzheimer's disease

Survival function graphs from SPSS survival analysis show comparisons of survival curves (incident AD curve) and hazard curves between low GL group (pattern 1, blue line) and high GL group (pattern 2, green line) in Figure 5. In the survival curve, incident AD appeared earlier in the higher GL intake group compared to the low GL intake group in men but p-value was not significant while low GL intake group had earlier AD age-onset compared to the higher GL intake group in women with significant p-value. The results were unchanged after addition of all non-nutrient covariates in Model II (Table 15).

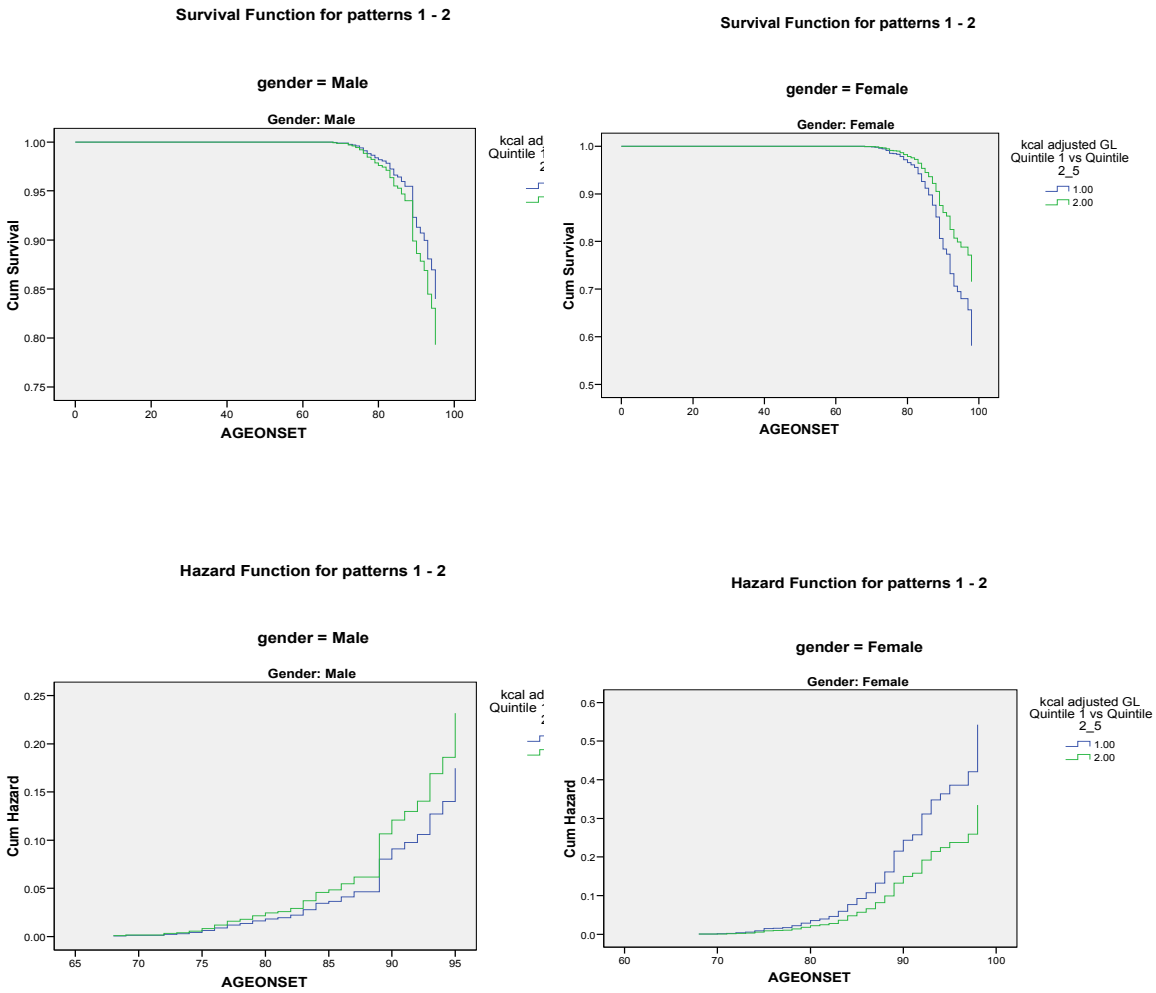

Figure 5. Survival & hazard curve (incident AD) comparison by gender (Model I)

Mean intake of total kcal and macro-nutrients such as carbohydrates, fat, protein, sugar, fiber, and saturated fat were compared by GL quintiles to examine a possibility of confounding factors by nutritional factors in Table 16 and 17. The result was that the first quintile group consumed the highest total kcal, protein, fat, SFA intake in women and the highest protein, fat, SFA intake in men.

The analysis of distribution of smoking and alcohol use by GL quintiles to explore the characteristics of the first quintile of GL intake showed that the number of current smokers and alcohol users were the highest percentage in GL quintile 1 in men and in GL quintile 1 and 2 in women in Table 18 - 21.

