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ASSOCIATION BETWEEN NUTRITION AND COGNITIVE FUNCTION IN COSTA RICAN OLDER ADULTS

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ASSOCIATION BETWEEN NUTRITION AND COGNITIVE FUNCTION IN COSTA
RICAN OLDER ADULTS

A Thesis
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Master of Science
Food, Nutrition and Culinary Sciences

by
Maria Catalina Aragon
August 2012

Accepted by:
Dr. Katherine L. Cason, Committee Chair
Dr. Cheryl J. Dye
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ABSTRACT

Older adults are among the fastest-growing segment of the world's population. In Costa Rica, life expectancy is comparable to developed countries, such as the United States and Western European countries. The loss of cognitive capacity is one of the most significant issues affecting the quality of life of older adults and their families. Although the causes of cognitive decline remain uncertain, it has been linked to cardiovascular risk factors such as diabetes mellitus and high blood pressure. Dietary fatty acids have an important role in these conditions, making it is plausible that they could play a role in cognitive deterioration

The purpose of this research is to examine the association among fatty acid intake, lipid profile, and cognitive health in Costa Rican elders. To examine these issues, a cross-sectional secondary data analysis was performed using public data from the Costa Rican Longevity and Healthy Aging Study, a nationally representative longitudinal survey of health and socioeconomic indicators of Costa Rican residents ages 60 and over in 2005 (n=2878). All data and specimens in the study were collected at the participants' homes, usually during two visits. Diet information was collected using a semi-quantitative food frequency questionnaire. Cognitive disability was assessed with an adaptation of the Mini-Mental State Examination (MMSE). Participants who answered the 15 items with fewer than 75% correct answers were considered to be "cognitively impaired." Serum lipid analyses were conducted by nationally certified laboratories. General characteristics between cognitively disabled and non-cognitively disabled participants were explored

using descriptive statistics. Regression models were controlled for age, caloric intake, and lipid medication.

The study found highly significant differences between cognitively disabled and non-cognitively disabled older adults. The demographic data indicated that adults with less than 75% accuracy on the MMSE were younger, had lower monthly income, and had completed fewer years of formal education. Important differences were also found in the health profile. Medical diagnoses of diabetes, stroke, and heart attack were significantly higher among the cognitively disabled. Non-cognitively disabled adults had a higher rate of medical diagnosis of dyslipidemia and presented a higher rate of metabolic syndrome. Anthropometric data confirmed that cognitively disabled elders had a lower BMI, lower body weight, and higher percentage of underweight. The dietary analysis revealed a lower energy, total fat, and monounsaturated fatty acids intake compared to their counterparts. The lipid profile from adults who were not cognitively disabled indicated significantly higher levels of LDL, triacylglycerides, and total cholesterol. The multiple regression analysis suggested a significant ($p < .050$), yet weak ($R^2 = .299$), association between MMSE score and serum lipid profile as well as dietary fatty acids.

Differences in Costa Rican elders' demographic, health, and diet characteristics were found between cognitively disabled individuals and those not disabled. Dietary fat intake and serum lipid profile were weakly associated with cognitive outcomes. Further research, particularly longitudinal studies, are needed to better examine this relationship.

DEDICATION

A mi familia, gracias por su amor incondicional y por el apoyo que he recibido durante este proceso. No lo hubiera logrado sin ustedes.

Mamá, you are my still role model. Thank you for watching over me. *Papá and Sonia*, all those Skype conversations kept me going. I don't think I believe in myself half as much as you both do. *Abu*, you taught me how to be free spirited and follow my dreams. *Fofi and T Gaby*, you always had words of wisdom and support for me, but most importantly, you made me feel like I had family right "next door". All of my *aunts, uncles, extended family and friends*, you always took care of me, in one way or another.

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CHAPTER ONE

INTRODUCTION

Older adults are among the fastest growing segments of the world population. The number and proportion of this population is increasing in both developing and developed countries; by 2015 people aged 65 or older will outnumber children under the age of five (World Health Organization, National Institute of Aging & National Institute of Health, 2011). Currently, in the entire world population, one out of every ten persons is over 60 years old (United Nations Population Fund, 2010). By 2025, the proportion of older adults is expected to reach 25% in North America, 21% in Eastern Asia, 14% in Latin America and 11% in South and Central Asia (United Nations Population Division, 2001). The majority of older people over the age of 60 years now live in developing countries, where the most rapid demographic changes are occurring, with predicted increases of 200-400 percent in their older populations during the next decades (WHO, 2000).

Mortality rates have declined due to improvement in social development, living standards, hygiene, sanitation and infectious disease prevention (United Nations Population Division, 2001). Life expectancy in the U.S. has increased from 47 years, for Americans born in 1900, to 77 years, for those born in 2001 (Centers for Disease Control and Prevention & The Merck Company Foundation, 2007). Recent data, establishes a life expectancy of 76 years for males and 81 years for females (CDC & National Center for Health Statistics, 2011). In low income countries, life expectancy has increased from 45

years in the 1950s to 64 years in the 1960s (UNPD, 2001). Additionally, fertility rates have fallen all over the world, mainly due to the development of effective contraceptive methods and improvements in women's education (WHO, 2000).

Increases in longevity and the proportion of people over the age of 60 years, is often regarded as a challenge to health systems as longer lives are commonly associated with a prevalence of disease (WHO, 2000). The leading causes of death have shifted dramatically from infectious diseases to non-communicable, chronic diseases and from younger to older individuals (UNPD, 2001). Disabilities associated with chronic illness also increase with advancing age (CDC, 2011).

The medical conditions most frequently encountered in this age group include cardiovascular disease, osteoarthritis, osteoporosis, depression, diabetes, sensory deficits, cognitive decline, and dementia (CDC & The Merck Company Foundation, 2007). The loss of cognitive capacity is one of the most important factors affecting the quality of life of older adults and their families and it is one of the main reasons that people are admitted into nursing homes (Gaugler, Duval, Anderson & Kane, 2007).

Most experts agree that the components of healthy cognitive function include language, thought, memory, executive function (the ability to plan and carry out tasks), judgment, attention, perception, remembered skills (such as driving) and the ability to live a purposeful life (National Research Council, 2000). Cognitive health is not limited to the absence of disease, it can range from optimal functioning, slight cognitive impairment, to severe dementia (Hendrie et al., 2006).

As the population ages, it is important to understand the influence of modifiable lifestyle factors such as diet on lifespan, as well as “healthspan”, including cognitive, mental and physical health maintenance into advanced age. The causes of cognitive decline remain uncertain; however they have been linked to cardiovascular disease and cardiovascular risk factors such as diabetes mellitus and high blood pressure (Naqvi et al., 2011).

Dietary fatty acids have an important role in cardiovascular disease, thus it is plausible that they could have a role in cognitive deterioration (Hunter, Zhang & Kris-Etherton, 2009). Fatty acids could be involved through several mechanisms; including atherosclerosis, thrombosis, and inflammation (Kalmijn, 2000).

There has been increasing interest in the hypothesis that fish consumption, polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) could play a protective role against cognitive decline. However, evidence of this relationship remains controversial. Results are also inconsistent in large cross-sectional studies focused on dietary intake, particularly fish and marine PUFA. Findings from longitudinal data are less controversial; but still disputed (Capurso et al., 2003; Morris et al., 2004). Several studies suggested that an increase of saturated fats could have negative effects on cognitive health (Kalmijn, Feskens, Launer & Kromhout, 1997; Freeman, Haley-Zitlin, Stevens & Granholm, 2011) while PUFA and monounsaturated fatty acids (MUFA) may have a protective effect (Capurso et al., 2003; Solfrizzi et al., 1999). Except for reports from an ongoing Chilean study (Hirsch, de la Maza, Barrera,

Gattas, Petermann & Bunout, 2002), there are no known studies on this topic in Latin American countries or developing nations.

1.1 Statement of Purpose

The aim of this research is to determine the association between diet, serum lipids and cognitive health in older adults.

1.2 Research Questions

This thesis will explore two research questions and hypotheses on the relationship of diet and nutrition to cognitive health by using secondary cross-sectional data from a population of Costa Rican older adults.

1. What is the relationship between fatty acid intake and cognitive health in Costa Rican elders?

Hypothesis (H₁): PUFA, particularly n-3 and n-6, will have a protective effect on cognitive health.

2. Is there an association between serum lipid profile and cognitive health in Costa Rican elders?

Hypothesis (H₂): A desirable serum lipid profile will have a protective effect on cognitive health.

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CHAPTER TWO

LITERATURE REVIEW

The average life expectancy in Costa Rica is 79 years: 77 years for men and 81 years for women (World Health Organization, 2009). This is the highest life expectancy in Latin America. When compared to life expectancy in the region the gap is even broader: Central American countries report a life expectancy ranging from 69 years in Guatemala and El Salvador to 74 years in Panama. Costa Rican life expectancy is comparable to that of developed countries such as the United States and Western European countries. In addition, compared to adult men over 60 years old, Costa Rican males have a longer life expectancy than white males in the United States (Brenes-Camacho & Rosero-Bixby, 2009; Rosero-Bixby, 1995). For men over 90 years old, life expectancy is one-half year more in Costa Rica than in any other country (Rosero-Bixby, 2008). Comparisons with the United States and Sweden show that the Costa Rican advantage comes mostly from a reduced incidence of cardiovascular diseases, coupled with a low prevalence of obesity (Rosero-Bixby & Dow, 2009). Of added importance to this comparison, is the fact that the Costa Rican Gross National Product is a small fraction of the Gross National Product for the United States or Western European countries (United Nations, 2009a).

The Costa Rican Social Security system is one important factor for the Costa Rican high life expectancy (de Bertodano, 2003; Rosero-Bixby, 2004a). While private health care is available, most health services since 1941 have been provided by the Costa

Rican social security system, known as *Caja Costarricense del Seguro Social* (CCSS). This system is funded from individual payroll deductions, contributions from the employers, and the government. Those who contribute to the CCSS are entitled to health insurance that allows them and their family to receive free health care services and medications at any public hospital, clinic or community health (Brenes-Camacho & Rosero-Bixby, 2008). The CCSS covers about 90% of the population including 9% of the individuals whose insurance is paid by the government. These percentages are higher among the elderly where 95% are covered and up to 22% have voluntary government-covered insurance (Rosero-Bixby, 2004b). People who consistently declare themselves as uninsured (10% of total population, 5% of the elderly) can still obtain health care from the CCSS units for a fee or for free if institutional social workers verify that the patients have no means to pay for health care services (de Bertodano, 2003).

Analyses of data from developed countries have found socioeconomic status (SES) and adult health to be significantly positively correlated with better health at higher SES (Seeman, Merkin, Crimmins, Koretz, Charette, & Karlamangla, 2008). Differences in SES and use of preventive health care services in older adults have also revealed SES disparities in health service utilization. People with higher SES were more likely to take advantage of most preventive services and utilization rates among uninsured seniors were lower than among their insured peers (Brenes-Camacho & Rosero-Bibxy, 2009). In contrast, research on both mortality and metabolic syndrome among Costa Ricans reveals that those who are better educated and wealthier are worse than those with lower SES strata. Nevertheless, quality-of-life related measures such as functional and cognitive

disabilities, physical frailty, and depression all clearly worsen with lower SES (Rosero-Bixby & Dow, 2009).

In some developed countries, an association of lower educational attainment with greater risk of mortality has been found (Kunitz, 2007) although in Costa Rica there are relatively minor associations between mortality and education among those aged 60 and above (Rosero-Bixby, Dow & Lacle, 2005). In contrast, a recent analysis in the United States of similarly aged individuals revealed substantial differentials by education, with mortality rates 5-6% higher per year for each year less of education (Steenland, Henley & Thun, 2002). To explore this association, data from older adults participating in National Health and Nutrition Examination Survey (NHANES) was compared to data from the Costa Rican Longevity and Healthy Aging Study (CRELES, or *Costa Rica Estudio de Longevidad y Envejecimiento Saludable*). Results indicate significantly lower hazardous levels of risk biomarkers at higher levels of education for more than half of the risk factors in the United States as compared with less than a third of the outcomes in Costa Rica (Rehkopf, Dow & Rosero-Bixby, 2009).

