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Effect Modification By Stroke To The Relationship Between Tooth Loss And Cognitive Decline

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EFFECT MODIFICATION BY STROKE TO THE RELATIONSHIP BETWEEN TOOTH
LOSS AND COGNITIVE DECLINE

by

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DEDICATION

To my family, friends, and colleagues, who supported me and encouraged me to challenge myself and make the best impact that I can on the world.

ACKNOWLEDGEMENTS

I would like to acknowledge the many people who made this thesis possible. First, I would like to thank my thesis chair, Dr. Anwar Merchant for his continuous support and guidance. I would like to thank my committee members, Dr. Feifei Xiao, Dr. Matthew Lohman, and Dr. Kellee White for providing their unique perspectives and insights. I would also like to thank the investigators from REGARDS, Dr. Virginia Howard, Dr. Suzanne Judd, and Dr. Fred Unverzagt for their direction and for allowing me to use the REGARDS data.

ABSTRACT

Background: A decline in cognitive functioning is one of the greatest burdens that older adults face. Studies indicate that periodontal disease is positively associated with cognitive decline. The link between stroke and cognitive decline is well-established, and literature supports that tooth loss and stroke are associated as well, but the role that stroke plays in the relationship between tooth loss and decline in cognitive functioning is, as of yet, unclear. This study uses data from the REGARDS cohort to examine the effect of stroke on the relationship between periodontal disease and cognitive function.

Methods: The REGARDS cohort is comprised of 30,000 African-Americans and white individuals, aged 45 and older, from the United States. While the primary objective of the REGARDS study was to determine the reasons for excess stroke mortality in African Americans and in the Southeastern United States, a large number of variables were collected from participants, among them, tooth loss, history of stroke, incident stroke, and a cognitive function score, which was collected annually. We used a Cox survival analysis approach to assess the impact of tooth loss on risk of cognitive decline. To examine stroke's impact on the relationship between tooth loss and cognitive function, we analyzed the interaction between tooth loss and stroke (incident and prevalent). As African-Americans tend to experience tooth loss, stroke, and cognitive decline differently than white Americans, we stratified our models by race. For each race, we constructed a

crude model and a model adjusted for a variety of demographic, lifestyle, and health characteristics.

Results: Interaction between tooth loss and stroke was not found to be significant in any model, on the additive or multiplicative scale. After adjustment for confounders, there was not sufficient evidence to suggest a positive relationship between tooth loss and cognitive decline among African Americans or white Americans, although there was much stronger evidence to support this relationship among white Americans.

Conclusions: We did not find evidence that stroke is an effect modifier between tooth loss and cognitive decline. Our findings indicated that there is likely an increased risk of cognitive decline among those who have lost more teeth in white Americans, but not African Americans. We recommend that stroke be examined as an effect modifier to tooth loss and cognitive decline in high-risk populations, where a significant relationship between tooth loss and cognitive decline has already been observed.

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CHAPTER 1

INTRODUCTION

1.1 Statement of the Problem

Periodontal disease is a painless, chronic infection of the supporting tooth structures, resulting in their weakening and tooth loss. Tooth loss is a known indicator of periodontal disease (Centers for Disease Control and Prevention, 2016). More than 47% of adults aged 30 years or older suffer from some form of periodontal disease, and it is more prevalent among men, individuals with less than a high school education, those below the federal poverty line, and smokers (Centers for Disease Control and Prevention, 2015). Periodontal infections, which increase with age, are associated with a wide range of health problems, including systemic health conditions such as cardiovascular disease and rheumatoid arthritis, as well as stroke and cognitive decline (Yamamoto, 2011).

Cognitive functioning encompasses the ability to speak, think clearly, remember, plan, make decisions, perceive, pay attention, and use thought processes to perform daily functions (Centers for Disease Control and Prevention, 2007). Cognitive decline is more common with increasing age, and can range from being very mild to being very extreme, as found in those with Alzheimer's disease or dementia (Centers for Disease Control and Prevention, 2007). Cognitive decline impacts the ability to perform normal daily functions and thus can lead to a loss of independence, negatively impacting quality of life. Dementia affects 11% of people aged 65 years or older and is the sixth leading cause of death in the United States. Dementia is a major cause of disability in the United

States, and in 2016, the estimated cost of care for those with Alzheimer's was \$236 billion (United States Department of Health and Human Services, 2017).

Studies indicate that tooth loss and periodontal disease are positively associated with cognitive decline (Kalakonda et al., 2016; Leira et al., 2017). The mechanism by which tooth loss leads to cognitive decline, however, is unclear. Many researchers believe that periodontal infections can lead to systemic inflammation, which can cause damage to the brain (Singhrao et al., 2014; Wu & Nakanishi, 2014). Microorganisms typically found in individuals with periodontal disease have been shown to cause inflammation and neuronal damage in the brains of mice (Poole et al., 2015). A number of other factors could also be influencing the association between tooth loss and cognitive decline. An unknown genetic predisposition could lead to both periodontal disease and cognitive decline. Poor diet, sedentary lifestyle, and socio-economic factors can contribute to both periodontal disease and reduced cognition. Additionally, periodontal disease leads to tooth loss, which can limit intake of nutrient-rich foods, which can contribute to cognitive decline. The degree to which the association between tooth loss and cognitive decline is explained by changes in diet and other factors has not been clearly established (Leira et al., 2017).

Stroke is another major health outcome found to be associated with tooth loss (You et al, 2013). There are several hypothesized mechanisms by which tooth loss and stroke are associated. It is possible that the microorganisms found in periodontal infections lead to systemic inflammation which can lead to stroke. It also possible that an unknown genetic predisposition causes both periodontal disease and stroke, or that poor diet predisposes individuals for periodontal disease and stroke. Stroke is also correlated

with cognitive decline, and the link between these has been well-established. Stroke occurs when blood supply to the brain is blocked or when a blood vessel in the brain ruptures, causing blood to spill into the area surrounding brain cells (National Institute of Neurological Disorders and Stroke, n.d.). This results in brain cell death, which can cause cognitive decline, depending on which regions of the brain are affected. The role of stroke in the relationship between tooth loss and cognitive decline, however, has yet to be determined. It is possible that tooth loss and stroke interact to produce an increased association of cognitive decline, or that these factors interact to produce a reduced association of cognitive decline. It is also possible that the association between tooth loss and cognitive decline is entirely or partially due to the association between tooth loss and stroke, which leads to cognitive decline. This thesis will focus on uncovering the degree to which stroke is an effect modifier to the relationship between tooth loss and cognitive decline.

Additionally, race may further modify the relationship between tooth loss, stroke, and cognitive decline. The primary objective of the REGARDS study was to better understand why African-Americans develop stroke at a much higher rate than white Americans (REGARDS Study, n.d.). In 2012, the percent of Non-Hispanic Blacks in the US who experienced a stroke was 3.9%, while it was only 2.4% in Non-Hispanic Whites (United States Department of Health and Human Services, 2016). Not only does a racial disparity exist for stroke, African-Americans also have a higher prevalence of tooth loss and periodontal disease (Centers for Disease Control and Prevention, 2017). Additionally, studies have indicated higher rates of dementia, Alzheimer's disease, and cognitive impairment among African-Americans than among their white counterparts

(Anderson et al., 2004). African-Americans are more likely to have lower levels of education, lower income, and have inadequate health insurance compared to non-Hispanic whites, all of which are factors that can prevent individuals from accessing the resources needed to prevent tooth loss, stroke, and cognitive decline, potentially confounding the relationship between them (United States Department of Health and Human Services, 2017). African-Americans also have a lower mean intake of vegetables per 1000 calories, a higher mean intake of added sugars per 1000 calories, and a higher level of sugar-sweetened beverage consumption than white Americans (Office of Disease Promotion and Health Prevention, 2017; Centers for Disease Control and Prevention, 2017). Poor diet contributes to tooth loss and stroke as well, and could potentially be responsible for African-Americans' increased risk of tooth loss, stroke, and cognitive decline. Even after controlling for a number of social and demographic factors, African-Americans experience worse health outcomes than other racial groups, so race itself or poorly-understood factors which are closely tied to race could be causing elevated systemic inflammation and worse outcomes with regard to tooth loss, cognitive decline, and stroke (United States Department of Health and Human Services, 2017). Because of the disparity between black Americans and white Americans in rates of tooth loss, stroke, cognitive decline, as well as several risk factors for these conditions, the relationship between tooth loss, stroke (incident and prevalent), and incident cognitive impairment will be evaluated separately for African-Americans and white Americans in this thesis.