Tabel 16. Mean intake of kcal & macro-nutrients (gram) by GL quintiles in men

GL Q/ 1000 kcals	Kcal	Protein	Carb	Fiber	Sugar	Fat	SFA
1	2107	102	229	17	115	88	31
2	2066	92	256	18	131	79	27
3	2135	90	282	20	143	77	27
4	2052	80	288	19	147	71	24
5	1922	69	301	19	162	56	19
Total mean	2060	87	270	19	138	75	26

GL=Glycemic Load, Carb=Carbohydrates, SFA=Saturated fatty acid, Trans FA=Trans fatty acid

Table 17. Mean intake of kcal & macro-nutrients (gram) by GL quintiles in women

GL Q/ 1000 kcals	Kcal	Protein	Carb	Fiber	Sugar	Fat	SFA
1	1983	102	222	18	109	80	28
2	1922	89	245	19	124	70	24
3	1934	85	260	20	133	67	23
4	1846	77	266	20	136	59	20
5	1758	64	279	20	147	50	17
Total mean	1882	82	256	19	131	64	22

GL=Glycemic Load, Carb=Carbohydrates, SFA=Saturated fatty acid, Trans FA=Trans fatty acid

Table 18. Smoking distribution by GL quintiles in men (n=1334)

		GL per 1000 kcals Quintiles				
		1	2	3	4	5
Smoking	Never	143 (17%)	184 (21%)	185 (21%)	182 (21%)	167 (19%)
	Former	107 (25%)	100 (23%)	80 (19%)	69 (16%)	71 (17%)
	Current	27 (59%)	12 (26%)	3 (7%)	2 (4%)	2 (4%)

Chi^2 test p-value, p<0.0000, Count (% within Ever/never smoker)

Table 19. Alcohol use distribution by GL quintiles in men (n=1337)

		GL per 1000 kcals Quintiles				
		1	2	3	4	5
Alcohol use	Never	164 (17%)	205 (21%)	195 (20%)	209 (22%)	198 (20%)
	Former	61 (23%)	66 (24%)	60 (22%)	41 (15%)	43 (16%)
	Current	53 (56%)	24 (25%)	13 (14%)	4 (4%)	1 (1%)

Chi^2 test p-value, p<0.0000, Count (% within Ever/never drinker)

Table 20. Smoking distribution by GL quintiles in women (n=1814)

		GL per 1000 kcals Quintiles				
		1	2	3	4	5
Smoking	Never	273 (16%)	321 (19%)	348 (21%)	361 (21%)	393 (23%)
	Former	24 (26%)	20 (22%)	18 (20%)	19 (21%)	11 (12%)
	Current	7 (27%)	10 (38%)	5 (19%)	4 (15%)	0

Chi^2 test p-value, p<0.0030, Count (% within Ever/never smoker)

Table 21. Alcohol use distribution by GL quintiles in women (n=1819)

		GL per 1000 kcals Quintiles				
		1	2	3	4	5
Alcohol use	Never	269 (16%)	320 (19%)	344 (20%)	362 (21%)	394 (23%)
	Former	21 (24%)	17 (20%)	17 (20%)	21 (24%)	10 (12%)
	Current	14 (32%)	14 (32%)	12 (27%)	2 (5%)	2 (5%)

Chi^2 test p-value, p<0.0000, Count (% within Ever/never drinker)

Mean servings of food groups among GL quintile groups were revealed that the first GL quintile group consumed higher intake in dairy foods, eggs, meats, fish, and alcohol and lower intake fruits and soft drink in Table 22 (men) and 23 (women). Vegetable intake was not associated with the low GL intake.

From Cox hazard regression analysis to detect a possible confounding among nutritional factors, the associations appeared in total kcal quartile 4 in women and in total SFA quartile 2 in women. After adjustment of those two nutritional factors and added interaction term between GL and total kcal or SFA separately in Cox hazard regression models (dependant variable: incident AD, independent variable: GL, adjusted covariate: total kcal and SFA plus their interaction term). The result from model-adjusted SFA showed the same result (no association in men and negative association in women) with the crude model indicating no confounding while the model-adjusted total kcal showed a different result (no association in both men and women) from the crude model indicating a possible confounder. After adjustment of all other demographic covariates plus controlling total kcal, no association between GL and incident AD became apparent in women in Table 24.

Table 22. Mean servings of food groups by GL quintiles in men

	GL Quintiles					
Food Groups	1	2	3	4	5	p-value
Dairy	2.4	2.4	2.4	2.2	1.9	0.0030
Fruits	1.9	2.3	2.6	2.6	3.1	0.0000
Vegetables	3.4	3.3	3.6	3.2	3.1	0.0733
Eggs	0.6	0.4	0.3	0.2	0.2	0.0000
Meat	1.4	1.2	1	0.8	0.7	0.0000
Fish	0.3	0.2	0.2	0.2	0.2	0.0000
Soft Drink	0.4	0.6	0.6	0.8	1.2	0.0000
Alcohol	0.4	0.2	0.1	0	0	0.0000