To determine the relationship between socialized health care and longevity, research has been conducted to explore the relationship between longevity and chronic disease management by both CCSS and private health care. In one study, the metabolic control of diabetes in community health care centers, regional clinics and hospitals, and a subsample of 542 CRELES participants with self-reported diabetes mellitus was assessed. Except for elevated levels of triacylglycerides and low density lipoproteins (LDL) in patients from community health centers, no statistical differences in the other

metabolic control indicators were seen across health care settings (Brenes-Camacho & Rosero-Bixby, 2008). Levels of metabolic control among elderly people with diabetes mellitus were found to be similar to those observed in industrialized countries (Brenes-Camacho & Rosero-Bixby, 2008).

A similar study of Costa Rican older adults, from this same data set, examined the prevalence, hypertension unawareness and treatment by demographic variables and found gender differences in prevalence, condition unawareness, and treatment with odds of being treated higher in educated individuals (Mendez-Chacon, Santamaria-Ulloa & Rosero-Bixby, 2008).

2.1 Allostatic Load

A framework which has gained popularity in the study of ageing and longevity is the allostatic load. Allostasis means “maintaining stability (or homeostasis) through change”; the concept was proposed by McEwen and Stellar (1993) to refer to wear and tear on the body. The allostatic load suggests that resting levels of the neuroendocrine markers become dysregulated through stress experienced over time.

The two main hypotheses established related to this subject, are that allostatic load is a measure of physiological dysregulation; and that allostatic load is a risk factor for morbidity and mortality (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). Both theories have been examined when looking at the unusually high longevity in Costa Rica. Results from this analysis were contrary to these hypotheses, since stressors were not associated with individual biomarker levels and levels of neuroendocrine allostatic

indicators (cortisol dehydroepiandrosterone sulfate, epinephrine, and norepinephrine) (Gersten, Dow & Rosero-Bixby, 2010).

There are some relatively new findings about the differentials and determinants of aging and longevity, particularly in developing countries. Although research on the impact of diet and supplementation in aging and longevity has been conducted in developed nations, little is known about the populations from developing countries.

2.2 Cardiovascular Disease and Fatty Acids

In 2008, chronic diseases accounted for 63% of the 57 million estimated deaths worldwide (WHO, 2010). In Costa Rica, during the 1970s, health indicators such life expectancy, infant mortality, health coverage and sanitation showed a noteworthy improvement (Rosero-Bixby, 1996). Death rates from infectious diseases declined sharply and rates of mortality from cardiovascular disease increased. Since then, cardiovascular disease, particularly myocardial infarction became the leading cause of deaths among Costa Rican adults (Rosello-Araya & Guzman-Padilla, 2004). Since the leading causes of death are linked to diet and other modifiable risk factors it is logical to think that these play a decisive role in aging and longevity.

Lipids are organic compounds that are insoluble in water and soluble in organic substances such as ether, acetone and chloroform (Jones & Kubow, 1998). They are important constituents of the diet due to their high energy value (9 kcal/g), but also because fat soluble vitamins and essential fatty acids are natural components of foods (Gurr, Harwood & Frayn, 2002).

Fats, a subgroup of lipids, are carboxylic esters derived from a single alcohol, glycerol, to which three fatty acids are attached. More specifically, the molecule is called triacylglycerol. Fatty acids linked to the glycerol portion of the triacylglycerol may vary in length of the carbon chain, degree of saturation and the spatial configuration (Gurr et al., 2002).

Fatty acids may be long-chain monocarboxylic acids. They usually contain an even number of carbon atoms, usually between 12 and 24. The chemical properties of fatty acids are derived from the coexistence of a carboxyl group and a hydrocarbon chain (Gurr et al., 2002). When all the hydrogen atoms of a fatty acid are bonded to carbon atoms, it is saturated. In turn, a fatty acid is unsaturated when there are one or more double bonds between carbon atoms, thus decreasing the number of hydrogen atoms that are bound (Jones & Kubow, 1998).

Double bonds between carbon atoms of an unsaturated fatty acid may have different configurations depending on the spatial orientation of the hydrogen atoms bonds. These configurations are called *cis* or *trans*, depending on whether the two hydrogen atoms are oriented in the same (*cis*) or in the opposite direction (*trans*) to the plane as defined by the double bond between carbons (Jones & Kubows, 1998).

Usually, in nature, the unsaturated fatty acid is *cis* oriented. This means the provision of the molecule is angled, with the vertex at the unsaturation. This spatial configuration causes the melting points of the unsaturated acids to be lower than the saturated counterparts. In contrast, the double bonds in the *trans* fatty acids (TFA) distort

the crystal symmetry, making it very similar to the saturated fatty acids and increasing its melting point (Gurr et al., 2002).

Some fatty acids cannot be synthesized by higher animals (including humans), and because its biological function is essential, it must be supplied in the diet. For this reason they are called essential fatty acids (Gurr et al., 2002). The consumption of an adequate intake of fatty acids, in addition to meeting the needs of energy and essential fatty acids helps to reduce the risk of cardiovascular disease. In the 1970s, the classic diet-heart hypothesis was proposed to explain the relationship between diet and cardiovascular disease risk (Hu & Willet, 2001).

2.2.1 n-6 Polyunsaturated fatty acids (n-6 PUFA)

The classic studies of Keys, Anderson and Grande (1965) and Hegsted, McGandy, Myers and Stare (1965) indicated that the both polyunsaturated and monounsaturated fatty acids had a neutral effect on serum cholesterol levels. However, current evidence has shown otherwise, corroborated by metabolic studies that n-6 PUFA decrease serum cholesterol (Ascherio, 2002). A compilation of several metabolic studies showed that vegetable oils, rich in linolenic acid (primary n-6 PUFA), have a strong cholesterol-lowering effect when they replace saturated fatty acids (SFA) in the diet (Grundy *et al.*, 1982). This coincides with the results of dietary intervention trials which showed that diets high in n-6 PUFA (17% energy intake), compared with diets low in fat (<30% energy intake) and high in carbohydrates (>60% energy intake), are more effective in lowering serum cholesterol levels and mortality rates of cardiovascular

disease (Sacks & Katan, 2002). Similarly, prospective cohort studies have shown an inverse association between intake of linoleic acid and risk of coronary heart disease (Hu, Mason & Willet, 2001).

In addition to its effect on serum cholesterol, linoleic acid appears to have other beneficial effects on cardiovascular disease. In the Nurses' Health Study (Salmeron et al., 2001), a high consumption of marine n-6 PUFA was associated with a significantly lower incidences of type 2 diabetes, as this may improve sensitivity to insulin. Additionally, animal studies have suggested an antiarrhythmic effect from sunflower oil, which is rich in linoleic acid, although it is less than the effect generated by fish oil (Hu et al., 2001).

Other studies have shown that the addition of a high amount of linoleic acid to a diet low in SFA lowers serum cholesterol levels by 15% which significantly reduces the risk of cardiovascular disease. Many controlled trials have shown that a 1% reduction in total serum cholesterol and LDL causes a decrease of about 1.5% in the incidence of cardiovascular disease (Renaud & Lanzmann-Petithory, 2001).

In response to the considerable scientific evidence showing the strong cholesterol-lowering effect of linolenic acid, dietary recommendations in the 1970s and 1980s strongly encouraged the consumption of this fatty acid. However, subsequent studies showed that an intake of linolenic acid greater than 10% of total energy intake, reduced concentrations of high density lipoprotein (HDL) (Rubio, 2002) leading to a pro-thrombotic and pro-aggregatory physiological state, characterized by increased blood viscosity, vasospasm, vasoconstriction and reduced bleeding time (Simopoulos, 1999).

2.2.2 *n-3 Polyunsaturated fatty acids (n-3 PUFA)*

Of the *n-3* PUFA, α -linolenic acid (C18:3n-3) is the most abundant in the diet and is found mainly in linseed oil (51%), canola (9%) and flaxseed oil, walnut oil and soybean (7%). It is also found in small amounts in nuts, dairy products, beans, broccoli and green leafy vegetables (Rubio, 2002).

The *n-3* PUFA long-chain Eicosapentaenoic acid (EPA) (C20:5n-3) and Docosahexaenoic acid (DHA) (C22:6n-3) are found in small amounts in the diet coming mainly from high-fat fish such as mackerel (2.5%), salmon (1.2%), sardines (1.2%), tuna (0.4%) and halibut (0.4%), although it may be synthesized in humans from α -linolenic acid (Simopoulos, 1991).

Several epidemiological studies have examined the association between consumption of *n-3* PUFA and risk of cardiovascular disease. In the Multiple Intervention Trial Risk Factors, men in the highest quintile of α -linolenic acid consumption showed a risk of cardiovascular disease 40% lower than in men in the lower quintiles of consumption (Dolecek, 1992). This coincides with the results of the Study of Health Professionals Follow-up (Ascherio et al., 1996) which associated a 1% increase in the consumption of α -linolenic acid with 40% lower risk of fatal cardiovascular disease. Likewise, the Finnish Study for Cancer Prevention with Alpha Tocopherol and Beta Carotene, revealed that men in higher quintiles of consumption of α -linolenic acid had 25% reduction in cardiovascular disease mortality (Pietinen et al., 1997).

In Costa Rica, Baylin, Kabagambe, Ascherio, Spiegelman and Campos (2003) showed an inverse association between levels of α -linolenic acid in adipose tissue and

nonfatal myocardial infarction. The risk of myocardial infarction was 63% lower in those subjects in the highest quintile of linoleic in adipose tissue than those in the lowest quintile. Additional population studies have demonstrated the protective effect of α -linolenic acid in the prevention of myocardial infarction (Ascherio et al., 1996; Djousse et al., 2004; Guallar et al., 1999) whereas other studies have found an increased risk from the intake of α -linolenic acid acid (Oomen et al., 2001a; Pedersen et al., 2000).

One possible explanation for these results is that α -linolenic acid and TFA come from similar sources, so it is difficult to distinguish their antagonistic effect. In the Cancer Prevention Study with Alpha Tocopherol and Beta Carotene, a clear association was evident only after adjustments for the intake of TFA (Pientinen et al., 1997). In addition, the association reported by Baylin et al (2003), was strengthened after adjustments for these fatty acids. Another viable explanation is that the cardioprotective effect of α -linolenic acid is higher in places like Costa Rica, where there is less consumption of fish species rich in EPA and DHA (Baylin et al., 2003).

The protective effect of α -linolenic acid can be achieved by direct action or mediated by its conversion to EPA and DHA (Connor, 2002). The mechanism of action is unclear, but among the potential biological effects are the reduction of plasma levels of triglyacylcerides and Very Low Density Lipoprotein (VLDL) in both normal subjects and those with hypertriglyceridemia, although the effect is higher in the latter (*Djousse et al.*, 2004; Connor, 2002). Similarly, one of the most noticeable effects of n-3 PUFA, is the ability to prevent cardiac arrhythmias by the modulation of sodium, potassium, and L-type calcium channels, inhibition of thromboxane production and by reducing the

concentration of non-esterified fatty acids in plasma and cell membranes which are believed to have pro-arrhythmic effects (Albert et al., 2002).

2.2.3 n-6 and-3 PUFA Ratio

In Western diets, high intake of n-6 PUFA has created an imbalance, with respect to the intake of n-3 PUFA, to the extent that the relationship of n-6:n-3 in Western diets ranges between 15-20: 1. It has been suggested that diets should maintain a relationship between the intake of n-6 and n-3 PUFAs of 4:1 or less. Both n-6 and n-3 are primary components in the production of eicosanoids. There is a competition among the two families of fatty acids for the enzymes involved in the conversion of α -linolenic acid and linolenic acid to EPA (Renaud & Lanzmann-Petithory, 2001; Simopoulos, 1999). In the Nurse's Health Study it was evident that there was a modest reduction in cardiovascular disease risk when the ratio of α -linolenic acid to linolenic acid was greater than 0.10 (1:10) (Hu et al., 2001).