Regular dental care helps to control periodontal disease, preventing tooth loss and improving oral health overall (Centers for Disease Control and Prevention, 2015). This is its own benefit, since tooth loss can limit a person's diet and quality of life (Centers for

Disease Control and Prevention, 2016). If tooth loss contributes to cognitive decline, however, then dental care can protect not only oral health but also brain health.

Identifying stroke as a potential effect modifier will help to clarify whether those who have suffered a stroke can benefit to a greater extent from regular dental care, and whether these individuals should be targeted for dental interventions.

1.2 Purpose and Objectives

The primary purpose of this thesis is to better understand the relationship between tooth loss and incident cognitive impairment using data from the REGARDS cohort. We wish to determine whether the association between teeth lost due to gum disease and cognitive decline is modified by incident and prevalent stroke, and we wish to determine this separately for African-Americans and white-Americans. We will also assess the relationship between tooth loss and animal fluency and word list learning scores.

Aim 1: To determine the association between tooth loss and incident cognitive impairment among African-Americans and white-Americans 45+ years old.

Hypothesis 1.1: Are African-Americans and white-Americans 45+ years old who have lost 1-16 teeth or 17 or more teeth due to gum disease at an elevated risk of experiencing cognitive decline compared to those who have lost no teeth due to gum disease?

Aim 2: To determine the extent to which stroke is an effect modifier to the relationship between tooth loss and incident cognitive impairment among African-Americans and white-Americans 45+ years old.

Hypothesis 2.1: Is stroke (incident and prevalent) an effect modifier in the relationship between the number of teeth lost due to gum disease and cognitive decline among African-Americans and white-Americans 45+ years old?

1.3 Significance of Research

While studies have shown that a positive association between tooth loss and cognitive decline exists, the research is not yet extensive, and this thesis can add to these findings. Additionally, stroke has yet to be explored as an effect modifier in the relationship between tooth loss and cognitive decline, and this thesis can help to illuminate the pathway between tooth loss and cognitive decline. Regular dental care, which protects against periodontal disease and prevents tooth loss, may also help to prevent cognitive decline. Depending on the degree and direction of effect modification by stroke in the association between tooth loss and cognitive decline, dental care may protect brain health to a greater extent among those who experience a stroke.

CHAPTER II

LITERATURE REVIEW

2.1 Tooth Loss and Cognitive Function

Tooth loss, periodontal disease, and oral disease have been shown to be correlated with a decline in cognitive functioning and increased incidence of disorders related to cognitive decline, including dementia and Alzheimer's disease. In a systematic review of the literature, Kalakonda et al found a positive association between periodontal disease and Alzheimer's disease, as well as a proposed mechanism to link the two conditions. Kalakonda et al proposed that the inflammatory molecules found in periodontal infections stimulate systemic inflammation, causing an increase in CRP levels. Through systemic pathways, these cytokines eventually reach the brain, and as brain cytokines pool, they activated glial cells in the brain. This causes an increase in β -amyloid, leading to neurodegeneration (Kalakonda et al., 2016). Leira et al found positive associations between periodontal disease and Alzheimer's via a meta-analysis. Leira et al found that those with periodontal disease had 1.69 times the odds of having Alzheimer's disease as those without periodontal disease (95% CI: 1.21 – 2.35), and those with severe forms of periodontal disease had 2.98 times the odds of having Alzheimer's disease as those without severe periodontal disease (95% CI: 1.58 – 5.62) (Leira et al., 2017). De Souza Rolim et al conducted a clinical trial and found that dental treatment led to a significant reduction in pain frequency and a significant improvement in quality of life and mandibular function among those with Alzheimer's (De Souza Rolim et al., 2014). In a

prospective cohort study, Batty et al found that having no teeth was associated with 1.48 times the risk of dementia (95% CI: 1.24 – 1.78) and 1.39 times the risk of cognitive decline (95% CI: 1.21 – 1.59). (Batty et al., 2013). Among individuals with Alzheimer's disease, Ide et al found an increased risk of cognitive decline associated with periodontitis which may be mediated through systemic inflammation (Ide et al., 2016). Using a case-control study design, Farhad et al found an association between chronic periodontitis and Alzheimer's and Martande et al found that in patients with Alzheimer's disease, periodontal disease appeared to be linked to level of cognitive functioning (Farhad et al., 2014; Martande et al., 2014).

Much of the literature focuses on the specific pathways that link periodontal and oral disease to a decline in cognitive functioning. Noble et al found that serum IgG levels to common periodontal microbiota were linked to an increased risk for developing incident Alzheimer's disease (Noble et al., 2014). Kamer et al uncovered an association between periodontal disease and brain amyloid load, and Sochocka et al demonstrated that poor periodontal health can lead to systemic infections, which can exacerbate neurodegenerative lesions and worsen dementia and Alzheimer's disease (Kamer et al., 2015; Sochocka et al., 2017). Additionally, poor diet can exacerbate periodontal disease, leading to cognitive decline, and tooth loss can limit the number of nutrient-rich foods that an individual can consume, also leading to cognitive decline (Yamamoto, 2011). De Souza Rolim et al demonstrated that that periodontal infections were more prevalent in those with Alzheimer's disease than their healthy counterparts, and Cestari et al found evidence of a linkage in the mechanisms for oral infections and the development of Alzheimer's disease (De Souza Rolim et al., 2014; Cestari et al., 2016).

Using data from the REGARDS cohort, Matthews et al found a positive association between self-reported tooth loss and cognitive decline before adjusting for potential confounders (Matthews et al., 2011).

Many studies focused on the biological plausibility of the relationship between periodontal disease and cognitive decline. Olsen et al discovered that oral infections can likely put individuals at increased risk for developing Alzheimer's disease (Olsen & Singhrao, 2015). Singhrao revealed that periodontal and other oral bacteria can spread to other organs and cause inflammation of the central nervous system. This prolonged stress on the brain's microglia can weaken their defense against invading pathogens and reduce neuron function, leading to cognitive decline (Singhrao et al., 2014). Feres et al found that as subgingival biofilms age, their composition makes them more susceptible to infection, allowing oral infections to spread more easily, putting individuals at higher risk of Alzheimer's disease (Feres et al., 2016). Wu et al found that the leptomenigeal cells associated with periodontitis can trigger systemic inflammation in the body, which can lead to Alzheimer's disease (Wu & Nakanishi, 2014). Fukushima-Nakayama et al discovered that in mice, reduced mastication, which often can result from tooth loss, can lessen neuronal activity and contribute to cognitive decline (Fukushima-Nakayama et al., 2016). Harding et al supports that not only does a positive relationship exist between periodontal disease and Alzheimer's disease, but improved memory can be found in those who underwent dental intervention (Harding et al., 2017).