Table 23. Mean servings of food groups by GL quintiles in women

	GL Quintiles					
Food Groups	1	2	3	4	5	p-value
Dairy	2.3	2.4	2.3	2.1	1.7	0.0000
Fruits	2.2	2.5	2.8	3	3.3	0.0000
Vegetables	4.1	3.9	3.9	3.7	3.6	0.1072
Eggs	0.3	0.2	0.2	0.2	0.1	0.0000
Meat	1.4	1.1	1	0.8	0.6	0.0000
Fish	0.3	0.2	0.2	0.2	0.2	0.0000
Soft Drink	0.3	0.4	0.5	0.6	0.9	0.0000
Alcohol	0.5	0.4	0.3	0.3	0.3	0.0000

Table 24. Cox proportional hazard models for AD by GL after controlling total kcal

			GL Q2-5 vs. Q1	
Model	At Risk, n	AD (%)	HR (95% CI)	*p* value
I[1]			1 (reference)	
Male	1346	58 (4.3)	0.967(0.28-3.40)	0.958
Female	1820	122 (6.7)	0.507 (0.25-1.01)	0.053
II[2]			1 (reference)	
Male	1245	56 (4.2)	2.899 (0.37-22.59)	0.31
Female	1632	106 (5.8)	0.703(0.26-1.92)	0.49

[1] is raw model adjusted for total kcal + interaction with GL

[2] is adjusted for education, MI, stroke, BMI, physical activity, smoking, alcohol use, APOE ε-4 alleles, multi-vitamins use, and total kcal + interaction with GL

GL = Glycemic Load; HR = Hazard ratio; CI = Confidence interval

AD = Alzheimer's disease

DISCUSSION

This study found that dietary energy-adjusted glycemic load (GL) was not associated with the risk of Alzheimer's disease when GL was categorized as dichotomy in which the first quintile (20%) was compared with combined upper level of quintiles (80%) and was used as the reference and total kcal was controlled as a confounder in elderly 65 years and older who lived or have lived in the Cache County, Northern Utah. These results included adjustment of covariates including education, MI, stroke, BMI, physical activity, smoking, alcohol use, APOE ε-4 alleles, and multi-vitamins use.

The reason for categorizing GL into two groups (Q1 vs. Q2-5) was that the percentage of dementia in non-diabetic men jumped from 4.4 % in Q1 to 7.8 % in Q2. It was almost twice and then the rate kept constant ranging from 7.8 to 9.2 % throughout Q5. Furthermore, after quintiles were transformed into this dichotomy, the association between dementia and GL in non-diabetic men became significant. Thus we expected that there might be a possible association between GL and AD in men. It was also thought possible to link the previous finding by Charoonruk in our Cache County Study: diabetes had 4 times greater risk for developing AD among men than non-diabetics (62).

The sample population of this study was started from people without diabetes and examined the effect of GL by comparing low GL group with high GL group related to AD. The reason of exclusion of diabetes from the sample population was that we wanted to estimate usual carbohydrate intake pattern in terms of glycemic index (GI) and glycemic load (GL), not affected or modified by other factors such as diabetes among baseline participants. The dietary treatment for diabetes affected the amount of carbohydrates

intake in both quality and quantity to control blood sugar, thus it consequently affected GL intake thereby confounded our dietary assessment.

If the association between high GL and the risk of dementia in men we found in the descriptive analysis appeared in Cox proportional hazard regression models in survival analysis, it would be possible to relate the former finding between diabetes and incident AD in men to the dietary characteristic of GL. However, our finding was no association in both men and women.

A negative association between GL and incident AD was appeared in women before we controlled total kcal as a confounder. We did not consider total kcal and other macro-nutrients in the previous two models as covariates. We examined total kcal and macro-nutrients to find why negative the finding was in women with very significant p-value and what characteristics of the lowest quintile in women have. We found suspicious characteristics of the first quintile of GL in women by mean distribution of macro nutrients across quintiles. Noticeable thing was that the lowest quintile group consumed the highest amount of kcal, protein, fat, and saturated fat. Men also had a similar pattern (second high in kcal intake and the highest intake in protein and fat), but women showed a prominent trend; total kcal, protein, and fat intake decrease with increasing GL whereas carbohydrates, sugar, and fiber intake increase with GL. Women in Q1 group consumed 225 more kcals, 38g more proteins, and 30g more fat per day compared to the Q5 mean intake. Table 17 summarized these characteristics.

After examination of possible confounding factors among total kcal and macro-nutrients, total kcal intake appeared as a possible confounder. As Cox hazard regression model was controlled with total kcal and added interaction term with GL, no association

was appeared in women. The significant level was closed to 0.05 and the confidence interval included 1.0, thus there might be other confounding factors between GL and incident AD. However, as the model adjusted for all other covariates including total kcal plus interaction with GL, the result remained the same (no association in both men and women) but the p-value became much greater in women thus underscoring the finding of association.