To improve the n-6/n-3 ratio some have proposed to promote the reduction of n-6 PUFAs. However, considering the significant cardio protective effect of them, the most viable solution seems to be replacing animal fat with vegetable oils, which contain both poly and monounsaturated fatty acids (Hu et al., 2001). This replacement can also increase consumption of n-3 PUFA, for various oils including canola and soybean have a significant content of ALA (Connor, 2002). Moreover, the consumption of at least two servings of fish per week may increase the amount of n-3 in the diet to achieve a ratio of n-3: n-6 without sacrificing desirable benefit of n-6 PUFA (Hu et al., 2001).

2.2.4 *Trans Fatty Acids (TFA)*

Oils rich in α -linolenic acid and linolenic acid, because of their susceptibility to oxidation, are often hydrogenated during processing, making the *cis* fatty acids in TFA. Functionally, these fatty acids act as SFA making fat more solid and stable at room temperature, but have been positively associated with the development of cardiovascular disease (Willet, 1998).

The replacement of *cis* oriented unsaturated fatty acids with TFA has been linked to increased levels of LDL and decreased levels of HDL (Ascherio, Katan, Zock, Stampfer & Willet, 1999). It has been proposed that TFA has a negative impact on the LDL/HDL ratio is approximately twice as much as SFA; an increase of 2% TFA consumption may boost the ratio of LDL/HDL by 0.1 (Ascherio et al., 1999). A 1-unit increase in this ratio is associated with a 53% increase in the risk of cardiovascular disease (Stampfer, Sacks, Salvini, Willet & Hennekens, 1991), so the average consumption of 2% of calories derived from TFA could be a predictor of a high number of deaths from this disease (Ascherio et al., 1999).

Dietary TFAs also increases serum triacylglycerols, LDL and liprotein levels while decreasing HDL (Hu et al., 2001; Sundram, Ismal, Hays, Jeyamalar & Pathmanatan, 1997). Meanwhile, Kyung and Campos (2003) have suggested that the effect of the intake of TFA on cardiovascular disease risk may be mediated by the effect of these fatty acids on LDL size. They found a significant correlation between increased intake of TFA and increased LDL size. The large LDL has high affinity for arterial

proteinglycans (Manning et al., 1994). Cell cholesterol particles are released to the connective tissue of the arterial wall (Rudel, Parko, Hedrick, Thomas & Williford, 1998).

Increased TFA may increase the risk of thrombosis, as these are capable of adversely affecting metabolism and the balance of prostanoids, in competing for the enzyme $\Delta 6$ desaturase with linoleic and α -linolenic acid (Hu & Willett, 2001). Likewise, it is suggested that the high uptake of TFA promotes insulin resistance in humans (Lovejoy, 1999). Research on TFA mechanisms reveals inconsistencies, however results from animal studies suggest that post-insulin receptor activation of insulin-stimulated serine/threonine protein kinase is impaired in muscle tissue from monkeys fed a high-TFA diet (Kavanagh et al., 2007).

The strongest evidence of the association between TFA consumption and cardiovascular risk, comes from four prospective studies: the Health Professionals Follow-up Study, the Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study, Nurses' Health Study and the Zutphen Aging Study. In these, the relative risk of cardiovascular disease associated with an absolute increase of 2% of energy from TFA, ranged from 1.28 (Oomen et al., 2001b) to 1.93 (Hu et al., 1999).

In the Nurses' Health Study, replacing 5% of energy from PUFAs with SFA was associated with reduced risk of cardiovascular disease of 42%. However, replacing 2% of the energy derived from TFA with PUFA was associated with a reduction of 53% (Hu *et al.*, 1999). In this study, each increase of 2% of total calories as TFA was associated with a 39% increase in the risk of Type 2 Diabetes Mellitus.

In Costa Ricans, a positive association between TFA 18:2 in adipose tissue and risk of nonfatal myocardial infarction has been shown. In addition, a positive association of 16:1 between *trans* isomer levels and risk of nonfatal myocardial infarctions was found (Baylin et al., 2003).

Baylin and colleagues (2003) also suggested that the 18:2 *trans* isomer may be more atherogenic than the 18:1 *trans*, although the first one is found more abundantly in the diet and adipose tissue. Lemaitre and colleagues (2002) have also reported a strong positive association between levels of 18:2 *trans* isomer in the membrane of red blood cells and risk of acute myocardial infarction.

In addition, clinical trials have shown that the *trans* 18:1 isomer adversely affect the lipoprotein profile (Hu et al., 2001) and have recently reported that patients with cardiovascular disease have a higher concentration of this isomer in the subcutaneous fat tissue (Dlouhy et al., 2003). However, epidemiological studies in Costa Rica (Baylin *et al.*, 2003) and elsewhere (Aro et al., 1995) have found no association between levels of 18:1 *trans* isomer in adipose tissue and risk of myocardial infarction.

In Costa Rican households, palm butter, margarine, dairy products and confectionery were the main sources of SFA in the diet of adolescents. Partially hydrogenated soybean oil was the main source of TFA, providing 34% of the total, while about 35% came from natural sources such as meat and dairy products. The rest was contributed by TFA palm butter, margarine, baked goods and others (Monge-Rojas, Campos & Fernández, 2005).

Compared to TFA of industrial origin, the effect of TFA of ruminant origin on cardiovascular disease risk is less clear. Experimental studies suggest that the latter may have an adverse effect on the lipid profile when consumed in amounts similar to those of industrial origin TFA (Mozzafarian & Willet, 2008). In contrast, epidemiological studies have found positive associations between TFA of ruminant origin and cardiovascular disease which is probably due to the fact that the levels of natural TFA consumption are relatively low. Additionally, there are differences between the natural and industrial isomers (Mozzafarian, 2008).

2.3 Dietary Guidelines and Fat Intake

Despite the lack of evidence that diets high in fat promote cardiovascular disease, most dietary recommendations have aimed at reducing total fat rather than fat quality (Erkkila, de Mello, Riseus & Laaksonen, 2008). More recent recommendations, including the Dietary Guidelines for Americans 2010 include within its key recommendation the reduction of SFA to less than 10% of total energy intake, replacing them with MUFA and PUFA. In addition, TFA intake is recommended to be as low as possible, especially if the TFA comes from synthetic sources, to use oils to replace solid fats, and to increase consumption of low fat dairy products and fish (United States Department of Agriculture & United States Department of Health and Human Services, 2010).

The Third Report of the National Cholesterol Education Program, Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) recommend the Therapeutic Lifestyle Changes Diet which includes

weight loss and physical activity and dietary modifications addressing both fat intake quantity and quality (National Institute of Health; National Heart, Lung and Blood Institute, 2002). Recommendations include:

- A total fat intake of 25-35% total energy intake
- PUFA up to 10% of total energy intake
- MUFA up to 20% of total energy intake
- SFA less than 7% of total energy intake

These guidelines do not include specific recommendations for TFA, establishing they have a LDL increasing effect and should be kept at low intake. N-3 PUFA are included as an optional recommendation; however, fish intake is encouraged. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV) guidelines are currently under review and are expected to be released in 2012 (Grundy et al., 2011).

The dietary guidelines for Costa Rica suggest that only 25% of the total energy should come from fat (Ministerio de Salud, 1997), however the recommendations of the National Academy of Sciences and the Food and Nutrition Board (2005), and the Institute of Nutrition of Central America and Panama (1994) established as appropriate a range of 25 to 30%. Recent studies indicate that most Costa Ricans usually have a fat intake less than or equal to 30%, which is supported by the results of nutrition surveys, revealing that only 35% in 1996 and 29% in 2001 of Costa Rican households exceeded the recommended fat intake (Ulate, 2006).

As a strategy to promote cardiovascular health in childhood and adolescence, and to prevent the development of cardiovascular disease in adulthood, the Committee on Atherosclerosis, Hypertension and Obesity in Youth of the American Heart Association (Williams et al., 2002) has emphasized the need to establish a diet low in saturated fat at an early age. The recommendations made by the committee included:

- The total fat should provide no more than 30% or less than 20% of energy intake.
- The SFA should provide less than 10% of energy intake.
- PUFA should provide up to 10% of energy intake.
- MUFA should provide 10-15% of energy intake.

There are no officially recognized recommendations for the intake of specific fatty acids. The Working Group on the Recommended Dietary Intakes (RDIs) for Essentiality of Fatty Acids, Omega-6 and Omega-3 has proposed recommendations for adults. The suggested adequate intake of linoleic acid is 2 % of total energy consumption and an upper limit of 3% (Simopoulos, 1999). Additionally, they suggested an adequate intake of α -linolenic acid corresponding to 1% of daily energy intake.

2.4 Fatty Acids, Chronic Disease and Cognitive Health

In order to understand the mechanisms by which fatty acids affect the risk of cognitive health decline in older adults, it is imperative to understand the pathophysiology of atherosclerosis. Many diseases are capable of producing circulation disorders in the coronary vessels and in cerebral and peripheral arteries. The most

common of these is atherosclerosis. This is a multifactorial disease that develops chronically before becoming clinically symptomatic. The consequences of this disease are coronary disease, stroke and occlusive disease of the peripheral arteries (Stary et al., 1995).

Various theories have been proposed to explain the pathogenesis of atherosclerosis, which include the theory of response to injury (Ross, 1993), the theory of modified lipoproteins (Steinberg & Witztum, 1990), the theory of retention of LDL (Williams & Tabas, 1995) and the immune hypothesis (Wick et al., 1997). A combination of these theories reveals four factors involved in the pathogenesis: the vascular endothelium, LDL, macrophages and smooth muscle cells. They participate in an excessive inflammatory fibro-proliferative endothelium and smooth muscle arterial wall injury (Moreno & Mitjavila, 2003). This results in a hardening and narrowing of the arterial intima, which may partially or completely block blood flow, causing, depending on the affected area, heart attack, gangrene, kidney failure, and other disease states (Moreno & Mitjavila, 2003).

These four hypotheses refer to an alteration in lipid profile as the main trigger of atherosclerotic plaque development. This plaque evolved chronically and silently, narrowing the arteries and leading to the development of vascular disease. Currently, scientific evidence has changed this view and notes that the influence of fatty acids in the development of chronic disease beyond the hypercholesterolemic effect. The fatty acid intake may affect thrombotic tendencies, heart rate, endothelial function, systemic

inflammation, insulin sensitivity and oxidative stress (Hu & Willett, 2001); all of which have been linked to longevity and cognitive function.

There is a strong relationship between increasing age and high blood pressure. Normal aging produces an increase in systolic blood pressure due to decreased artery elasticity because of the thinning and fragmentation of vascular elastin and the collagen deposition (Copstead & Banasik, 2006; Rosendorff et al., 2007). Until about 50 years of age, both systolic and diastolic blood pressure rise. After this, systolic blood pressure continues to rise; diastolic blood pressure tends to fall (Vasan et al., 2002). There is also epidemiological data that suggests an inversely proportional relationship between age of hypertension diagnosis and cardiovascular risk (National Research Council, 2000).

2.4.1 Dietary Fatty Acids and Cognitive Health

The causes of cognitive impairment are unknown. There are some studies on the role of the diet in cognitive decline in older adults (Vizuete, Robles, Rodriguez-Rodriguez, Lopez-Sobaler & Ortega, 2010). Recent studies have suggested that dietary fatty acids may play a role in the development of cognitive decline associated with aging or dementia (Solfrizzi et al., 2005; van de Rest et al., 2009).