2.2 Tooth Loss and Stroke

Many studies indicate a positive relationship between tooth loss and stroke. Joshipura et al found that men with 24 or less teeth had 1.57 times the risk of

experiencing a stroke compared to men with more than 24 teeth (95% CI: 1.24 – 1.98), and Vedin et al found an increased risk of stroke in those with no teeth as compared to those with 26-32 teeth (HR: 1.67, 95% CI: 1.15 – 2.39) (Joshi et al., 2003; Vedin et al., 2017). Iwasaki et al showed that among a cohort of Japanese adults over age 75, each tooth lost was associated with a medical cost of 226 JPY (100 JPY = 95 US dollars) due to stroke, after adjusting for confounders. (Iwasaki et al., 2017). Grau et al determined periodontal disease to be a risk factor for cerebral ischemia through a case-control study (Grau et al., 2004). Desvarieux et al demonstrated tooth loss to be associated with subclinical atherosclerosis, and Elter et al found periodontitis to be associated with stroke (Desvarieux et al., 2003; Elter et al., 2003). The relationship between tooth loss and stroke may be modified by race. You et al found tooth loss to vary with race and be associated with stroke (You et al., 2009). African-Americans have higher risk of tooth loss and stroke than white Americans (United States Department of Health and Human Services, 2016; Centers for Disease Control and Prevention, 2017). There could be many reasons for these associations; for example, African-Americans could experience stroke at a higher rate simply because they experience tooth loss at a higher rate, and periodontal disease (marked by tooth loss) leads to stroke. It is possible that a factor very closely tied to race, such as socio-economic status or stress is influencing the rate at which African-Americans experience tooth loss and stroke. It is also possible that an underlying genetic factor present in African-Americans causes both tooth loss and cognitive decline.

2.3 Stroke and Cognitive Function

It is well-established that stroke leads to a decline in cognitive function. Stroke occurs when blood supply to the brain is blocked or when a blood vessel in the brain

ruptures, causing blood to spill into the area surrounding brain cells. This results in brain cell death, which can cause cognitive decline, depending on which regions of the brain are affected (National Institute of Neurological Disorders and Stroke, n.d.). Stroke can cause deficits with regard to language, thought, memory, perception, and/or attention. Recovery of cognitive function for those who have suffered a stroke varies from no recovery/gradual worsening to complete recovery. (Stein et al., 2015).

A meta-analysis conducted by Pendlebury et al showed that after stroke, 10% of those examined developed dementia, and after recurrent stroke, more than a third developed dementia (Pendlebury & Rothwell, 2009).

Tatemichi et al found that stroke can lead to a decline in memory, orientation, language, and attention, independent of physical decline. In this cohort, 35.2% of patients with stroke suffered from cognitive impairment, while only 3.8% of controls were cognitively impaired (Tatemichi et al., 1994). Seshadri et al demonstrated through the Framingham Offspring Study that those at high risk for stroke tend to experience poorer cognitive functioning, even if they are stroke-free and dementia-free (Seshadri et al., 2004). Zhu et al discovered that not only does stroke lead to dementia, dementia and cognitive impairment are associated with higher incidence of stroke among those aged 75 or older (Zhu et al., 2000).

2.4 Summary

According to the literature, it would appear that a positive correlation does exist between tooth loss and cognitive decline. Multiple studies have been able to show that those who experience tooth loss are at higher risk for cognitive decline. While the specifics of proposed mechanisms for this association differ across studies, researchers

tend to agree that the bacteria found in periodontal infections spread to other organs in the body, causing systemic inflammation, which can impair neuron function over time, contributing to cognitive decline. There is not yet sufficient information to indicate whether this association differs between African-Americans and whites. The literature also indicates that stroke is positively correlated with both tooth loss and cognitive decline but does not clearly establish whether or not stroke is an effect modifier to this relationship. Furthermore, being African-American is positively correlated with tooth loss, stroke, and cognitive decline, but it is unclear if race confounds and/or modifies any relationships between these three variables. Therefore, we would like to examine the extent to which stroke is an effect modifier to the relationship between tooth loss and cognitive decline, and we like to do so separately for African-Americans and white Americans.

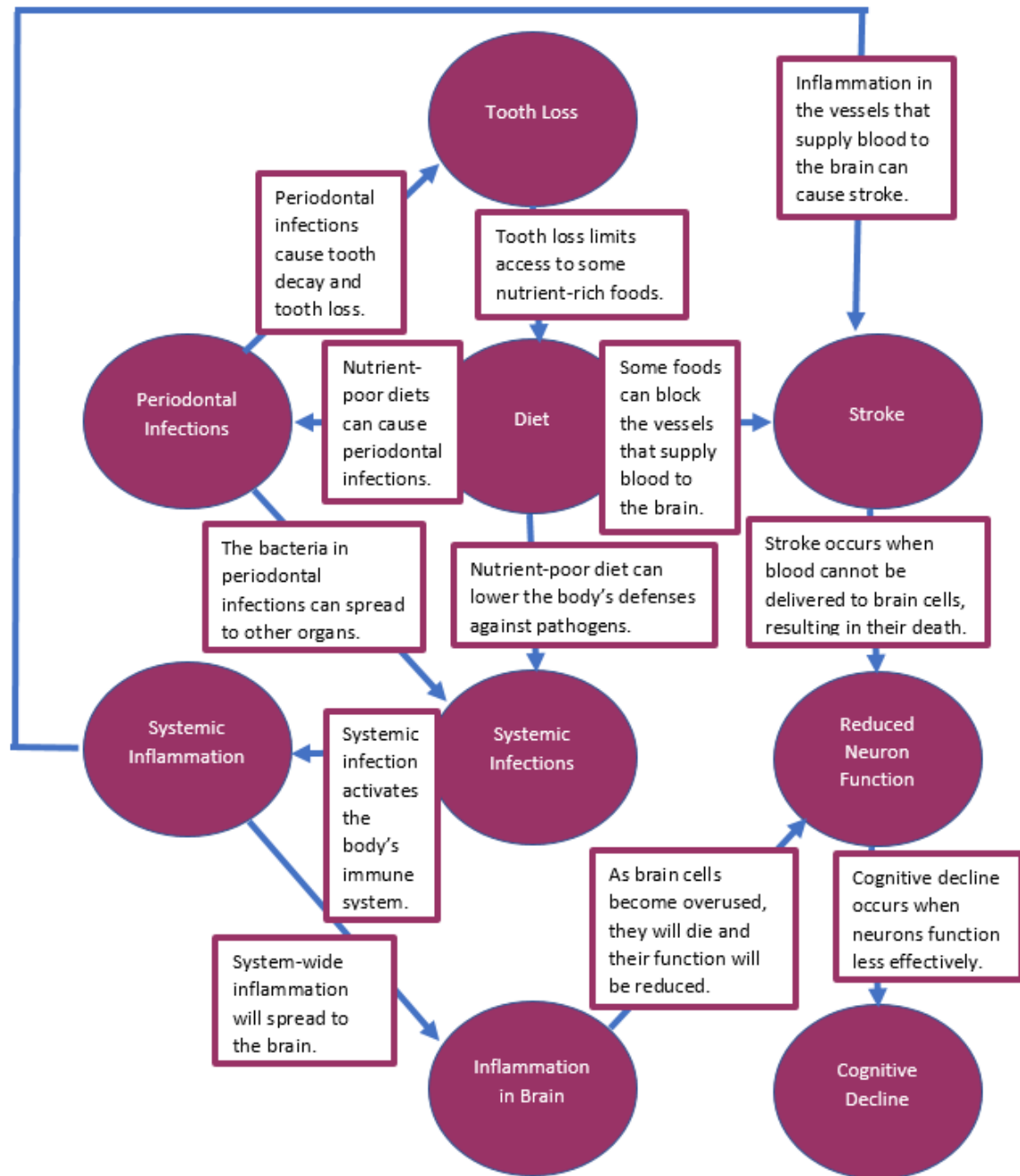


Figure 2.1 Causal diagram depicting the relationship between tooth loss, stroke, and cognitive decline.