Another thing to point out is dietary intake patterns of smoking and alcohol users. Both smokers and alcohols user had the exact same pattern: never users had higher GL intake, former users were middle, and current users had the lowest GL intake. Alcohol contains no glucose and a minimal amount of carbohydrates, so GI = 0, at the same time, GL = 0 because of zero GI value. Alcohol has 7 kcal per g and it is greater than carbohydrates (4 kcals/ g) but has zero GL value. Thus alcohol intake might partly contribute to increase total kcal but decrease overall dietary GL intake. The life style of alcohol users may also include smoking. Both habits tend to have an association with dietary habits too. In other words, alcohols users tend to be more likely to smoke compared with non-alcohol users and tend to have unhealthy diets such as eating less fruits and vegetables.

Table 18– 23 may explain these complicated characteristics of the low GL quintile group of people. The percentage of smoking and alcohol use was higher in the low GL group and it was appeared clear in men due to more people in smoking and alcohol use compared to women. In the mean serving intake of food groups, the low GL quintile group consumed more dairy foods, eggs, meats, fish, and alcohol and less fruits and soft drink. Vegetable intake was not associated with GL and appeared a similar number of

servings throughout the quintiles.

To summarize, the low GL group had unique characteristics in life style factors, macro-nutrients intake, and pattern of food use: higher percentage of smoking and alcohol user in life style factors, high kcal, protein, fat, and saturated fat intake in macro-nutrients intake, and more specifically higher dairy, meat, eggs, alcohol intake and lower fruits intake in the pattern of food use indicating that they more likely had unhealthy life style and dietary pattern. The inverse relationship between GL and total kcal may partly be explained by life style factors, particularly alcohol intake may have contributed to this relationship because this group consisted of a large percentage of alcohol users and alcohol had high kcal and zero GL value.

Last, there might be a possible reason for the no association in men. Men had a consistent positive relationship between GL and dementia or AD, but significant level did not support its association. Maybe, because of small number of sample size (n of AD = 58 among 1347 elderly men) partly due to a large number of exclusion for valid dietary assessment. Thus, continued follow-up of both men and women is important.

To conclude, intakes of most nutrients tend to be positively correlated with total energy intake (114), but carbohydrates intake in terms of GL was negatively correlated with total kcal and other macro-nutrients such as protein and fat intake. Although GL was adjusted for total kcal, total energy intake still affects the relation between GL and incident AD. The life style factors such as smoking and alcohol use and their dietary pattern also are associated with GL value. Therefore, GL alone may be of limited value to examine the relationship between carbohydrates intake and AD. The pattern of food use among carbohydrates containing foods may better reveal carbohydrates-intake related to

incident AD.

Further research on total kcal intake related to incident dementia or AD among people with or without APOE ε-4 alleles genotypes should be examined. Based on previous finding in Cache County Study, that fruits, vegetables, and fish intake were associated with reduced risk of cognitive decline, whole grain intake among total carbohydrates intake related to incident dementia or AD is suggested as an important topic for further exploration.

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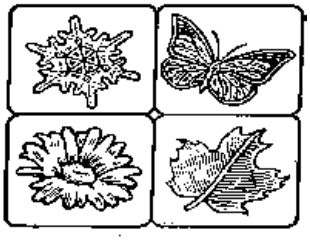
APPENDIX

BASELINE FOOD FREQUENCY QUESTIONNAIRE

CACHE COUNTY STUDY ON MEMORY, HEALTH, AND AGING

UTAH STATE UNIVERSITY



CACHE COUNTY STUDY ON MEMORY IN AGING
NUTRITION QUESTIONNAIRE
Conducted by: Utah State University

Marking Instructions

Please follow these few simple rules in completing this questionnaire.

1. Use only a pencil. (Please DO NOT use a pen)
2. Darken completely the circle of the answer you choose
3. Erase cleanly any answer that you wish to change
4. Make no stray marks of any kind on the form
5. For food that you never or rarely eat, please mark the first column labeled "None or Less than once a month. Please do not leave any food items blank.
6. Please note the correct way to mark the answers.

Correct Mark				Incorrect Mark			
□	□	□	□	□	□	□	□

Please answer the following. Check the appropriate gender, and fill in your height, weight, and age

Male_____ Female_____

Height_____ Weight_____ Age_____

THANK YOU!!!!

DIETARY SUPPLEMENTS

PLEASE INDICATE WHICH, IF ANY, OF THE FOLLOWING SUPPLEMENTS YOU ARE CURRENTLY TAKING. PLEASE ANSWER "YES" OR "NO" FOR ANY SUPPLEMENT LISTED.

1. Do you regularly take multivitamins
   □ NO> PLEASE GO TO QUESTION 2
   □YES> CONTINUE:
      (A) How many years have you taken multivitamins?
         □ 0-1 years □ 5-9 years
         □ 2-4 years □ 10 or more years
      (B) What specific brand do you use?_____

Excluding multivitamins, do you take any of the following supplements listed below?