One of the first studies was a population-based study conducted in France by Pradignac et al. The association among macronutrient intake and cognitive function was studied in 226 men and 215 women, aged 65 or more, free living and in good health. A positive relationship between fatty acid intake and the Mini Mental State Examination (MMSE) was found in women. In men, alcohol and PUFA intake was associated with an

improvement in functional and cognitive parameters. PUFA intake was also related to mobility in men. However, this study had a low response rate and these findings may be explained as indicators of better health status (Pradignac, Schlienger, Velten, & Mejean, 1995).

A similar study from Spain assessed the association between dietary intake and global cognitive functions using the MMSE and the Pfeiffer's Mental State Questionnaire (PMSQ) in 260 free living mentally healthy older subjects. Subjects with adequate scores in the MMSE (>28 pts) had lower intake of SFA, MUFA and cholesterol (Ortega et al., 1997). This study included macro and micro nutrients assessment, but did not include TFA intake.

The Italian Longitudinal Study on Aging examined the relationship between macronutrients and cognitive impairment in a population-based sample of 278 subjects aged 65 to 84. MMES, selective attention (Digit Cancellation Test) and episodic memory (Babcock Story Recall Test) were used to assess cognitive status, while a semi-quantitative food frequency questionnaire was used to evaluate macronutrient energy intakes. Cross-sectional results pointed toward an inverse relationship between MUFA, PUFA and cognitive decline (Solfrizzi et al., 2006). In this same study, a significant inverse association between MUFA intakes and selective attention was highlighted (Solfrizzi et al., 1999).

Contrasting results were found by van de Rest *et al* (2008) in a similar study conducted in the United States. This study used a battery of tests including MMSE, memory tests, language test and perceptual speed and attention in 1025 elder men. Cross-

sectional analysis found no association between fatty fish or PUFA (van de Rest *et al.*, 2008).

Conflicting results were also found in studies of the association between plasma concentration of omega-3 PUFA and prevalence and incidence of cognitive impairment and dementia. Data from the Canadian Study of Health and Aging found no significant difference in omega-3 PUFA plasma concentrations between controls and both prevalent cases of cognitive impairment and dementia (Laurin, Verreault, Lindsay, Dewailly & Holub, 2003). This is consistent with a population-based Italian study of 191 elders where no association was found between plasma phospholipid fatty acids and results from the MMSE (Manzato *et al.*, 2003).

Results from Conquer *et al.* (2000), point in the opposite direction, suggesting that low levels of n-3 fatty acids in the plasma may be a risk factor for cognitive impairment, Alzheimer's disease and/or dementia. However, statistical analyses from this study do not consider confounding factors such as age and educational level. Another limitation is that no dietary intakes or histories were done; therefore, it is unclear if the subjects presently consume, or consumed in the past, diets that were lower in PUFAs.

Older adults with mild to severe cognitive impairment or any form of dementia may alter their diet as a result of their disease. In addition, dietary intakes can be altered by cognitive decline and impairment. Longitudinal studies can provide data to identify these observations.

A three-year long prospective study examined the effects of dietary fatty acids on cognitive decline in 482 women. Dietary intake was assessed with Food Frequency

Questionnaire (FFQ) while cognitive status was evaluated with various tests including Consortium to Establish a Registry for Alzheimer's disease (CERAD) word list learning, constructions and word fluency tests. Results showed no association between cognitive decline and intake of saturated fat, *trans* fat or dietary cholesterol intake. MUFA intake was associated with lower cognitive decline, particularly in the visual and memory domains (Naqvi et al., 2011).

The Chicago Health and Aging Project followed 3718 subjects over 65 years old for six years. Dietary intake was evaluated with a 139-item FFQ. Cognitive change was measured at 3 and 6 years follow-ups with the East Boston Memory Test (EBT) of immediate and delayed recall and the MMSE and the Symbol Digit Modalities test for perceptual-motor speed (SDMT). Results suggest that a diet high in saturated and *trans* fats may be associated with cognitive decline in older adults (Morris, Evans, Tangney, Bienias & Wilson, 2004). Dietary fish intake was inversely associated with cognitive decline, while there were no consistent associations with n-3 PUFAS (Morris et al., 2005).

At the moment, the longest longitudinal study of the relationship between cognitive health and diet, called the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) was conducted in Finland. A population of 1449 people aged 65 to 80 years was followed for a total average of 21 years. A FFQ was used for dietary assessment. To determine the presence or absence of mild cognitive impairment, evaluations of cognitive and executive global functions, memory, and psychomotor skills were conducted. Abundant saturated fat at midlife was associated with poorer global cognitive function

and prospective memory after adjusting for confounders. In contrast, high intake of PUFA was associated with better semantic memory. Furthermore, frequent fish consumption was associated with better global cognitive function and semantic memory. Further, higher PUFA–SFA ratio was associated with better psychomotor speed and executive function (Eskelinen et al., 2008).

2.5 Dietary Patterns and Cognitive Decline

The traditional Mediterranean diet pattern is characterized by an abundance of plant foods (cereals, bread, fruits, nuts, potatoes); non-processed locally grown foods; locally grown fresh fruit as dessert; sweets eaten a few times a week; olive oil as the main source of fats; daily consumption of dairy products, low to moderate amounts of fish and poultry; low consumption of red meats, up to four eggs per week, and low to moderate consumption of red wine, usually with meals (Willet et al., 1995). This dietary pattern has been associated with a reduced risk of total mortality, cardiovascular diseases and cancer (de Logeril & Salen, 2006; Sofi, Cesari, Abbate, Gensini & Casini, 2008; Willet et al., 1995). The Mediterranean diet has also been associated protection against cognitive decline in older adults, because it combines foods and nutrients that may have potentially protective effects against cognitive dysfunction: fish, MUFA, antioxidants, folates, cobalamine (vitamin B₁₂) and red wine (Feart et al., 2009).

A number of studies have looked into the role that specific foods and nutrients of this diet may have on the protective role against dementia of cognitive decline. These, studies on isolated nutrients or food have conflicted results (Feart, Samieri & Barberger-

Gateau, 2010), perhaps because the analyses of single nutrients or foods ignore important interactions among components. People do not eat nutrients or just one type of food; they have dietary patterns that are better suited to the dietary patterns analysis approach.

Scarmeas et al., (2009) studies the association between the Mediterranean diet and Mild Cognitive Impairment (MCI), which identifies people who are in the transition between normal aging and dementia or Alzheimer's disease. Results from this longitudinal multiethnic community study in New York (n=1393) suggest an association between the Mediterranean diet and reduced risk of developing MCI, and a reduced risk of MCI conversion to Alzheimer's disease (Scarmeas et al., 2009). In this study sample, the association of a subsample of 262 of incident cases of Alzheimer's disease was also investigated. Higher adherence to the Mediterranean diet was found to be associated with a reduction of Alzheimer's disease risk (Scarmeas, Stern, Tang, Mayeux & Luchsinger, 2006).

A prospective cohort study of 1410 adults over 65 years old conducted in Bordeaux, France, evaluated adherence to the Mediterranean diet while assessing cognitive health with four neuropsychological tests, including the MMSE (Feart *et al.*, 2009). Results showed that a higher adherence to this type of diet was positively associated with fewer MMSE errors; however, this was not consistent with the cognitive tests (Feart et al., 2009).

Nurk et al., 2007 examined fish and seafood consumption and cognitive performance in the Hordaland Health Study in Norway. This study has a sample of 2,031 subjects ages 70 to 74 and used six different cognitive tests, including the MMSE. There

was a positive dose-dependent association between fatty fish intake and cognition (Nurk et al., 2007).

The Zutphen Elderly Study (The Netherlands) followed 210 subjects ages 70-89 during for five years. Dietary information was collected using the cross-check dietary history method and MMSE was used for cognitive assessment. Fish consumption was associated with decreased cognitive decline. Furthermore, combined intake on EPA and DHA seemed to have a dose-dependent relation with reduced cognitive decline (van Gelder et al., 2007).

Since the evidence remains inconclusive, the Mediterranean diet pattern and fish intake, does not fully explain the better health of persons with this kind of dietary pattern, although it may contribute to it. Moreover, this diet may indirectly represent an indicator of a complex set of favorable lifestyle factors that altogether may contribute to better health outcomes.

2.6 Supplement Use and Cognitive Health

Nutrient supplementation of both micronutrients and macronutrients are widely used to improve diet quality and contribute to the maintenance of good health across the life span. Assessments of the association of supplement use and cognitive health has been limited by the finding that those who seem to have healthier lifestyles are also more likely to use supplements (Conner, Kirk, Cade & Barrett, 2001).

In a nested case-control study, fish oil users were matched with nonusers, and cognitive function was related to erythrocyte n-3 fatty acid composition. Results

suggested that food supplement use and erythrocyte n-3 content are associated with better cognitive aging (Whalley et al., 2008)

A comprehensive literature revealed only two randomized clinical trials resulting in publication on PUFA supplementation on elderly subjects. The first study was conducted by Terano et al 1999 in Japan. The Older People and n-3 Long-Chain Polyunsaturated Fatty Acids Study (OPALS) study conducted in the United Kingdom recruited 867 participants ages 70–79 years; at baseline, all were free of dementia and diabetes, had a minimum of 25 out of 30 in the MMSE score and did not report daily fish oil supplement consumption. Subjects were randomly assigned into a double-blind controlled trial of daily capsules providing EPA, DHA or olive oil. A standardized battery of cognitive tests was used, including but not limited to subjective memory assessment, tests of prospective memory, story recall (immediate and delayed), verbal fluency, location memory (immediate and delayed) and symbol-letter substitution. After 24 months, results supported the theory that high levels of fish consumption, especially fatty fish, were associated with better cognitive function in later life (Dangour et al., 2009).

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CHAPTER THREE

MATERIALS AND METHODS

3.1 Study design

This is a cross-sectional secondary data analysis from the Costa Rican Longevity and Healthy Aging Study (CRELES, or *Costa Rica Estudio de Longevidad y Envejecimiento Saludable*) public use data files (Rosero-Bixby, Fernández, & Dow, 2005a). All terms and conditions from the Inter-University Consortium for Political and Social Research (ICPSR) for the use of this data base have been met (see Appendix A). CRELES is a nationally representative longitudinal survey of health and socioeconomic indicators of Costa Rican residents ages 60 and over in 2005. It was the first nationally representative survey to investigate older adult health levels in the country.

The principal investigator is Luis Rosero-Bixby; co-principal investigators are Xinia Fernández (University of Costa Rica) and William H. Dow (University of California, Berkeley). The study design and data collection were conducted by the University of Costa Rica's *Centro Centroamericano de Población* (CCP) in collaboration with the *Instituto de Investigaciones en Salud* (INISA), with the support of the Wellcome Trust (grant 072406). Additional collaborating public entities include the Costa Rican Office of Social Security (CCSS) and the National Council of Senior Citizens (CONAPAM).

This study was approved by the Ethical Science Committee of the University of Costa Rica in its March 17, 2004, session (reference: VI-763-CEC-23 -04), research project number 828-A2 -825 (see Appendix B). All of the databases of the study are anonymous

(i.e., names and identifiers have been removed) to avoid breaches in the privacy of the participants. For secondary data analysis, The Clemson University Office of Research Compliance determined that this thesis does not involve human subjects as defined in the federal regulations governing the protection of human subjects in research [45 CFR 46.1029(f)] (see Appendix C). Therefore, it was not subject to the Institutional Review Board review.

3.2 Sampling

The sample was drawn from Costa Rican residents in the 2000 population census who were born in 1945 or before, with an over-sample of the oldest old (ages 95 and over), including an in-depth longitudinal survey in a subsample of 3,000 of these individuals. The inclusion criteria are residence in Costa Rica, regardless of nationality, and a birth date prior to 1946 (i.e., 60 years or older at the time of the first interview).