CHAPTER III

METHODS

3.1 Study Design

The REGARDS cohort is comprised of 30,000 African-American and white individuals, aged 45 years and older, from the United States. Its primary objective is to uncover why stroke disproportionately affects African-Americans and those living in the Southeastern US. Participants were recruited between January 2003 and October 2007, and follow-up is still ongoing. Those participating in the study were recruited via mail or telephone; data were collected via a telephone interview, at-home exam, and three self-administered questionnaires, and included information on participants' demographic characteristics, lifestyles, psychosocial attributes, cognition, and stroke risk factors. Participants were followed-up at six-month intervals to determine newly occurring cognitive impairment. In this prospective analysis, participants of the REGARDS study, who were free of cognitive impairment and had information on tooth loss, stroke, and cognitive impairment (N = 20,003) were followed up from 2005 to 2016 to evaluate the degree to which stroke modified the relation between tooth loss and cognitive impairment.

3.2 Measurement of Exposure

Tooth loss was ascertained via the telephone questionnaire. The interviewer asked, "Have you lost any of your teeth due to gum disease?", and if the participant answered "Yes", then the interviewer asked the participant, "How many teeth have you

lost due to gum disease?”, and the participant would answer with the number of teeth he or she had lost. We categorized tooth loss as having lost 0 teeth due to periodontal disease, having lost 1-16 teeth, or having lost 17 or more teeth. This categorization was used in previous REGARDS studies (You et al, 2009).

3.3 Measurement of Outcome

Cognitive function was scored using a six-question screener during the initial telephone interview and continued to be administered annually during follow-up telephone interviews. This screener contains six items, developed from the Mini-Mental State Examination, Blessed Dementia Rating Scale, and the Word List Recall. In the first question, the interviewer named three objects, and asked the participant to repeat and remember the words. No points were awarded for this question. In the second question, the interviewer asked the participant, without looking at a calendar or a watch, what year it was. If the participant could correctly identify the current year, he or she was awarded one point. The third question asked the participant what month it is, and the fourth question asked the participant what day of the week it was. For each item answered correctly, the participant was awarded one point. The fifth question asked the participant to name the three objects mentioned in the first question, and for each object correctly remembered, the participant was awarded one point. The cognitive function score ranged from 0-6. We classified those scoring ≤ 4 defined as cognitively impaired, as this cutoff point was used in previous REGARDS studies. When comparing the results of the screener to clinical diagnoses, its sensitivity was found to be 95.2%, and its specificity was found to be 86.7%. These sensitivity and specificity scores were found when

cognitive impairment was defined as missing three or more items on the cognitive screener (Callahan et al., 2002). This screener is available in Appendix A.

3.4 Measurement of Effect Modifier

History of stroke at baseline was also determined via telephone questionnaire, in the first section of the telephone interview. Participants were asked whether they had ever been told by a physician that they had experienced a stroke, and if they answered “yes”, they were asked how many strokes they had experienced, how old they were when they experienced their first stroke, and how old they were when they experienced their last stroke. Participants were also asked whether or not they had been told by a physician that they had suffered a mini-stroke or transient ischemic attack, whether they had ever had sudden painless weakness on one side of their body, whether they had ever had sudden numbness or a dead feeling on one side of their body, whether they had ever had sudden painless loss of vision in one or both eyes, whether they had ever suddenly lost one half of their vision, whether they had ever suddenly lost the ability to understand what people were saying, and whether they had ever suddenly lost the ability to express themselves verbally or in writing. Participants were considered stroke-free at baseline only if they answered “no” to all eight questions. This questionnaire, the Questionnaire for Verifying Stroke-Free Status (QVSFS), was assessed by comparing its results to clinical diagnoses of those at selected clinics, using the same criteria of an answer of “yes” to any of the questions being classified as having a history of stroke. The questionnaire was found to have a negative predictive value of 96% and a positive predictive value of 71% when using an answer of “no” to define individuals as stroke-

free, using clinical diagnoses as a comparison (Jones et al., 2001). These questions are available in Appendix B.

Participants were followed-up at six-month intervals to determine their incident stroke status. Using the same questions from the QVSFS at baseline, events that required hospitalization and physician assessments of stroke symptoms were ascertained. Proxy respondents identified at baseline were interviewed if the participant was unable to complete the telephone follow-up call for medical reasons. If the participant reported hospitalization or a physician visit for stroke-like symptoms, then the hospital and/or physician's contact information was collected. Medical records were then used to determine whether a stroke event occurred. If a death was reported, the death certificate and medical records for 28 days preceding the death are collected and analyzed to determine incident stroke. The methods for event verification are based on those used in previous clinical trials, including the Vitamin Intervention for Stroke Prevention (VISP) trial and the Asymptomatic Carotid Atherosclerosis Study, and observational studies, including the Insulin Resistance Atherosclerosis Study (IRAS) and the ARIC study.

3.5 Measurement of Potential Confounders

Race

Race was assessed during the telephone questionnaire. Participants were asked whether they were White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander American Indian, Alaska Native or some other race. Participants were classified as white or black, and if they responded that they were any race other than white or black, they were not included in the study. Participants were recruited so that within each region strata, about half were black and half were white.

Sex

Sex was assessed during the telephone questionnaire. Interviewers only asked participants what their sex was if they were unable to determine based on the participant's voice. Participants were classified as either male or female, and were recruited so that, within each region-race stratum, about half were male and half were female.

Age

Age was determined during the telephone questionnaire. Participants were asked for their date of birth. Only those age 45 or older were eligible to participate. Age is categorized as 45 to 54, 55 to 64, 65 to 74, 75 to 84, or 85 years or older (Matthews et al., 2011).

Geographic Region

The REGARDS sample was selected from a commercially available nationwide list purchased through Genesys Inc. Participants were selected so that 30% would be from the stroke belt (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas), 20% from the stroke buckle (a region along the coastal plain of North Carolina, South Carolina, and Georgia), and 50% from the remainder of the continental United States. Participants were asked to confirm their address in the telephone questionnaire. Participants are classified as residing in a stroke-belt state or a non-stroke-belt state (Matthews et al., 2011).

Income

Income was ascertained during the telephone interview. We will categorize income as less than \$20,000, \$20,000 to \$34,999, \$35,000 to \$74,999, or \$75,000 or more per year (Matthews et al., 2011).

Education

Participants were asked what the highest grade or year of school they had completed was during the telephone interview. Education is categorized as no high school diploma, high school diploma or GED, some college but no degree, or college degree or higher (Matthews et al., 2011).

Access to Health Insurance

Participants were asked whether they had health insurance during the telephone interview. Responses were documented as “yes” or “no”.

Population Density

Participants were asked to report the city where they lived. Based on the size of their census tract, participants were categorized into rural (<25% urban), mixed (25-75% urban), or urban (>75% urban).

Alcohol Consumption

Alcohol use was determined during the telephone questionnaire. Participants were asked if they drank alcohol, when they started drinking alcohol, how frequently they drank alcohol, and how much alcohol they consumed. Participants were classified as non-alcohol drinkers (0 drinks per week), moderate alcohol drinkers (0-7 drinks per week for women, 0-14 drinks per week for men), or heavy alcohol drinkers (more than 7 drinks per week for women, more than 14 drinks per week for men).