2. Do you regularly take Vitamin A?
   □ NO> PLEASE GO TO QUESTION 3
   □ YES> CONTINUE:
      (A) How many years have you taken multivitamins?
         □ 0-1 years □ 5-9 years
         □ 2-4 years □ 10 or more years
      (B) What dose do you take per day?
         □ less than 8,000 IU □ 22,001 IU or more
         □8,001 to 13,000 IU □ Don't know
         □ 13,001 to 22,000 IU

3. Do you regularly take Vitamin C?
   □ NO> PLEASE GO TO QUESTION 4
   □YES> CONTINUE:
      (A) How many years have you taken multivitamins?
         □ 0-1 years □ 5-9 years
         □ 2-4 years □ 10 or more years
      (B) What dose do you take per day?
         □ less than 400 mg □ 1301 mg or more
         □ 401 to 700 mg □ Don't know
         □ 701 to 1300 mg

4. Do you regularly take Vitamin C?
   □ NO> PLEASE GO TO QUESTION 5
   □ YES> CONTINUE:
      (A) How many years have you taken multivitamins?
         □ 0-1 years □ 5-9 years
         □ 2-4 years □ 10 or more years
      (B) What dose do you take per day?
         □ less than 100IU □ 504 IU or more
         □ 101 to 300 IU □ Don't know
         □ 301 to 500 IU

5. Do you regularly take Calcium?
   □ NO> PLEASE GO TO QUESTION 6
   □ YES> CONTINUE:
      (A) How many years have you taken multivitamins?
         □ 0-1 years □ 5-9 years
         □ 2-4 years □ 10 or more years
      (B) What dose do you take per day?
         □ less than 400 mg □ 1301 mg or more
         □ 401 to 900 mg □ Don't know
         □ 901 to 1300 mg

6. Do you regularly take Vitamin D?
   □ NO> PLEASE GO TO QUESTION 7
   □ YES> CONTINUE:
      (A) How many years have you taken multivitamins?
         □ 0-1 years □ 5-9 years
         □ 2-4 years □ 10 or more years
      (B) What dose do you take per day?
         □ less than 200 IU □ 1,000 IU or more
         □ 201 to 400 IU □ Don't know
         □ 401 to 1,000 IU

7. Do you regularly take Vitamin B6?
   □ NO> PLEASE GO TO QUESTION 8
   □ YES> CONTINUE:
      (A) How many years have you taken multivitamins?
         □ 0-1 years □ 5-9 years
         □ 2-4 years □ 10 or more years
      (B) What dose do you take per day?
         □ less than 10 mg □ 80 mg or more
         □ 10 to 39 mg □ Don't know
         □ 40 to 79 mg

8. Do you regularly take Selenium?
   □ NO> PLEASE GO TO QUESTION 9
   □ YES> CONTINUE:
      (A) How many years have you taken multivitamins?
         □ 0-1 years □ 5-9 years
         □ 2-4 years □ 10 or more years
      (B) What dose do you take per day?
         □ less than 80 mcg □ 251 mcg or more
         □ 81 to 130 mcg □ Don't know
         □ 131 to 250 mcg

FOR OFFICE USE ONLY		
(A)	(B)	(C)
1 2 3 4 5 6 7 8 9 0	1 2 3 4 5 6 7 8 9 0	1 2 3 4 5 6 7 8 9 0
□ □ □ □ □ □ □ □ □ □	□ □ □ □ □ □ □ □ □ □	□ □ □ □ □ □ □ □ □ □
1 2 3 4 5 6 7 8 9 0	1 2 3 4 5 6 7 8 9 0	1 2 3 4 5 6 7 8 9 0
□ □ □ □ □ □ □ □ □ □	□ □ □ □ □ □ □ □ □ □	□ □ □ □ □ □ □ □ □ □

9. Do you regularly take Iron?
□NO> PLEASE GO TO QUESTION 10
□YES> CONTINUE:
(A) How many years have you taken multivitamins?
□ 0-1 years □ 5-9 years
□ 2-4 years □ 10 or more years
(B) What dose do you take per day?
□ 50 mg or less □ 401 mg or more
□ 51 to 200 mg □ Don't know
□ 201 to 400 mg

10. Do you regularly take Zinc?
□ NO> PLEASE GO TO NEXT SECTION
□YES> CONTINUE:
(A) How many years have you taken multivitamins?
□ 0-1 years □ 5-9 years
□ 2-4 years □ 10 or more years
(B) What dose do you take per day?
□ less than 25 mg □ 101 mg or more
□ 26 to 75 mg □ Don't know
□ 76 to 100 mg

11. DO YOU TAKE ANY OF THE FOLLOWING OTHER SUPPLEMENTS:

Cod liver oil .....□ Yes .....□ No	Folic acid..... □ Yes .....□ No
Other fish oil .....□ Yes .....□ No	Iodine ..... □ Yes .....□ No
Niacin.....□ Yes .....□ No	Brewer's Yeast..... □ Yes .....□ No
Beta-caroten .....□ Yes .....□ No	Magnesium..... □ Yes .....□ No
Thiamine (vitamin B1).....□ Yes .... □ No	Any others? ..... □ Yes .....□ No
B-complex vitamins.....□ Yes .... □ No	If yes, please specify_____ _____

For each food listed, please mark a circle for how often during the past year, on average, you have eaten the serving size specified. Be sure to mark a circle for every food listed. If you never eat the food listed mark the circle in the first column.