A random selection was made from the database of the Census of Population of 2000 (Instituto Nacional de Estadística y Censo, 2000). Sampling was stratified by 5-year age groups, varying from 1% of the population born from 1941 to 1945 up to 100% of the population born before 1905 (over 95 years old at the time of the first data collection round). A subsampling of 60 of the 102 health areas in Costa Rica covering 59% of the national territory, was selected (see Figure 1). According to the 2000 Census (INEC, 2000) this subsample of nearly 5,000 people met the inclusion criteria, making it possible to locate and interview 2,827 individuals (n=1,329 men, n=1,498 women). The no-answer rates can be categorized into several groups: 19% of people were deceased by

date of contact, 18% of people could not be located (mostly due to inaccurate addresses), 2% had changed residence, and 4% declined to be interviewed. Among those who were interviewed, 95% gave a blood sample, 92% gave a urine sample.

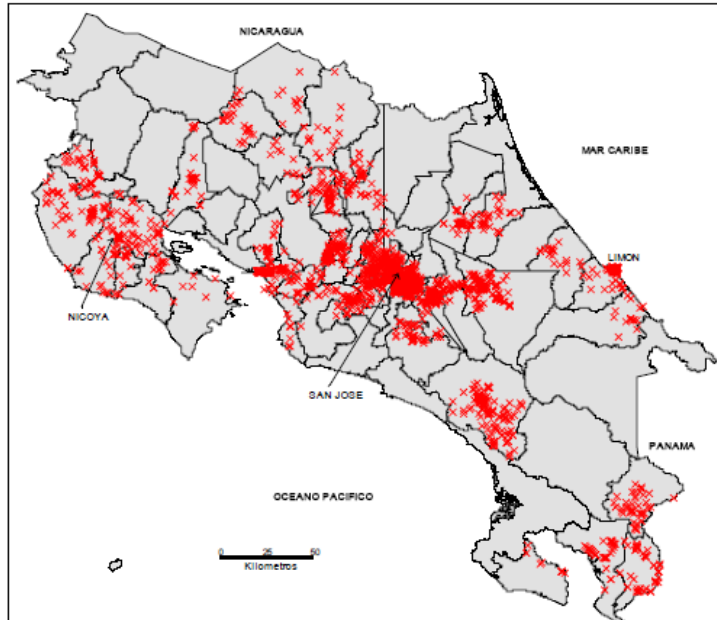


Figure 3.1 Map of the interviewed subjects from the selected Health Areas (Rosero-Bixby, Fernández & Dow, 2005b).

3.2 Data Collection

Baseline household interviews were conducted between November 2004 and September 2006, with two-year follow-up interviews. CRELES public use data files contain information on a broad range of topics, including self-reported physical health, psychological health, living conditions, health behaviors, healthcare utilization, social support, and socioeconomic status.

A field team of five interviewers, two phlebotomists, and a field supervisor collected the information and the blood and urine specimens using a continuous fieldwork design over a period of nearly 2 years. All data and specimens in the study were collected at the participants' homes, usually during two visits, using personal digital assistants (PDAs), also known as palm computers, with software applications developed by CCP for this study. To ensure a good level of dependability, the PDA data collection was tested during the pilot study by registering answers in both paper and pencil and PDA (Hidalgo-Cespedes, Rosero-Bixby, & Antich-Moreno, 2007). The PDA software did not allow registering inconsistent data, entering data outside of the range, and/or skipping the sequence of questions. Once the interview was completed, the data were ready for analysis, without the possibility of transcription errors (Hidalgo-Cespedes et al., 2007).

During the first visit, participants provided informed consent and answered a 90-minute long questionnaire. During the second visit, typically conducted early in the morning the day after the initial interview, urine samples, blood samples and anthropometric measures were collected by trained personnel.

3.3.1 Diet.

A semi-quantitative questionnaire based on Willet *et al.*'s (1985) questionnaire, was developed specifically for Costa Rican populations (Campos *et al.*, 1991). This questionnaire asks for the average consumption during the previous year (prior to the day of the survey). The nine options to categorize consumption frequency range from "never or less than once a month" to "6 or more times a day." Information about vitamins and

nutritional supplements as well as most frequently used type of fat or oil for cooking (shortening, margarine, etc.) at home was also requested. For each individual, the intake of energy and other nutrients was calculated by multiplying the frequency of consumption of each food by the nutritional content of the respective portion. Using stepwise regression, CRELES researchers reduced the original 147-item FFQ to an abbreviated version, identifying 27 tracer foods in addition to the type of oil used for cooking. This step was done to gather information on the nutrients of greater interest as well as reduce the interview time (Rosero-Bixby et al., 2005b)

3.3.2 Cognitive disability.

Cognitive disability was assessed using a 15-item scale (Cronbach's $\alpha = 0.72$) adaptation of the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975; Quiroga, Albala, & Klaasen, 2004; Rosero-Bixby & Dow, 2009). Participants who answered fewer than 75% of the 15 items correctly were considered to be "cognitively impaired."

3.3.3 Lipid profile.

Clinical laboratories involved in the blood analyses were certified by a national reference center of clinical chemistry that is a part of the Ministry of Health. These laboratories conduct internal reliability tests as part of their quality control procedures. In addition, blinded reliability analyses were conducted by the CRELES research team: Batches of 20 to 40 random samples were reanalyzed for each biomarker in a control

laboratory. For all lipid analyses, correlations above 0.9 were found between laboratories. Systematic differences were found for HDL and triacylglyceride values from two clinical laboratories. In response, these values were adjusted with equations estimated by regression using the validation batches (Mendez-Chacon, Rosero-Bixby, Fernandez-Rojas, & Barrantes-Jimenez, 2007).

3.4 Analysis

Collected data from CRELES are available to the public at the ICPSR, the National Archive of Computerized Data on Aging, and the National Institute of Aging's website (ICPSR, 2010). Data are available for SPSS and SAS software and are divided into 10 data sets: anthropometry and mobility, biomarkers, diet, elderly people, household members, insurance, medications, non-resident children, pensions, and recoded variables. In addition to these files, this website provides questionnaire sets; information about weighing, sampling, and data collection procedures; and a codebook. The codebook includes variable names, variable types, missing values, ranges, and labels (e.i., 1= yes, 0 = no).

Statistical analyses were conducted using IBM SPSS Statistics version 19 (IBM Corporation, Somers, NY, 2010). The first step was to identify which variables will be used from the nearly one nine hundred variables recorded. All data sets were revised once variables were identified; unneeded variables were dropped, and all necessary variables from different data sets were merged into a new file. In addition to variables related to the research questions, variables needed for data identification and analysis

(e.i., identification, health areas, non-response weight, and age) were included in the new database. To confirm to normality, tests of skew and kurtosis were conducted. Significance tests for skew and kurtosis were not used because, in large sample sizes, they are likely to be significant even when skew and kurtosis are not significantly different from normal (Field, 2010).

To obtain nationally representative data, all descriptive statistical analyses were conducted while weighing for the variable “ponderator” (Rosero-Bixby, Fernández, & Dow, 2005c). This sampling weight was used to correct for two factors: (1) oversampling of the oldest-old individual and (2) the higher non-response rate among younger men with high SES who are living in urban settings. The results provided data that replicate the structure by sex, age, urban residence, and education of the population of Costa Ricans born in 1945 or before and still living in 2005.

General characteristics between cognitively disabled and non-cognitively disabled subjects were explored using descriptive statistics. *T*-test statistics were used to assess significant differences between means for age, years of schooling, and income. Chi square tests were conducted to compare categorical differences such as sex, residence, and previously diagnosed medical conditions (hypertension, diabetes, etc). When looking at the serum lipid profiles, data from participants using lipid-lowering medication were removed to avoid bias.

The effects on cognitive health were examined using two cognitive health variables: cognitive scale and cognitive disability. The cognitive scale was standardized to scores between 0 and 100. The cognitive disability variable was dichotomized: 1 being

the absence of cognitive disability and 0 being the presence of cognitive disability. The cutoff point was inaccurately responding to fewer than 12 out of 15 (75%) of the items on the MMSE. A value of “0” was assigned whenever the participant needed a proxy for the interview.

In addition, new variables needed to be created using information from the data set. In the CRELES data set, fatty acid intake is reported in grams per day. When using this variable to compare energy intake, nutrients were adjusted by energy intake (Willet, 1998). Fat intake was also intake examined as total energy and grams per day. Saturated, monounsaturated, polyunsaturated, and *trans* fatty acid variables reported in grams per day, were transformed into a calorie percentage using the following formula:

$$\text{Percentage of calories per day}_i = [(\text{Fat}_i \text{ g/day} * 9 \text{ kcal/g}) * \text{total calorie intake}_i] * 100$$

For the linear regression models, variables were entered according to the potential influence each variable may have on the dependent variable according to findings from previous research. All variables found to be not significant ($p > 0.05$) were removed from the model. This model was controlled for age, caloric intake and lipid medication. In addition to the regression analysis, descriptive statistics (mean, standard deviation, and correlation), 95% confidence intervals, and an analysis of variance (ANOVA) were completed. A logic regression model was created to assess the relationship between these variables and the presence or absence of cognitive impairment.

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CHAPTER FOUR

ASSOCIATION BETWEEN NUTRITION, HEALTH INDICATORS AND COGNITIVE FUNCTION IN COSTA RICAN OLDER ADULTS

In Preparation for *Journal of Nutrition and Aging*

4.1 Introduction

Older adults are among the fastest-growing segment of the world's population. The number and proportion of this population is increasing in both developing and developed countries. In five years, the number of people aged 65 or older will outnumber children under the age of five (World Health Organization, National Institute of Aging & National Institute of Health, 2011). In Costa Rica, life expectancy is comparable to developed countries such as the United States and Western European countries. Of added importance to this comparison, is the fact that the Costa Rican gross national product (GNP) is a small fraction of the GNP for American or Western European countries (United Nations, 2009). Increases in longevity and the proportion of people over the age of 60 years are often regarded as a challenge to health systems as longer lives are commonly associated with an increased prevalence of disease (World Health Organization, 2000). The loss of cognitive capacity is one of the most important factors affecting the quality of life of older adults and their families. In addition, it is one of the main reasons that people are admitted into nursing homes (Gaugler, Duval, Anderson, & Kane, 2007). The causes of cognitive decline remain uncertain; however, it has been linked to cardiovascular disease and risk factors such as diabetes mellitus and high blood

pressure (Naqvi et al., 2011). Dietary fatty acids play an important role in cardiovascular disease; thus, it is plausible that they could have a role in cognitive deterioration as well (Hunter, Zhang & Kris-Etherton, 2009). Fatty acids could be involved through several mechanisms, including atherosclerosis, thrombosis, and inflammation (Kalmijn, 2000). Increasing interest has emerged in the hypothesis that the consumption of fish, polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docohexanoic acid DHA could play a protective role against cognitive decline. Several studies have suggested that an increase of saturated fats could have negative effects on cognitive health (Kalmijn, Feskens, Launer & Kromhout, 1997; Morris et al., 2003), while PUFA and MUFA may have a protective effect (Capurso et al., 2003; Solfrizzi et al., 1999).

Still relatively few findings exist about the differentials and determinants of aging and longevity. Although research on the impact of diet on aging and longevity has been conducted in developed nations, little is known about the populations from developing countries. The purpose of this current research is to examine the association between fatty acid intake, lipid profile, and cognitive health in Costa Rican elders. We had the opportunity to examine these issues using data from the Costa Rican Longevity and Healthy Aging Study (CRELES, or *Costa Rica Estudio de Longevidad y Envejecimiento Saludable*) public use data files (Rosero-Bixby, Fernández & Dow, 2005a).

4.2 Materials and Methods

This is a cross-sectional secondary data analysis from CRELES's public use data files (Rosero-Bixby et al., 2005a). CRELES is a nationally representative longitudinal

survey of health and socioeconomic indicators of Costa Rican residents ages 60 and over in 2005. The study design and data collection were conducted by the University of Costa Rica's *Centro Centroamericano de Población* (CCP) in collaboration with the *Instituto de Investigaciones en Salud* (INISA), with the support of the Wellcome Trust (grant 072406). Additional collaborating public entities included the Costa Rican Office of Social Security (CCSS) and the National Council of Senior Citizens (CONAPAM). This study was approved by the Ethical Science Committee of the University of Costa Rica.