Smoking Status

Smoking status was assessed during the telephone questionnaire. Participant were asked if they had smoked at least 100 cigarettes in their lifetime. Those who answered “no” will be classified as “never smokers”. Those who answered “yes” were asked whether they smoke cigarettes now, even occasionally. Those who answered that they do not smoke now are classified as “past smokers” and those who answered that they do are classified as “current smokers”.

Physical Activity

Via the telephone questionnaire, participants were asked how many times per week they engaged in physical activity rigorous enough to work up a sweat. Participants are categorized as 0 times per week, 1-3 times per week, or 4 or more times per week.

Relationship Status

Participants were asked about their relationship status during the telephone interview. Participants were categorized as married, single, divorced, or widowed.

BMI

BMI was calculated as kilograms per square meter. Height and weight measurements were taken during the in-home exam. BMI is classified as normal (18.5-24.9 kg/m²), underweight (< 18.5 kg/m²), overweight (25-29.9 kg/m²), or obese (> 30 kg/m²) (Matthews et al., 2011).

Diabetes

Diabetes is defined as having a fasting glucose level of more than 126 mg/dL, having a non-fasting glucose level greater than 200 mg/dL, or taking medicine or insulin for diabetes. Blood glucose was assessed via the laboratory assay collected during the in-

home exam, and medication inventory was also taken during the in-home exam (Matthews et al., 2011).

Hemoglobin Count

Hemoglobin count was assessed via the laboratory assay collected during the in-home exam. Hemoglobin was recorded as a continuous variable.

Hypertension

We defined hypertension as having systolic blood pressure of 140 mmHg or greater, diastolic blood pressure of 90 mm Hg or greater, or self-reporting hypertension, confirmed by medication use. Participants were asked if they had hypertension during the telephone questionnaire, and blood pressure measurements and medication inventory were taken during the in-home exam.

Hyperlipidemia

We defined hyperlipidemia as having a total cholesterol level of 240 mg/dL or greater, a low-density lipoprotein cholesterol level of 160 mg/dL or greater, a high-density lipoprotein cholesterol level of 40 mg/dL or lower, or using lipid-lowering medication. Blood cholesterol was assessed via the laboratory assay collected during the in-home exam, and medication inventory was also taken during the in-home exam (Matthews et al., 2011).

Depression

Depression was assessed during the telephone questionnaire. Questions were taken from the four-item version of the Center for Epidemiological Studies-Depression scale. Scores can range from 0 to 12. Depression is analyzed as a continuous variable.

Stress Level

Stress level was assessed during the telephone questionnaire. Questions were taken from Cohen's Perceived Stress Scale. Scores can range from 0 to 16. Stress level is analyzed as a continuous variable.

History of Heart Disease

During the telephone questionnaire, participants were asked whether a doctor or health professional had ever told them that they had a myocardial infarction or heart attack. Participants answered either 'yes' or 'no'. Participants were also asked if they had ever had coronary bypass surgery, such as a graft, CABG or a bypass procedure on the arteries of their heart, to which they answered 'yes' or 'no'. Participants were asked if they had ever had an angioplasty or stenting of a coronary artery with or without placing a coil in the artery to keep it open as well, to which they answered 'yes' or 'no'. Participants are considered not to have a history of heart disease at baseline only if they answered 'no' to all three questions.

3.6 Statistical Analysis

We assessed the relationship between tooth loss, stroke, and cognitive decline using Cox proportional hazards models. The models were evaluated using incident cognitive impairment as the primary outcome, tooth loss as the primary exposure, and stroke (incident and prevalent) as an interaction term. Statistical analysis was performed using SAS software version 9.4. Potential confounders were identified using a priori knowledge, evidence in the literature, and directed acyclic graphs (DAGs). We adjusted for gender, age, region, income, education level, health insurance, population density, alcohol consumption, smoking status, physical activity, marital status, BMI, diabetes,

hemoglobin count, hypertension, hyperlipidemia, history of heart disease, depression, and stress level. Confounders found to alter model estimates by more than 10% upon removal remained in the model. Separate models were developed for African-Americans and white Americans. Rate ratios and 95% confidence intervals were calculated, with tooth loss categorized as no teeth lost, 1-16 teeth lost, or 17 or more teeth lost. We assessed stroke as an effect modifier on both the additive and the multiplicative scale. We computed Kaplan Meier curves and plotted log cumulative hazards to assess whether proportional hazards assumptions were met for categorical variables and constructed Schoenfeld residual curves to assess proportionality of hazards for continuous variables. The proposed models are as follows:

Model 1

$$\log(h(t)) = \alpha_1 x_{11} + \alpha_2 x_{12} + \alpha_3 x_2 + \alpha_4 x_{11} x_2$$

x_{11} = 1 if 1-16 teeth lost, 0 if not

x_{12} = 1 if 17 or more teeth lost, 0 if not

x_2 = 1 if stroke has occurred, 0 if not

Model 2

$$\log(h(t)) = \alpha_1 x_{11} + \alpha_2 x_{12} + \alpha_3 x_2 + \alpha_4 x_{11} x_2 + \alpha_5 x_{12} x_2 \sum_{i=1}^k \beta_i z_i$$

x_{11} = 1 if 1-16 teeth lost, 0 if not

x_{12} = 1 if 17 or more teeth lost, 0 if not

x_2 = 1 if stroke has occurred, 0 if not

z = gender, age, region, income, education level, health insurance, population density, alcohol consumption, smoking status, physical activity, marital status, BMI, diabetes,

hemoglobin count, hypertension, hyperlipidemia, history of heart disease, depression, and stress level

Where stroke was not found to be an effect modifier, an additional model without the interaction term for tooth loss and stroke ($\alpha_3 x_1 x_2$) was constructed.

CHAPTER IV

RESULTS

4.1 Sample Characteristics

There was a total of 20,003 participants after excluding those with missing data on tooth loss, stroke, or cognitive score and those who were cognitively impaired at baseline. About 89.3% of participants had lost no teeth due to periodontal disease, 4.7% lost 1-16 teeth, and 6.1% lost 17 or more teeth due to periodontal disease. These three exposure groups were significantly different with regard to race and most covariates ($\alpha = 0.05$). About 91.8% of white Americans had lost no teeth due to periodontal disease at baseline, compared to only 85.2% of African Americans. Tooth loss due to gum disease was more common amongst females, older participants, participants residing in the stroke-belt or buckle, lower-income participants, those with lower education levels, participants without health insurance, urban participants, people who drink no alcohol, current or past smokers, sedentary participants, single, widowed, and divorced participants, obese participants, diabetic participants, hypertensive participants, participants with hyperlipidemia, participants with a history of heart disease, and participants with a history of stroke. The average hemoglobin count (mg/dL) was 13.7

for those who lost no teeth, 13.6 for those who lost 1-16 teeth, and 13.5 for those who lost 17-32 teeth. The average depression score was 54.3 for those who lost no teeth, 52.7 for those who lost 1-16 teeth, and 53.0 for those who lost 17 or more teeth, while the average stress score was 3.1 for those who lost no teeth, 3.7 for those who lost 1-16 teeth, and 3.7 for those who lost 17 or more teeth due to periodontal disease.