DAIRY FOODS	**AVERAGE USE FOR PAST 12 MONTHS**								
	NONE OR LESS THAN 1 PER MO.	1-3 PER MO.	1 PER WK.	2-4 PER WK.	5-6 PER WK.	1 PER DAY	2-3 PER DAY	4-5 PER DAY	6 PER DAY
Skim or low fat milk (8 oz. glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Whole milk (8 oz. glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Chocolate milk or cocoa (8 oz. glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cream or half-and-half, e.g. coffee, whipped (Tbs)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sour cream (Tbs)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Non-dairy coffee whitener (tsp)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sherbet, ice milk, or frozen yogurt (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ice cream (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Yogurt (1 cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cottage or ricotta cheese (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cream cheese (1 oz.)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other cheese, e.g. American, cheddar, etc., plain or as part of a dish (1 slice or 1 oz. serving)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Margarine (1 tsp, added to food or bread; exclude use in cooking	☐	☐	☐	☐	☐	☐	☐	☐	☐
Butter (1 tsp), added to food or bread; exclude use in cooking.	☐	☐	☐	☐	☐	☐	☐	☐	☐
FRUITS	☐	☐	☐	☐	☐	☐	☐	☐	☐
Raisins (1 oz. or small pack) or grapes (1/2 c)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Prunes (7 prunes or ½ cup)	□	□	□	□	□	□	□	□	□
Bananas (1)	□	□	□	□	□	□	□	□	□
Cantaloupe (1/4 melon)	□	□	□	□	□	□	□	□	□
Avocado (1/2 fruit or ½ cup)	□	□	□	□	□	□	□	□	□
Fresh apples or pears (1)	□	□	□	□	□	□	□	□	□
Apple juice or cider (small glass)	□	□	□	□	□	□	□	□	□
Oranges (1)	□	□	□	□	□	□	□	□	□
Orange Juice (small glass)	□	□	□	□	□	□	□	□	□
Grapefruit (1/2)	□	□	□	□	□	□	□	□	□
Grapefruit juice (small glass)	□	□	□	□	□	□	□	□	□
Other fruit juices (small glass)	□	□	□	□	□	□	□	□	□
Strawberries, fresh, frozen or canned (1/2 cup)	□	□	□	□	□	□	□	□	□
Blueberries, fresh, frozen or canned (1/2 cup)	□	□	□	□	□	□	□	□	□
Peaches, apricots or plums (1 fresh, or ½ cup canned)	□	□	□	□	□	□	□	□	□
VEGETABLES	□	□	□	□	□	□	□	□	□
Tomatoes (1)	□	□	□	□	□	□	□	□	□
Tomato juice, V8 (small glass)	□	□	□	□	□	□	□	□	□
Tomato sauce (1/2 cup) e.g. spaghetti sauce	□	□	□	□	□	□	□	□	□
Salsa or red chili sauce (1 Tbs)	□	□	□	□	□	□	□	□	□
Tofu or soybeans (3-4 oz.)	□	□	□	□	□	□	□	□	□
String (green) beans (1/2 cup)	□	□	□	□	□	□	□	□	□
Broccoli (1/2 cup)	□	□	□	□	□	□	□	□	□
Cabbage or cole slaw (1/2 cup)	□	□	□	□	□	□	□	□	□
Cauliflower (1/2 cup)	□	□	□	□	□	□	□	□	□
Brussels sprouts (1/2 cup)	□	□	□	□	□	□	□	□	□
Carrots, raw (1/2 carrot or 4 sticks)	□	□	□	□	□	□	□	□	□
Carrots, cooked (1/2 cup) or carrot juice (2-3 oz.)	□	□	□	□	□	□	□	□	□
Red Beets—not greens (1/2 cup)	□	□	□	□	□	□	□	□	□
Corn (1 ear or ½ cup frozen or canned)	□	□	□	□	□	□	□	□	
Peas or lima beans (1/2 cup fresh, frozen, or canned)	□	□	□	□	□	□	□	□	□
Mixed vegetables (1/2 cup)	□	□	□	□	□	□	□	□	□
Beans or lentils, baked or dried (1/2 cup)	□	□	□	□	□	□	□	□	□