4.2.1 Study population

The sample was drawn from Costa Rican residents in the 2000 population census who were born in 1945 or before, with an over-sample of the oldest-old (ages 95 and over). The inclusion criteria required living in Costa Rica, regardless of nationality, and to birth date before 1946, meaning participants had to be 60 years or older at the time of the first interview. A random selection was made from the database of the Census of Population of 2000 (Insituto Nacional de Estadística y Censo, 2000). Sampling was stratified by five-year age groups, varying from 1% of the population born in 1941-1945 up to 100% of the population born before 1905 (over 95 years old at the time of the first data collection round). The no-answer rates can be classified as following: 19% of people deceased by date of contact, 18% of people could not be located (mostly due to the inaccurate addresses), 2% had changed residence and 4% declined to be interviewed. From those who were interviewed, 95% gave a blood sample, 92% gave a urine sample and almost 25% of all subjects needed a proxy (usually a close relative).

4.2.3 Data collection

Baseline household interviews were conducted between November 2004 and September 2006, with two-year follow-up interviews. A field team of five interviewers, two phlebotomists and a field supervisor collected the information and the blood and urine specimens using a continuous fieldwork design over a period of nearly 2 years. All data and specimens in the study were collected at the participants' homes, usually during two visits. They were collected using personal digital assistants (PDAs), also known as palm computers, with software applications developed by CCP for this study. During the first visit, participants provided informed consent and answered a 90 minute long questionnaire. During a second visit, which was typically held early in the morning the day after the initial interview, urine samples, blood samples and anthropometric measures were collected by trained personnel (Rosero-Bixby, Fernández & Dow, 2005b).

Information on the participants' diet was collected using a previously validated Food Frequency Questionnaire (FFQ) (Campos et al., 1991). This is a semi-quantitative questionnaire based the Willett et al's (1984) questionnaire, developed specifically for Costa Rican populations (Campos et al., 1991). The questionnaire asks for the average consumption during the previous year (prior to the day of the survey). The nine options to categorize consumption frequency are a range from "never" or "less than once a month" up to "6 or more times a day". Information about vitamins and nutritional supplements as well as type of fat or oil used most frequently for cooking (shortening, margarine, etc.) at home was also requested. For each individual, energy and nutrient intake were calculated by multiplying the frequency of consumption of each food by the nutritional content of

the respective portion. Using stepwise regression, CRELES researchers reduced the original FFQ to an abbreviated version, identifying 27 tracer foods in addition to the type of oil used for cooking. This process resulted in information on the nutrients of greater interest and the ability to reduce the interview time.

Cognitive disability was assessed with a 15-item scale (Cronbach alpha = 0.72) adaptation of the Mini-Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975; Quiroga, Albala, & Klaasen, 2004; Rosero-Bixby & Dow, 2009). Participants who answered fewer than 75% of the 15 items correctly were considered to be “cognitively impaired.”

Clinical laboratories involved in the blood analyses were certified by a national reference center of clinical chemistry that is a part of the Ministry of Health. These laboratories conduct internal reliability tests as part of their quality control procedures. In addition, blinded reliability analyses were conducted by the CRELES research team. For this, batches of 20 to 40 random samples were reanalyzed for each biomarker in a control laboratory. For all lipid analyses, correlations above 0.9 were found between laboratories. Systematic differences were found for HDL and triacylglyceride values from two clinical laboratories. In response, these values were adjusted with equations estimated by regression using the validation batches (Mendez-Chacon, Rosero-Bixby, Fernandez-Rojas & Barrantes-Jimenez, 2007).

4.2.4 Statistical Data

Statistical analysis was conducted using IBM SPSS Statistics version 19 (IBM, 2010). The effects on cognitive health were examined on two cognitive health variables: cognitive scale and cognitive impairment. The cognitive scale was standardized to scores between 0 and 100. The cognitive impairment variable was dichotomized, with 1 being the absence of cognitive impairment and 0 being the presence of cognitive impairment. The cutoff point was inaccurately responding to fewer than 12 out of 15 (75%) of the items on the MMSE. A value of “0” was assigned whenever the subject needed a proxy for the interview.

To obtain nationally representative data, all descriptive statistical analyses were conducted weighting for the variable “ponderator” (Rosero-Bixby, Fernández & Dow, 2005c). This sampling weight will correct for two factors: (1) oversampling of the oldest-old individuals and (2) the higher non-response rate among younger men with high SES and who are living in urban settings. General characteristics between cognitively disabled and non-cognitively disabled participants were explored using descriptive statistics. *T*-test statistics were used to assess significant differences between means for age, years of schooling and income. Chi square tests were conducted to compare categorical differences such as sex, residence and previously medically diagnosed conditions (hypertension, diabetes, etc). In terms of the lipid profiles, data from subjects using lipid lowering medication was removed to avoid bias.

For the regression models, variables were entered according to the potential influence they may have over the dependent variable according to findings from

previous research. All variables found not to be significant ($p > 0.05$) were removed from the model. The model was controlled for age, caloric intake, lipid medication, and stroke. In addition to the regression analysis, descriptive statistics, 95% confidence intervals, and analysis of variance (ANOVA) were completed.

4.3 Results

As shown in Table 4.1, the study population has a mean age of 70.5 years. Highly significant differences ($p < 0.01$) were found between mean ages from cognitively disabled and non-cognitively disabled adults. The cognitively disabled population included a greater percentage of women ($p < 0.05$). No relevant differences were found in living settings. For all cases, more than half of the participants were living within the Great Metropolitan Area (GMA), which includes the city of San Jose and surrounding metropolitan areas (406km²). Most of the population reported some years of elementary education. Noteworthy differences were found in years of education, where the cognitively disabled population reported a smaller average of school years ($p < 0.01$). Important differences were also found in monthly income; cognitively disabled participants presented a low mean monthly income in comparison to the non-cognitively disabled. In addition, the majority of the cognitively disabled population was found to have an income below the poverty line (less than US\$100/month) ($p < 0.01$), whereas for the general study population and the non-cognitively disabled one third fell below the poverty line.

Table 4.1 General Characteristics of the CRELES Study Participants^a

Characteristics	CRELES (n=2827)	Cognitive Disability		p- value
		Yes (n=314)	No (n=2505)	
Men (%)	47.5	41.1	48.3	.017*
Age (years)	70.5 (±8.1)	79.1 (±9.5)	69.37 (±7.2)	.000**
60-69 (%)	53.5	17.8	58.3	
70-79 (%)	32.0	33.5	31.3	
≥80 (%)	15	48.7	10.4	
Living in GMA (%)	53.0	51.1	53.2	.473
Education (years)	5.2 (±4.2)	2.8 (±3.3)	5.5 (±4.2)	.000**
No formal education (%)	13.7	33.7	11.2	
Elementary (%) (1 st - 6 th grade)	64.8	59.6	65.4	
High school education (%) (7 th -11 th grade)	11.9	3.5	13.0	
Higher education (%)	9.6	3.2	10.4	
Monthly income (US\$)	458.8	186.8	493.0	.000**
	(±1332.9)	(±346.6)	(±1394.3)	
<US\$100/month (%)	39.0	56.3	36.9	
US\$100 - US\$399/month (%)	41.8	33.8	36.8	
>\$399/month (%)	19.2	9.9	26.3	

^aMissing values weighted

* p<0.05 **p<0.01

General health information evidenced a more positive health profile for non-cognitively disabled participants (Table 4.2). Statistical significance differences were found in the ratio of cognitively disabled elders who had been medically diagnosed with stroke and heart attack (p<0.01), and other heart conditions (p<0.05). A higher percentage of elders without cognitive disability reported a diagnosis of dyslipidemia

($p < 0.01$). Metabolic syndrome and BMI were also found to be higher among the non-cognitively impaired ($p < 0.001$); however, these variables are not medical diagnoses but outcomes calculated from collected biomarkers and anthropometric measurements.

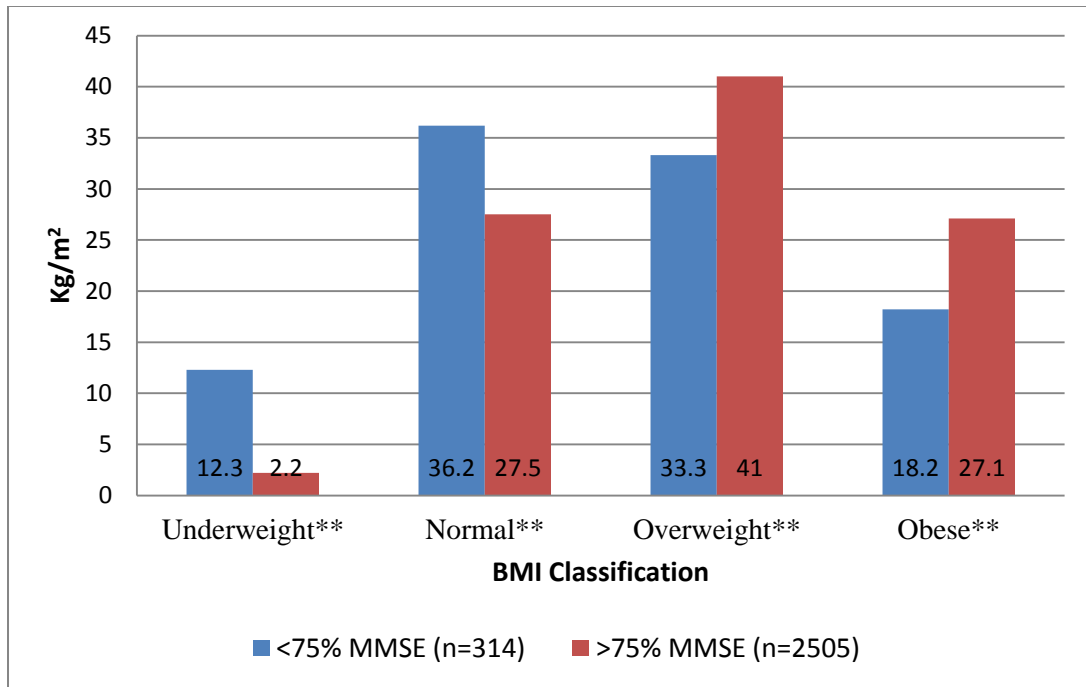
Table 4.2 General Health Characteristics of the CRELES Study Participants^a

Characteristics	CRELES (n=2827)	Cognitive Disability		p-value
		Yes (n=314)	No (n=2505)	
Diagnosed conditions				
Hypertension (%)	48.2	51.2	47.9	.214
High Cholesterol (%)	39.1	29.1	40.3	.000**
Diabetes (%)	20.8	21.8	20.6	.566
Stroke (%)	3.8	15.9	2.3	.000**
Heart attack (%)	4.6	8.1	4.1	.009**
Other heart conditions (%)	12.0	17.0	11.4	.013*
Metabolic syndrome (%)	47.1	39.0	48.0	.006**
Mean Weight (lbs)	145.5	129.4	147.2	.000**
	(±30.4)	(±31.1)	(±29.9)	
Mean BMI (kg/m ²)	26.9 (±5.2)	24.8 (±5.4)	27.1 (±5.2)	.000**

^aMissing values weighted

* $p < 0.05$ ** $p < 0.01$

Differences in BMI are also reflected in all four BMI categories (WHO, 2002). As shown in Figure 4.1, the percentage of cognitively disabled older adults classified as underweight and normal is significantly higher than non-cognitively disabled ($p < 0.010$). Furthermore, the percentage of non-cognitively disabled older adults classified as overweight and obese is significantly larger than the cognitive disabled ($p < 0.010$).



* p<0.05 ** p<0.01

Figure 4.1 BMI classification and cognitive disability

When comparing energy and macronutrient intake between those considered cognitively disabled (<75% right answers in the MMSE) and those who are not (Table 4.3), energy and MUFA were greater in the latter group (p<0.01 and p<0.05 respectively). TFA intake was higher in participants with cognitive disability (p<0.01). No significant differences were found in protein and dietary cholesterol intake between groups.