Table 4.1 Baseline Characteristics by Number of Teeth Lost, (% or mean \pm SD (n))

Baseline Characteristic		0 teeth lost (n = 17854)	1-16 teeth lost (n = 937)	17-32 teeth lost (n = 1212)	P-value
Race	African-American	85.2 (6562)	6.1 (470)	8.7 (671)	<0.0001
	White	91.8 (11292)	3.8 (467)	4.4 (541)	
Gender	Female	88.8 (10771)	5.0 (600)	6.3 (759)	0.0267
	Male	90.0 (7083)	4.3 (337)	5.8 (453)	
Age (in years)	45-54	91.8 (3078)	5.4 (182)	2.7 (92)	<0.0001
	55-64	90.3 (6911)	4.8 (365)	4.9 (377)	
	65-74	87.5 (5312)	4.4 (269)	8.1 (492)	
	75-84	87.1 (2279)	4.1 (106)	8.8 (231)	
	85+	88.7 (274)	4.9 (15)	6.5 (20)	
Region	Stroke-belt	89.0 (6224)	4.5 (315)	6.6 (458)	0.0041
	Stroke-buckle	88.2 (3883)	5.3 (232)	6.5 (287)	
	Non-stroke-belt	90.0 (7747)	4.5 (390)	5.4 (467)	
Income (\$ per year)	<\$20,000	81.6 (2547)	5.8 (182)	12.6 (392)	<0.0001
	\$20,000-34,999	87.2 (3974)	4.8 (218)	8.0 (364)	
	\$35,000-74,999	90.7 (5649)	5.2 (325)	4.1 (252)	
	\$75,000+	95.8 (3461)	2.9 (106)	1.3 (46)	
	Refused	89.4 (2223)	4.3 (106)	6.4 (158)	
Education	No HS	80.1 (1583)	5.2 (102)	14.8 (292)	<0.0001
	HS or GED	86.3 (4375)	5.1 (260)	8.5 (433)	
	Some college	89.7 (4969)	5.1 (284)	5.2 (286)	
	College degree+	93.4 (6918)	3.9 (290)	2.7 (201)	
Health Insurance	Yes	89.5 (16656)	4.5 (836)	6.1 (1126)	<0.0001

	No	86.4 (1181)	7.3 (100)	6.3 (86)	
Population Density	Rural	91.0 (1859)	4.1 (84)	4.9 (101)	0.0525
	Mixed	90.0 (1843)	4.4 (90)	5.6 (115)	
	Urban	88.9 (12342)	4.8 (667)	6.3 (874)	
Alcohol Consumption	Non-drinker	88.0 (5818)	4.7 (339)	7.3 (497)	<0.0001
	Moderate	91.4 (6697)	4.5 (320)	4.1 (361)	
	Heavy	89.0 (5109)	6.0 (273)	5.0 (333)	
Smoking	Never	92.8 (8887)	3.4 (329)	3.8 (366)	<0.0001
	Past	87.7 (6628)	5.3 (401)	7.0 (529)	
	Current	81.5 (2271)	7.3 (204)	11.2 (313)	
Physical Activity (rigorous)	0 times/week	87.4 (5818)	5.1 (339)	7.5 (497)	<0.0001
	1-3 times/week	90.8 (6697)	4.3 (320)	4.9 (361)	
	4+ times/week	89.4 (5109)	4.8 (273)	5.8 (333)	
Relationship Status	Married	91.0 (10950)	4.2 (501)	4.9 (588)	<0.0001
	Single	87.3 (967)	6.5 (72)	6.2 (69)	
	Widowed	86.4 (2998)	4.7 (163)	8.9 (308)	
	Divorced	87.3 (2556)	5.7 (168)	7.0 (205)	
	Other	83.6 (383)	7.2 (33)	9.2 (42)	
BMI	Underweight	89.0 (170)	3.1 (6)	7.9 (15)	0.0061
	Normal	90.3 (4333)	4.3 (207)	5.4 (257)	
	Overweight	89.7 (6419)	4.7 (335)	5.6 (404)	
	Obese	88.3 (6810)	4.9 (378)	6.8 (522)	
Diabetes	Yes	83.7 (3147)	5.4 (202)	10.9 (411)	<0.0001
	No	90.7 (14051)	4.4 (687)	4.9 (756)	
Hypertension	Yes	87.4 (9832)	5.0 (558)	7.6 (858)	<0.0001
	No	91.6 (7979)	4.3 (377)	4.1 (353)	
Hyperlipidemia	Yes	88.1 (9749)	4.8 (532)	7.1 (784)	<0.0001
	No	90.9 (7457)	4.4 (362)	4.7 (387)	
History of Heart Disease	Yes	84.6 (2608)	5.0 (154)	10.4 (322)	<0.0001
	No	90.2 (14942)	4.6 (761)	5.2 (869)	
Stroke	Yes	84.4 (3144)	5.8 (215)	9.8 (365)	<0.0001
	No	90.4 (14710)	4.4 (722)	5.2 (847)	
Mean ± SD					
Hemoglobin (g/dL)		13.7 ± 1.4	13.6 ± 1.5	13.5 ± 1.6	<0.0001
Depression (score ranges 0-100)		54.3 ± 8.1	52.7 ± 9.4	53.0 ± 9.8	<0.0001
Stress Level (score ranges 0-16)		3.1 ± 2.8	3.7 ± 3.1	3.7 ± 3.3	<0.0001

*P-values were based on chi-square test or analysis of variance.

*Population density was defined as rural if city of residence was <25% urban, mixed if 25-75% urban, and urban if >75% urban.

*Alcohol consumption was classified as non-drinker if participants consumed no alcohol, moderate if women consumed 0-7 drinks/week or men consumed 0-14 drinks/week, and heavy if 7+ drinks/week for women or 14+ drinks/week for men

*BMI (kg/m²) was classified as underweight if <18.5, normal if 18.5-24.9, overweight if 25-29.9, and obese if >30

*Diabetes is defined as having a fasting glucose level of more than 126 mg/dL, having a non-fasting glucose level greater than 200 mg/dL, or taking medicine or insulin for diabetes.

*Hypertension is defined as having systolic blood pressure of 140 mmHg or greater, diastolic blood pressure of 90 mm Hg or greater, or self-reporting hypertension, confirmed by medication use.

*Hyperlipidemia is defined as having a total cholesterol level of 240 mg/dL or greater, a low-density lipoprotein cholesterol level of 160 mg/dL or greater, a high-density lipoprotein cholesterol level of 40 mg/dL or lower, or using lipid-lowering medication.

*Stroke occurring at any point before cognitive impairment.

4.2 Cox Regression Models and Hazard Ratios

We obtained four survival models: a crude model and an adjusted model, both for African-American and for white participants.

African-American, Crude Model

$$\text{Log}(h(t)) = -0.06561(\text{tooth loss}_{1-16}) + 0.39814(\text{tooth loss}_{17-32}) + 0.21980(\text{stroke}) + 0.05488(\text{tooth loss}_{1-16})(\text{stroke}) + -0.06203(\text{tooth loss}_{17-32})(\text{stroke})$$

Table 4.2 Modification of the Effect of Tooth Loss on Cognitive Impairment by Stroke (African American)

	0 teeth lost HR (95% CI)	1-16 teeth lost HR (95% CI)	HRs (95% CI) for tooth loss within stroke strata
No stroke (incident or prevalent)	1.000	0.936 (0.760-1.154)	0.936 (0.760-1.154)
Stroke (incident or prevalent)	1.246 (1.128-1.376)	1.233 (0.910-1.67)	0.989 (0.725-1.351)

Measure of effect modification on additive scale: RERI (95% CI) = 0.051 (-0.395-0.496)

Measure of effect modification on multiplicative scale: ratio of HRs (95% CI) = 1.056 (0.726-1.537); *P* = 0.774

Hazard ratios are unadjusted.