Dark orange (winter) squash (1/2 cup) (acorn, butternut squash)	□	□	□	□	□	□	□	□	□
Eggplant, zucchini or other summer squash (1/2 cup)	□	□	□	□	□	□	□	□	□
Yams or sweet potatoes (1/2 cup)	□	□	□	□	□	□	□	□	□
Spinach, cooked (1/2 cup)	□	□	□	□	□	□	□	□	□
Spinach, raw as in a salad (1 cup serving)	□	□	□	□	□	□	□	□	□
Kale, mustard or chard greens (1/2 cup)	□	□	□	□	□	□	□	□	□
Iceberg or head lettuce (1 cup serving)	□	□	□	□	□	□	□	□	□
Romaine or leaf lettuce (1 cup serving)	□	□	□	□	□	□	□	□	□
Celery (2-4 4” sticks)	□	□	□	□	□	□	□	□	□
Sweet green or red peppers (3 slices or ¼ pepper)	□	□	□	□	□	□	□	□	□
Onions as a garnish, or in salad (1 slice)	□	□	□	□	□	□	□	□	□
Onions as a vegetable, rings or in soup (1 onion)	□	□	□	□	□	□	□	□	□
EGGS, MEATS, ETC.									□
Eggs (1)	□	□	□	□	□	□	□	□	□
Chicken with skin (4-6 oz.)	□	□	□	□	□	□	□	□	□
Chicken without the skin (4-6 oz.), includes grilled chicken sandwich	□	□	□	□	□	□	□	□	□
Turkey, including ground turkey (4-6 oz. or 2 turkey dogs)	□	□	□	□	□	□	□	□	□
Hot dogs 91)	□	□	□	□	□	□	□	□	□
Bacon (2 slices)	□	□	□	□	□	□	□	□	□
Processed meats, e.g. sausage, salami, bologna, etc. (1 piece or slice)	□	□	□	□	□	□	□	□	□
Hamburger (1 patty)	□	□	□	□	□	□	□	□	□
Taco or tostado (1)	□	□	□	□	□	□	□	□	□
Burrito (1)	□	□	□	□	□	□	□	□	□
Enchilada (2)	□	□	□	□	□	□	□	□	□
Beef, pork or lamb as a sandwich or mixed dish, e.g. stew, casserole, lasagna, chili etc.	□	□	□	□	□	□	□	□	□
Pork as a main dish, e.g. ham or chops (4-6 oz.)	□	□	□	□	□	□	□	□	□
Beef or lamb as a main dish, e.g. steak, roast (4-6 oz)	□	□	□	□	□	□	□	□	□
Liver: beef, calf, or pork (4 oz)	□	□	□	□	□	□	□	□	□
Liver: chicken or turkey (2 oz)	□	□	□	□	□	□	□	□	□
Canned tuna fish (3-4 oz)	□	□	□	□	□	□	□	□	□
Dark meat fish, e.g. mackerel, salmon, sardines, bluefish, swordfish (3-5 oz.)	□	□	□	□	□	□	□	□	□
Fried fish, e.g. fish sticks, fish and chips style fish (3-5 oz.)	□	□	□	□	□	□	□	□	□
Other fish (3-5 oz.)	□	□	□	□	□	□	□	□	□
Shrimp, lobster, scallops as a main dish	□	□	□	□	□	□	□	□	□

BREADS, CEREALS, STARCHES									
Cold breakfast cereal (1 cup)									
Cooked oatmeal/cooked oat bran (1 cup)									
Other cooked breakfast cereal (1 cup)									
Instant breakfast beverage, e.g. Carnation									
White bread (slice), including pita bread									
Dark bread (slice), including pita bread									
English muffins, bagels, or dinner rolls (1 each)									
Muffins or biscuits (1 each)									
White rice (1 cup)									
Pasta, e.g. spaghetti, noodles, etc (1 cup)									
Tortillas (1-10 inch shell)									
Other grains, e.g. bulgur, kasha, couscous, etc (1 cup)									
Pancakes or waffles (2 each)									
French fried potatoes (4 oz. or size of small fries order)									
Potatoes, baked, boiled (1each), or mashed (1 cup)									
Potato chips or corn chips (small bag or 1 oz.)									
Crackers, e.g. Triscuits, Wheat Things (5 each)									
Pizza (2 slices)									
BEVERAGES									
Plain water, bottled or tap (1 cup or 8 oz. glass)									
Hawaiian Punch, lemonade, or other non-carbonated fruit drinks (1 glass, bottle, can)									
Low-calorie cola, e.g. Diet Coke with caffeine (can)									
Low-calorie caffeine-free cola (can)									
Other low-calorie carbonated beverage, e.g. Fresca, Diet 7-UP (can)									
7-Up, diet ginger ale (can)									
Coke, Pepsi, or other cola with sugar (can)									
Caffeine Free Coke, Pepsi, or other cola with sugar (can)									
Other carbonated beverages with sugar, e.g. Sprite, Root beer (can)									
Regular Beer (1 glass, bottle, or can)									
Light Beer (1 glass, bottle, or can)									
Red wine (4 oz. glass)									
White Wine (4 oz. glass)									