Table 4.3 Dietary Intake in Relation to Cognitive Disability^{ab}

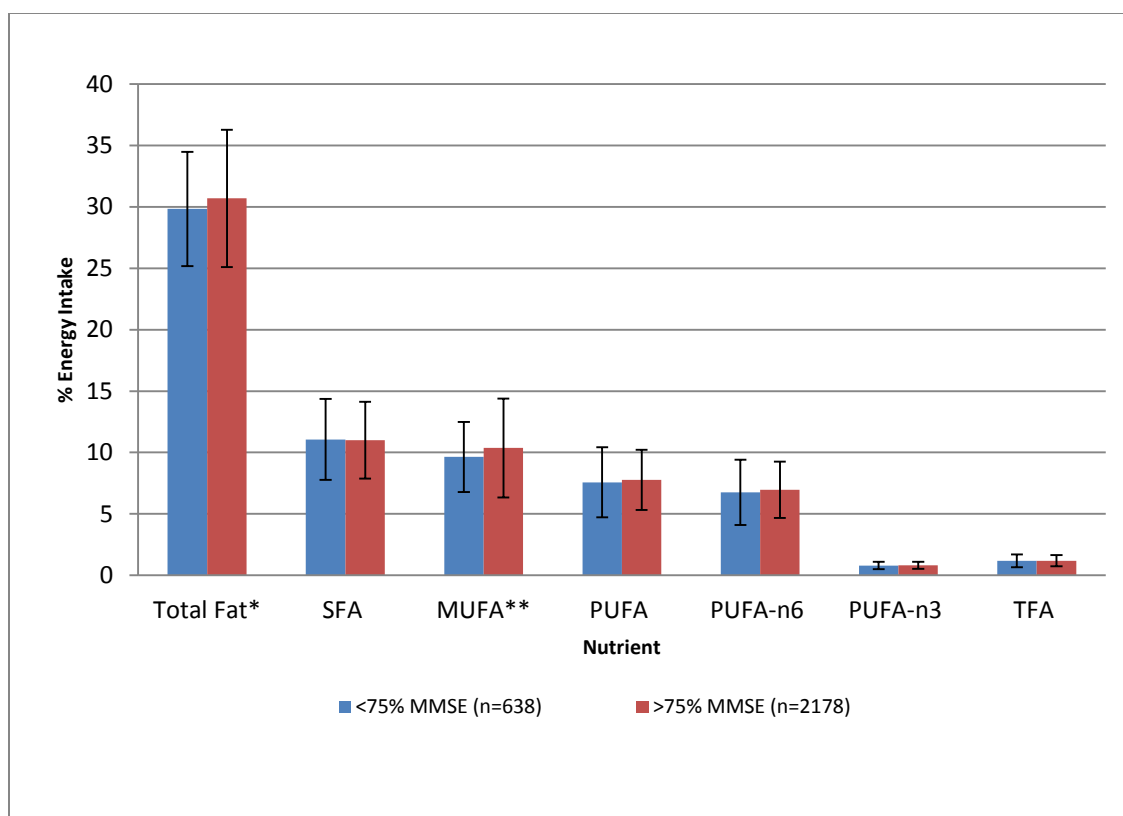
Nutrient	Cognitive Disability (mean ±SD)		t-test
	Yes (n=314)	No (n=2505)	
Energy (kcal)	1983.84 ±718.13	2178.47 ±730.72	.000**
Protein (g)	70.55 ±9.32	69.96 ±9.61	.284
Carbohydrates (g)	308.43 ±29.56	307.82 ±35.63	.738
Total Fat (g)	74.09 ±10.64	74.70 ±14.23	.369
Dietary Cholesterol (mg)	253.93 ±104.10	246.01 ±110.88	.230
SFA (g)	27.67 ±7.17	26.89 ±7.48	.080
MUFA (g)	24.16 ±7.79	25.35 ±11.01	.016*
PUFA (g)	18.22 ±5.38	18.62 ±5.32	.207
n-6 PUFA (g)	16.23 ±4.98	16.64 ±4.96	.203
n-3 PUFA (g)	1.92 ±.61	1.95 ±.61	.441
TFA (g)	3.16 ±.89	2.97 ±.95	.001**

^a Missing values weighted

^b Nutrients adjusted for energy intake.

* p<0.05 ** p<0.01

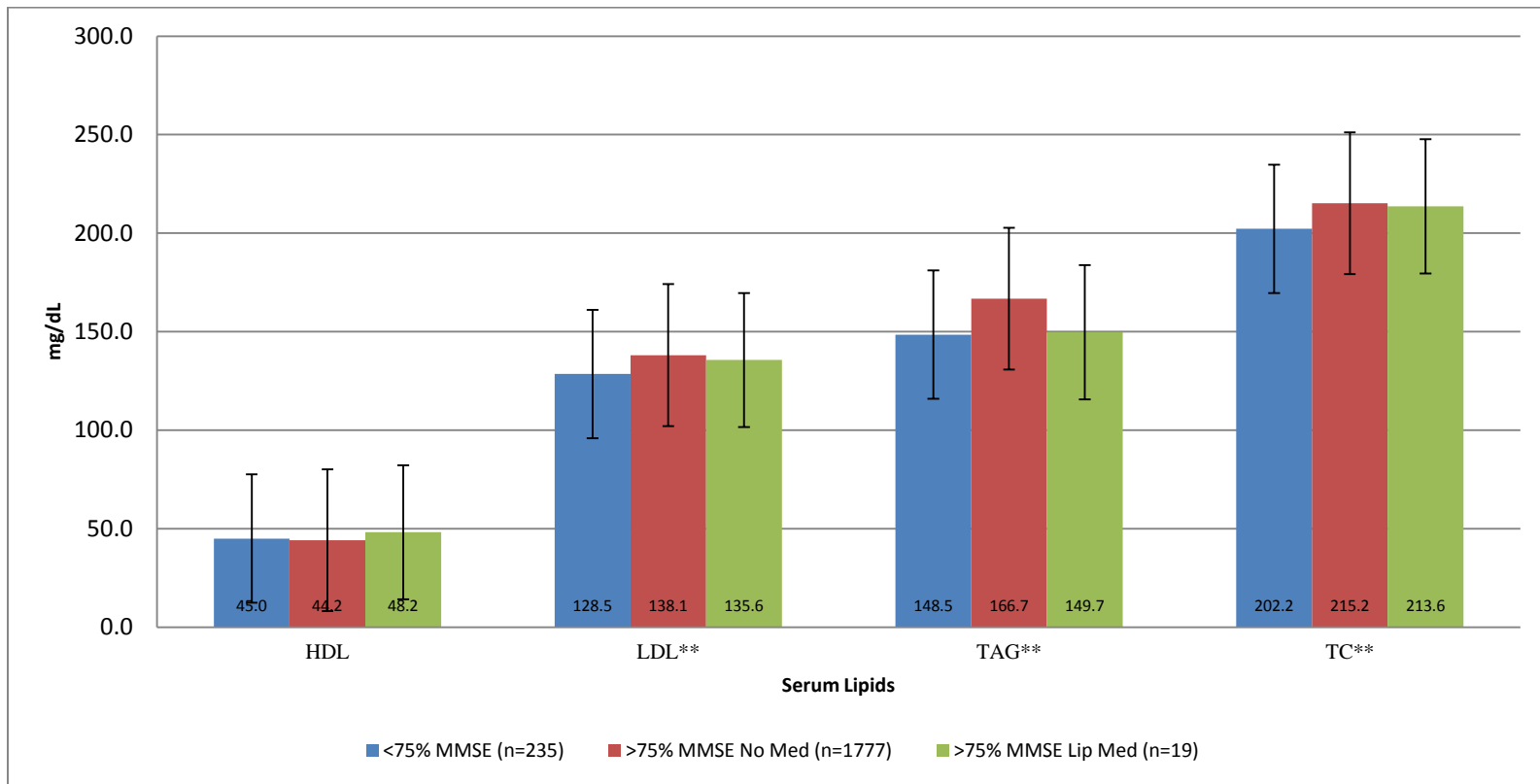
Figure 4.2 compares differences in energy and macronutrient intake between cognitively disabled and non-cognitively disabled participants. Energy, total fat, and MUFA intake were significantly greater in non- cognitively disable subjects (p<0.01). No significant differences were found in SFA, TFA and PUFA intake.



* $p < 0.05$ ** $p < 0.01$

Figure 4.2 Fat intakes and cognitive disability

The lipid profile from cognitively disabled individuals was compared to the lipid profile of that of non-cognitively disabled. Non-cognitively disabled individuals were grouped according to their use of lipid medications. Only one cognitively disabled elder reported using lipid medication. (Figure 4.3).



TC = Total Cholesterol

TAG = Triacylglycerides

* p<0.05

** p<0.01

Figure 4.3 Serum lipid profile and cognitive disability

Contrary to our expectations, the lipid profile of non-cognitively impaired participants who were not taking lipid medications was more detrimental; total cholesterol, LDL, and triglycerides were significantly higher in this population ($p < 0.01$) than their cognitively impaired counterparts. No noteworthy differences were found in HDL. No significant differences were found between those who reported taking lipid medications and those who did not.

The linear regression analysis was done using the scale of cognitive performance as the outcome variables, adjusting for age and lipid medication (Table 4.4). This scale was based on MMSE results, with 100 representing a good outcome and 0 an undesired outcome. Participants who required a proxy during the interview were automatically assigned a score of 0. The model chosen presented an $R^2 = 0.299$ and a significance of 0.000, meaning 29% of the variance can be explained by this model. A positive association was found with total fat intake (β coefficient = 3.9, $p < 0.01$), n-6 PUFA (β coefficient = 1.336, $p < 0.05$) and n-3 PUFA (β coefficient = .221 $p < 0.05$). In contrast, PUFA, MUFA, SFA and TFA were found to be negatively associated ($p < 0.01$) with MMSE score. Total serum cholesterol was negatively associated with cognitive scale performance and n-6 PUFA (β coefficient = -1.754, $p < 0.01$), while HDL, LDL, and triacylglyceride (TAG) were found to be positively associated with a better performance on the MMSE ($p < 0.01$).

Table 4.4 Linear regression analysis of dietary fat and intake and serum lipids as predictors of MMSE score.

Variables	Linear Regression Model ($R^2 = .299$ $p < 0.001$)			
	β Coefficient	95% CI		p-value
		Lower	Upper	
Total Fat (%)	3.944	3.485	15.334	.002**
PUFA (%)	-3.389	-26.655	-5.157	.004**
MUFA (%)	-2.623	-15.180	-3.298	.002**
SFA (%)	-2.505	-15.417	-3.341	.002**
Total Cholesterol (mg/dL)	-1.754	-.724	-.176	.001**
LDL (mg/dL)	1.564	.189	.737	.001**
n-6 PUFA (%)	1.336	-.003	13.455	.050
HDL (mg/dL)	.486	.162	.678	.001**
TFA (%)	-.471	-19.210	-5.761	.000**
TAG(mg/dL)	.461	.044	.155	.000**
n-3 PUFA (%)	.221	1.780	16.449	.015*

TC = Total Cholesterol

TAG = Triacylglycerides

* $p < 0.05$

** $p < 0.01$

Table 4.5 shows the logistic regression using the absence or presence of cognitive disability as the outcome variable. Several models were proposed; however, the only model that showed statistical significance for both the model and variables included total fat and total cholesterol variables only. Total fat intake presented an odds ratio of .970 ($p < 0.050$). As total fat intake increases, the odds of being cognitively disabled decreases. In contrast, the total serum cholesterol odds ratio was 1.996 ($p < 0.010$); thus, as serum cholesterol increases, the chance of cognitive impairment doubles.