Table 4.3 Modification of the Effect of Tooth Loss on Cognitive Impairment by Stroke (African American)

	0 teeth lost HR (95% CI)	17-32 teeth lost HR (95% CI)	HRs (95% CI) for tooth loss within stroke strata
No stroke (incident or prevalent)	1.000	1.489 (1.282-1.729)	1.489 (1.282-1.729)
Stroke (incident or prevalent)	1.246 (1.128-1.376)	1.744 (1.432-2.23)	1.399 (1.135-1.725)

Measure of effect modification on additive scale: RERI (95% CI) = 0.005 (-0.238-0.248)

Measure of effect modification on multiplicative scale: ratio of HRs (95% CI) = 0.940 (0.727-1.215); $P = 0.6359$

Hazard ratios are unadjusted.

*Type 3 analysis of results indicated a p-value of 0.845 for overall interaction between tooth loss and stroke on effect on cognitive decline on the multiplicative scale.

$$\text{Log}(h(t)) = -0.050(\text{tooth loss}_{1-16}) + 0.377(\text{tooth loss}_{17-32}) + 0.215(\text{stroke})$$

Table 4.4 Effect of Tooth Loss on Cognitive Impairment (African American)

	Hazard Ratio (95% CI)	P-Value
Test for Trend	1.179 (1.109-1.253)	<0.0001
1-16 Teeth Lost*	0.951 (0.799-1.133)	0.5768
17-32 Teeth Lost*	1.458 (1.286-1.652)	<0.0001

Hazard ratios adjusted for stroke.

*0 teeth lost as reference category

Among African-Americans, stroke was not found to be an effect modifier to the relationship between tooth loss and cognitive decline on the additive or the multiplicative scale in the crude model. Overall, it was found that tooth loss due to gum disease was associated with an elevated risk of cognitive decline, with each increase in level of tooth loss presenting an 17.9% increase in rate of cognitive decline. Those who lost 1-16 teeth

due to gum disease did not see a significant difference in rate of cognitive decline, compared with those who lost no teeth due to gum disease, while those who lost 17-32 teeth had a 45.8% elevation in risk of cognitive decline, compared with those who lost no teeth.

African-American, Adjusted Model

$$\begin{aligned} \text{Log}(h(t)) = & -0.03216(\text{tooth loss}_{1-16}) + 0.04123(\text{tooth loss}_{17-32}) + 0.12181(\text{stroke}) + \\ & 0.28494(\text{tooth loss}_{1-16})(\text{stroke}) + 0.04463(\text{tooth loss}_{17-32})(\text{stroke}) - 0.52359(\text{female}) - \\ & 0.33696(\text{age}_{45-54}) + 0.61178(\text{age}_{65-74}) + 0.95819(\text{age}_{75-84}) + 1.41677(\text{age}_{85+}) - \\ & 0.25115(\text{income}_{\$20K-\$34K}) - 0.29027(\text{income}_{\$35K-\$74K}) - 0.41362(\text{income}_{\$75K+}) - \\ & 0.08342(\text{income}_{\text{refused}}) - 0.31451(\text{education}_{\text{high school}}) - 0.32875(\text{education}_{\text{some college}}) - \\ & 0.48697(\text{education}_{\text{college grad}}) + 0.18037(\text{no insurance}) + 0.25531(\text{urban}_{\text{mixed}}) + \\ & 0.20501(\text{urban}_{\text{rural}}) - 0.40787(\text{alcohol}_{\text{heavy}}) - 0.14596(\text{alcohol}_{\text{moderate}}) - \\ & 0.19835(\text{smoke}_{\text{current}}) - 0.14100(\text{smoke}_{\text{past}}) - 0.07206(\text{exercise}_{1-3/\text{week}}) + \\ & 0.08809(\text{exercise}_{4+/\text{week}}) - 0.10693(\text{BMI}_{\text{underweight}}) - 0.11314(\text{BMI}_{\text{overweight}}) - \\ & 0.19416(\text{BMI}_{\text{obese}}) + 0.00505(\text{diabetes}) - 0.01714(\text{hemoglobin}) + \\ & 0.00420(\text{hyperlipidemia}) + 0.09995(\text{heart disease}) - 0.01272(\text{depression}) \end{aligned}$$

Table 4.5 Modification of the Effect of Tooth Loss on Cognitive Impairment by Stroke (African American)

	0 teeth lost HR (95% CI)	1-16 teeth lost HR (95% CI)	HRs (95% CI) for tooth loss within stroke strata
No stroke (incident or prevalent)	1.000	0.968 (0.747-1.256)	0.968 (0.747-1.256)
Stroke (incident or prevalent)	1.130 (0.987-1.292)	1.454 (0.987-1.293)	1.288 (0.893-1.856)
Measure of effect modification on additive scale: RERI (95% CI) = 0.230 (-0.120-0.579)			
Measure of effect modification on multiplicative scale: ratio of HRs (95% CI) = 1.329 (0.850-2.080); <i>P</i> = 0.212			

Hazard ratios are adjusted for gender, age, income, education, health insurance, population density, alcohol consumption, smoking status, exercise, BMI, diabetes, hemoglobin count, hyperlipidemia, history of heart disease, and depression level.

Table 4.6 Modification of the Effect of Tooth Loss on Cognitive Impairment by Stroke (African American)

	0 teeth lost HR (95% CI)	17-32 teeth lost HR (95% CI)	HRs (95% CI) for tooth loss within stroke strata
No stroke (incident or prevalent)	1.000	1.042 (0.865-1.255)	1.042 (0.865-1.255)
Stroke (incident or prevalent)	1.130 (0.987-1.292)	1.231 (0.931-1.627)	1.090 (0.815-1.457)

Measure of effect modification on additive scale: RERI (95% CI) = 0.042 (-0.270-0.353)

Measure of effect modification on multiplicative scale: ratio of HRs (95% CI) = 1.046 (0.743-1.471); $P = 0.785$

Hazard ratios are adjusted for gender, age, income, education, health insurance, population density, alcohol consumption, smoking status, exercise, BMI, diabetes, hemoglobin count, hyperlipidemia, history of heart disease, and depression level.

*Type 3 analysis of results indicated a p-value of 0.455 for overall interaction between tooth loss and stroke on effect on cognitive decline on the multiplicative scale.

$$\begin{aligned}
 \text{Log}(h(t)) = & 0.04657(\text{tooth loss}_{1-16}) + 0.05390(\text{tooth loss}_{17-32}) + 0.14578(\text{stroke}) - \\
 & 0.52338(\text{female}) - 0.33392(\text{age}_{45-54}) + 0.61150(\text{age}_{65-74}) + 0.95592(\text{age}_{75-84}) + \\
 & 1.41808(\text{age}_{85+}) - 0.25186(\text{income}_{\$20K-\$34K}) - 0.29113(\text{income}_{\$35K-\$74K}) - \\
 & 0.41279(\text{income}_{\$75K+}) - 0.08369(\text{income}_{\text{refused}}) - 0.31831(\text{education}_{\text{high school}}) - \\
 & 0.33152(\text{education}_{\text{some college}}) - 0.49064(\text{education}_{\text{college grad}}) + 0.17840(\text{no insurance}) + \\
 & 0.24922(\text{urban}_{\text{mixed}}) + 0.20490(\text{urban}_{\text{rural}}) - 0.40149(\text{alcohol}_{\text{heavy}}) - 0.1466(\text{alcohol}_{\text{moderate}}) \\
 & - 0.19559(\text{smoke}_{\text{current}}) - 0.14301(\text{smoke}_{\text{past}}) - 0.07026(\text{exercise}_{1-3/\text{week}}) + \\
 & 0.08859(\text{exercise}_{4+/\text{week}}) - 0.10829(\text{BMI}_{\text{underweight}}) - 0.11367(\text{BMI}_{\text{overweight}}) - \\
 & 0.19416(\text{BMI}_{\text{obese}}) + 0.00510(\text{diabetes}) - 0.01710(\text{hemoglobin}) + \\
 & 0.00331(\text{hyperlipidemia}) + 0.09968(\text{heart disease}) - 0.01273(\text{depression})
 \end{aligned}$$

Table 4.7 Effect of Tooth Loss on Cognitive Impairment (African American)

	Hazard Ratio (95% CI)	P-Value
Test for Trend	1.029 (0.953-1.113)	0.464
1-16 Teeth Lost*	1.049 (0.845-1.301)	0.666
17-32 Teeth Lost*	1.055 (0.898-1.241)	0.514

Hazard ratio adjusted for gender, age, income, education, health insurance, population density, alcohol consumption, smoking status, exercise, BMI, diabetes, hemoglobin count, hyperlipidemia, history of heart disease, depression level, and stroke.