Liquor, e.g. whiskey, gin, etc (1 drink or shot)	□	□	□	□	□	□	□	□	□
Dark tea with caffeine (1 cup), not herbal tea	□	□	□	□	□	□	□	□	□
Green tea or herbal tea (1 cup)	□	□	□	□	□	□	□	□	□
Coffee with caffeine (1 cup)	□	□	□	□	□	□	□	□	□
Decaffeinated coffee (1 cup)	□	□	□	□	□	□	□	□	□
SWEETS, BAKED BGOODS, MISC									□
Chocolate (bar or packet) e.g. Hershey's M & M's	□	□	□	□	□	□	□	□	□
Candy bars, e.g. Snicker, milky way, Reeses	□	□	□	□	□	□	□	□	□
Candy other than chocolate (1 oz)	□	□	□	□	□	□	□	□	□
Cookies, home baked (1)	□	□	□	□	□	□	□	□	□
Cookies, ready make (1)	□	□	□	□	□	□	□	□	□
Brownies (1)	□	□	□	□	□	□	□	□	□
Doughnuts (1)	□	□	□	□	□	□	□	□	□
Cake, home baked (1 slice)	□	□	□	□	□	□	□	□	□
Cake, ready make (1 slice)	□	□	□	□	□	□	□	□	□
Pie, homemade (1 slice)	□	□	□	□	□	□	□	□	□
Pie, ready made (1 slice)	□	□	□	□	□	□	□	□	□
Sweet roll, coffee cake or other pastry, home baked (1 each)	□	□	□	□	□	□	□	□	□
Sweet roll, coffee cake or other pastry, ready made (1 each)	□	□	□	□	□	□	□	□	□
Jams, jellies, preserves, syrup, or honey (1 Tbs)	□	□	□	□	□	□	□	□	□
Peanut butter (1 Tbs)	□	□	□	□	□	□	□	□	□
Popcorn (1 cup)	□	□	□	□	□	□	□	□	□
Peanuts (small packet or 1 oz.)	□	□	□	□	□	□	□	□	□
Other nuts (small packet or 1 oz.)	□	□	□	□	□	□	□	□	□
Oat bran, added to food (1 Tbs)	□	□	□	□	□	□	□	□	□
Other bran, added to food (1Tbs)	□	□	□	□	□	□	□	□	□
Wheat germ (1 Tbs)	□	□	□	□	□	□	□	□	□
Chowder or cream soup (1 cup)	□	□	□	□	□	□	□	□	□
Olive oil salad dressing (1 Tbs)	□	□	□	□	□	□	□	□	□
Other oil and vinegar dressing, e. g. Italian (1 Tbs)	□	□	□	□	□	□	□	□	□
Mayonnaise or other creamy salad dressing (1 Tbs)	□	□	□	□	□	□	□	□	□
Salt added at table (1 shake)	□	□	□	□	□	□	□	□	□
Garlic (1 clove or 4 shakes)	□	□	□	□	□	□	□	□	□

FOOD PREPARATION	
1.	Do you eat cold breakfast cereal? □ NO> PLEASE GO TO NEXT QUESTION □ YES> What kind do you usually eat?_____

2.	How many teaspoons of sugar do you add to your beverages or food each day? □ 0-1 □ 2-4 □ 5-9 □10 or more
3.	When you have beef or lamb as a main dish, how is the meat cooked? □ Rare □ medium □ well □ Medium rare□ medium well □ do not eat meat
4.	How much of the visible fat on your beef, pork, or lamb do you remove before eating? □ remove all visible fat □ remove none □ remove most visible fat □do not eat meat □ remove small part of visible fat
5.	How often do you eat food that is fried at home? (exclude Pam-type spray) □ less than once per week □ 4-6 times per week □ 1-3 times per week □ daily
6.	How often do you eat fried food away from home? (e.g. french fries, fried chicken, fried fish). □ less than once per week □ 4-6 times per week □ 1-3 times per week □ daily
7.	What type and brand of cooking oil or fat do you usually use at home (e.g. corn oil, Mazola brand; lard) Type:_____ Brand:_____
8.	How does the amount of food you eat now compare to the amount you ate five years ago? □ I eat almost the same □ I eat less now □ I eat more now
9.	What was the main source of your drinking water over the past year? □ city system □ rural or county system □ private well □ bottled water □ other (please specify_____)

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YOUR ACTIVITES

1. About how many hours per day do you spend in light activity, such as walking, shopping, child care, cooking, carrying light objects, cleaning, and repairing?

   Hours per day_____

2. About how often do you take part in moderate physical activities including bowling, golf,

light swimming, gardening, walks over 15 minutes, fishing, light bicycling, or other light sports.

□Usually every day
□ 2-6 times a week
□ About once a week
□ A few times a month
□ A few times a year
□ Rarely or never

3. About how often do you take part in vigorous physical activity including jobbing, tennis, racquetball or squash, lap swimming, aerobics, vigorous bicycling, skiing, hiking, hunting or other vigorous sports…
   - Usually every day
   - 2-6 times a week
   - About once a week
   - A few times a month
   - A few times a year
   - Rarely or never

4. How often do you talk on the telephone with family, friends, or neighbors?
   - Usually every day
   - 2-6 times a week
   - About once a week
   - A few times a month
   - A few times a year
   - Rarely or never

5. How often do you get together with family, friends, or neighbors? This includes meeting in your own home, meeting in other's homes, or going out together.
   - Usually every day
   - 2-6 times a week
   - About once a week
   - A few times a month
   - A few times a year
   - Rarely or never

6. How often do you attend meetings of social clubs, groups, or organizations such as bridge clubs, book clubs, hospital volunteer, gardening clubs, Rotary club, Kiwanis, VFW, etc.
   - Usually every day
   - 2-6 times a week
   - About once a week
   - A few times a month
   - A few times a year
   - Rarely or never

Thank you for completing this questionnaire. Please make sure that no questions or pages have been skipped. Please place it in the postage-paid envelope that has been provided and seal it. Please return it to us in the mail.

Thank you for your time and cooperation. You have made an important contribution to our study of nutrition and health.

Utah State University