Table 4.5 Logistic regression correlated of dietary fat intake and serum cholesterol as predictors of cognitive disability

Variables	Logistic Regression Model (Nagelkerke R ² = .331 p<0.000)			
	Odds Ratio	95% CI		p-value
		Lower	Upper	
Total Fat (%)	.970	.947	.993	.010*
Total Cholesterol (mg/dL)	1.996	1.993	1.998	.001**

* p<0.05 ** p<0.01

4.4 Discussion

This study found highly significant differences between cognitively disabled and non-cognitively disabled older adults. Demographic data showed that adults who scored less than 75% on the MMSE were younger, had lower income, and had fewer years of formal education. Important differences were also found in the health profile. Medical diagnoses of diabetes, stroke, and heart attack were significantly higher among the cognitively disabled. Non-cognitively disabled adults had a higher rate of medical diagnosis of dyslipidemia and presented a higher rate of metabolic syndrome according to study samples and data. Anthropometric data confirmed that cognitively disabled elders had a lower BMI, lower body weight, and a higher percentage of underweight. Dietary analysis revealed a lower energy, total fat and MUFA intake in comparison to their counterparts. Lipid profile of non-cognitively disabled adults exposed significantly higher levels of LDL, triacylglycerides and total cholesterol. The multiple regression analysis

suggested a significant ($p < .050$), yet weak ($R^2 = .299$), association between MMSE score and serum lipid profile and dietary fatty acids (β coefficients < 3.9).

Confidence in these findings is strengthened by the following factors. The study included a large population-based sample, increasing the external validity of the findings. Diet and cognitive health were assessed using previously validated instruments, that have been widely used in epidemiological studies. Statistical analyses were controlled for age, caloric intake, and the use of lipid medications.

The sample of cognitively disabled adults was older and included more women, which likely stems from the fact that women's life expectancy is higher than men's and the risk of dementia increases sharply with age (World Health Organization, National Institute of Aging & National Institute of Health, 2011). Cognitively disabled subjects also reported lower education, suggesting that education may be a protective factor against cognitive decline. Results from previous research on education and cognitive decline are controversial. In their literature review, Anstey and Christensen (2000), implied that most studies using the MMSE, which measures crystallized cognition (vocabulary, general knowledge), found a negative association between education and cognitive decline; meanwhile studies using fluid measures of cognitive health (pattern recognition, abstract reasoning, and problem-solving) did not find such associations (Anstey & Christensen, 2000). Furthermore, results from an 8-year population-based study concluded that education does not appear to protect against cognitive decline, but when using the MMSE, less educated individuals may be diagnosed with dementia earlier (Muniz-Terrera, Matthews, Denning, Huppert & Brayne, 2009). The MMSE is a reliable

tool for measuring cognitive health; however, it does not assess the type of cognitive dysfunction. Some conditions such as Alzheimer's disease, stroke or ischemic dementia have been linked with lifestyle and health choices (Luchsinder & Mayeux, 2004; Solfrizzi, Panza & Capurso, 2003) whereas others, such as traumatic brain injury, are not.

This same confounder could apply to the differences found in monthly income, where almost half of the cognitively impaired adults were found to be living under the poverty line (<US\$100/month). Nevertheless, a robust body of literature supports the association between socioeconomic status and health association may continue into old age, although gradients appear smaller at older ages (Crimmins, 2005; Turra & Goldman, 2007).

The prevalence of high cholesterol being greater in the non-cognitively disabled adults contradicts previous findings. First, dyslipidemia risk increases with age (Grundy et al., 2011); the older adults in this group are on average younger than the cognitively disabled participants. Second, high cholesterol is increasingly recognized as a risk factor for ischemic stroke, silent ischemic white-matter lesions, and vascular dementia (Kivipelto et al., 2001; Launer et al., 2000; Skoog et al., 1996). These results can be attributed to the fact that high cholesterol was self-reported and is frequently undiagnosed (Grundy et al., 2011); highlighting the limitation of the self-reported nature of the CRELES information which might be affected by reporting bias.

Cognitively impaired participants presented lower body weight, lower BMI, and lower metabolic syndrome prevalence. Furthermore, more cognitively impaired adults were classified as underweight and normal than their counterparts. It is possible that these

differences can be attributed to changes in diet and lifestyle due to the cognitive impairment which may interfere with their access to foods, ability to prepare their own meals and ability to chew and/or swallow certain foods. These assumptions could also explain the differences found in the dietary analysis and serum lipid profile.

Large population-based studies have examined dietary intake and serum lipid profile; however, results have been conflicting. In France, Pradignac, Schlienger, Velten, and Mejean (1995) found a positive relationship between fatty acid intake and the MMSE in women. A similar study in Spain found that participants with adequate scores on the MMSE (>28 pts) had lower intake of SFA, MUFA and cholesterol (Ortega et al., 1997). The Italian Longitudinal Study on Aging indicated an inverse relationship between MUFA and PUFA, and cognitive decline (Solfrizzi et al., 2006).

Contrasting results were found by van de Rest et al (2008) in a similar study conducted in the United States. Their study used a battery of tests including MMSE, memory tests, language test, perceptual speed and attention with 1,025 elderly men. A Cross-sectional analysis found no association between fatty fish or PUFA (van de Rest *et al.*, 2008).

Results from Conquer et al (2000), point in the opposite direction, suggesting that low levels of n-3 fatty acids in the plasma may be a risk factor for cognitive impairment, Alzheimer's disease, and/or dementia. However, statistical analyses from their study do not consider confounding factors, such as age and educational level. Another limitation is that no dietary intakes or histories were done; therefore, it is unclear if the participants consumed at the time or in the past, diets that were lower in PUFAs.

One important limitation of the current study is the fact that this is cross-sectional analysis and cannot address cause-and-effect relationships, namely, cognitive disability affecting dietary intake or dietary intake affecting cognitive disability. The use of FFQs for dietary assessment include restrictions imposed by a fixed list of foods based on relatively few diet constituents, reliance on memory, perception of portion sizes, and interpretation of questions. In addition, there is no data on the validity of the FFQ in cognitively impaired subjects, and some of the cognitively disabled individuals needed a proxy for the interview who may or may not have been fully aware of the personal history (eg. years of formal education) or dietary intake of the participant. Furthermore, cognition in the elderly is believed to be shaped by long-term exposures (Launer, 2005).

In conclusion, differences in demographic, health, and diet characteristics emerged between cognitively disabled Costa Rican elders and their counterparts. Dietary fat intake and serum lipid profile are weakly associated with cognitive outcomes. Further research, particularly longitudinal studies, are needed to better examine this relationship. Finally, residual confounding by unknown risk factors is possible, such as a generally healthier lifestyle of individuals with better dietary intake, which may play an important role in altering the outcomes. Such possibility cannot be excluded.

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APPENDIX

Appendix A

Interuniversity Consortium for Political and Social Research (ICPSR) terms of Use

Terms of Use

Please read the terms of use below. If you agree to them, click on the "I Agree" button to proceed. If you do not agree, you can click on the "I Do Not Agree" button to return to the home page.

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- To use these datasets solely for research or statistical purposes and not for investigation of specific RESEARCH SUBJECTS, except when identification is authorized in writing by ICPSR (netmail@icpsr.umich.edu)
- To make no use of the identity of any RESEARCH SUBJECT discovered inadvertently, and to advise ICPSR of any such discovery (netmail@icpsr.umich.edu)

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2. You are collaborating with other AUTHORIZED USERS to analyze the data for research or instructional purposes.

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Disclaimer

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If ICPSR determines that the terms of this agreement have been violated, ICPSR will act according to our policy on terms of use violations. Sanctions can include:

- ICPSR may revoke the existing agreement, demand the return of the data in question, and deny all future access to ICPSR data.
- The violation may be reported to the Research Integrity Officer, Institutional Review Board, or Human Subjects Review Committee of the user's institution. A range of sanctions are available to institutions including revocation of tenure and termination.
- If the confidentiality of human subjects has been violated, the case may be reported to the Federal Office for Human Research Protections. This may result in an investigation of the user's institution, which can result in institution-wide sanctions including the suspension of all research grants.
- A court may award the payment of damages to any individual(s)/organization(s) harmed by the breach of the agreement.

Definitions

authorized user

A faculty member, staff member, or student at a member institution

ICPSR

Inter-university Consortium for Political and Social Research

member institution

An institutional member of ICPSR

Official/Designated Representative

An individual appointed to represent a university's interests in ICPSR. This individual is also charged with providing user support to campus users.

promise of confidentiality

A promise to a respondent or research participant that the information the respondent provides will not be disseminated without the permission of the respondent; that the fact that the respondent participated in the study will not be disclosed; and that disseminated information will include no linkages to the identity of the respondent. Such a promise encompasses traditional notions of both confidentiality and anonymity. Names and other identifying information regarding respondents, proxies, or other persons on whom the respondent or proxy provides information, are presumed to be confidential.

research subject

A person or organization observed for purposes of research. Also called a respondent. A respondent is generally a survey respondent or informant, experimental or observational subject, focus group participant, or any other person providing information to a study or on whose behalf a proxy provides information.

Appendix B

University of Costa Rica Ethical Sciences Committee Approval



UNIVERSIDAD DE COSTA RICA
VICERRECTORÍA DE INVESTIGACIÓN
COMITÉ ÉTICO CIENTIFICO
Teléfonos:(506) 207-5840/207-5006 Telefax: (506) 224-9367

22 de marzo del 2004
VI-763-CEC-23-04

Señor
Dr. Luis Rosero
Investigador
Centro Centroamericano de Población

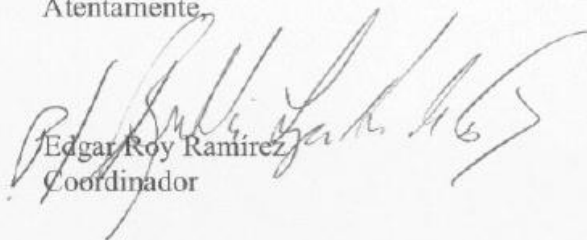
Estimado señor:

El Comité Ético Científico en su Sesión No. 63, del 17 de marzo, 2004 sometió a consideración el Consentimiento Informado de la Etapa 6 "Estudio de Longitudinal de la salud y mortalidad del adulto mayor" del proyecto 828-A2-825 "Mortalidad del adulto mayor en Costa Rica"

Después del análisis respectivo este Comité decide aprobar para el proyecto 828-A2-825 "Mortalidad del adulto mayor en Costa Rica" aprobar el Consentimiento Informado de la Etapa 6 con el nombre: "CRELES- "Costa Rica Estudio de Longitudinal de la salud y mortalidad del adulto mayor".

Se le informa que este proyecto continuara bajo el lineamiento del Comité Ético Científico razón por lo cual el nuevo número y nombre de la investigación pasara a ser: 828-A4-325 "CRELES: Costa Rica: estudio de longevidad y envejecimiento saludable"

Atentamente,


Edgar Roy Ramirez
Coordinador



Appendix C

Clemson University Office of Research Compliance (ORC) Review

Dear Catalina and Katherine,

The Clemson University Office of Research Compliance (ORC) has determined that the project identified above **does not involve human subjects** as defined in the Federal regulations governing the protection of human subjects in research [45 CFR 46.102(f)] and is, therefore, **not subject to IRB review**.

As per our conversation this afternoon and my review of the website from which the CRELES data are available (<http://www.icpsr.umich.edu/icpsrweb/NACDA/studies/26681?archive=NACDA&q=creles>), at this time, this project will not involve either “intervention or interaction” with living individuals, or the collection or use of “identifiable private information” about living individuals. Therefore, IRB review is not required.

Please contact this office again if there are any changes to this project that might bring it under the purview of the IRB. It is the responsibility of the ORC to determine whether any specific research project falls within the definition of research with human subjects, as provided by Federal regulations and institutional policy.

Thank you for contacting us to check on whether your project required IRB review and approval.

Good luck with this project and please feel free to contact me if you have any questions.

Best,

Laura