*0 teeth lost as reference category

After adjusting for gender, age, income, education, health insurance, population density, alcohol consumption, smoking status, exercise, BMI, diabetes, hemoglobin count, hyperlipidemia, history of heart disease, depression level, stroke was not found to be an effect modifier to the relationship between tooth loss and cognitive decline on the additive or the multiplicative scale, among African Americans. Overall, it was found that those who lost teeth due to gum disease were not at a significantly elevated risk of cognitive decline compared to those who did not.

White, Crude Model

$$\text{Log}(h(t)) = 0.20877(\text{tooth loss}_{1-16}) + 0.52904(\text{tooth loss}_{17-32}) + 0.17333(\text{stroke}) - 0.03030(\text{tooth loss}_{1-16})(\text{stroke}) - 0.03884(\text{tooth loss}_{17-32})(\text{stroke})$$

Table 4.8 Modification of the Effect of Tooth Loss on Cognitive Impairment by Stroke (White)

	0 teeth lost HR (95% CI)	1-16 teeth lost HR (95% CI)	HRs (95% CI) for tooth loss within stroke strata
No stroke (incident or prevalent)	1.000	1.232 (0.994-1.527)	1.232 (0.994-1.527)
Stroke (incident or prevalent)	1.189 (1.078-1.312)	1.423 (0.963-2.099)	1.195 (0.804-1.778)

Measure of effect modification on additive scale: RERI (95% CI) = 0.002 (-0.431-0.435)
 Measure of effect modification on multiplicative scale: ratio of HRs (95% CI) = 0.970 (0.656-1.619); $P = 0.895$
 Hazard ratios are unadjusted.

Table 4.9 Modification of the Effect of Tooth Loss on Cognitive Impairment by Stroke (White)

	0 teeth lost HR (95% CI)	17-32 teeth lost HR (95% CI)	HRs (95% CI) for tooth loss within stroke strata
No stroke (incident or prevalent)	1.000	1.697 (1.403-2.054)	1.697 (1.403-2.054)
Stroke (incident or prevalent)	1.189 (1.078-1.312)	1.942 (1.498-2.516)	1.633 (1.247-2.138)

Measure of effect modification on additive scale: RERI (95% CI) = 0.029 (0.283-0.340)
 Measure of effect modification on multiplicative scale: ratio of HRs (95% CI) = 0.962 (0.691-1.338); $P = 0.818$
 Hazard ratios are unadjusted.

*Type 3 analysis of results indicated a p-value of 0.9671 for overall interaction between tooth loss and stroke on effect on cognitive decline on the multiplicative scale.

$$\text{Log}(h(t)) = 0.20180(\text{tooth loss}_{1-16}) + 0.51669(\text{tooth loss}_{17-32}) + 1.16883(\text{stroke})$$

Table 4.10 Effect of Tooth Loss on Cognitive Impairment (White)

	Hazard Ratio (95% CI)	P-Value
Test for Trend	1.285 (1.192-1.385)	<0.001
1-16 Teeth Lost*	1.224 (1.012-1.480)	0.0376
17-32 Teeth Lost*	1.676 (1.431-1.965)	<0.0001

Hazard ratios adjusted for stroke.

*0 teeth lost as reference category

Among white Americans, stroke was not found to be an effect modifier to the relationship between tooth loss and cognitive decline on the additive or the multiplicative

scale in the crude model. Overall, it was found that tooth loss due to gum disease was associated with an elevated risk of cognitive decline, with each increase in level of tooth loss presenting an 28.5% increase in rate of cognitive decline. Those who lost 1-16 teeth due to gum disease had a 22.4% elevation in rate of cognitive decline, compared with those who lost no teeth due to gum disease, while those who lost 17-32 teeth had a 66.8% elevation in risk of cognitive decline, compared with those who lost no teeth.

White, Adjusted Model

$$\begin{aligned} \text{Log}(h(t)) = & 0.13464(\text{tooth loss}_{1-16}) + 0.13673(\text{tooth loss}_{17-32}) + 0.05889(\text{stroke}) + \\ & 0.03511(\text{tooth loss}_{1-16})(\text{stroke}) + 0.09683(\text{tooth loss}_{17-32})(\text{stroke}) - 0.52348(\text{female}) - \\ & 0.45437(\text{age}_{45-54}) + 0.62999(\text{age}_{65-74}) + 1.25146(\text{age}_{75-84}) + 1.57478(\text{age}_{85+}) - \\ & 0.18594(\text{income}_{\$20K-\$34K}) - 0.23108(\text{income}_{\$35K-\$74K}) - 0.35394(\text{income}_{\$75K+}) - \\ & 0.28977(\text{income}_{\text{refused}}) - 0.34585(\text{education}_{\text{high school}}) - 0.50740(\text{education}_{\text{some college}}) - \\ & 0.54493(\text{education}_{\text{college grad}}) - 0.00869(\text{urban}_{\text{mixed}}) + 0.12848(\text{urban}_{\text{rural}}) - \\ & 0.07599(\text{alcohol}_{\text{heavy}}) - 0.12392(\text{alcohol}_{\text{moderate}}) + 0.14713(\text{smoke}_{\text{current}}) + \\ & 0.05556(\text{smoke}_{\text{past}}) - 0.01310(\text{exercise}_{1-3/\text{week}}) - 0.01511(\text{exercise}_{4+/\text{week}}) + \\ & 0.15484(\text{diabetes}) - 0.07661(\text{hemoglobin}) - 0.01365(\text{hyperlipidemia}) + 0.06074(\text{heart} \\ & \text{disease}) - 0.0001114(\text{depression}) + 0.02444(\text{stress}) \end{aligned}$$

Table 4.11 Modification of the Effect of Tooth Loss on Cognitive Impairment by Stroke (White)

	0 teeth lost HR (95% CI)	1-16 teeth lost HR (95% CI)	HRs (95% CI) for tooth loss within stroke strata
No stroke (incident or prevalent)	1.000	1.144 (0.885-1.480)	1.144 (0.885-1.480)
Stroke (incident or prevalent)	1.061 (0.941-1.196)	1.257 (0.792-1.994)	1.185 (0.742-1.894)
Measure of effect modification on additive scale: RERI (95% CI) = 0.041 (-0.471-0.554)			

Measure of effect modification on multiplicative scale: ratio of HRs (95% CI) = 1.036 (0.607-1.767); $P = 0.897$

Hazard ratios are adjusted for gender, age, income, education, population density, alcohol consumption, smoking status, exercise, diabetes, hemoglobin count, hyperlipidemia, history of heart disease, depression level, and stress level.

Table 4.12 Modification of the Effect of Tooth Loss on Cognitive Impairment by Stroke (White)

	0 teeth lost HR (95% CI)	17-32 teeth lost HR (95% CI)	HRs (95% CI) for tooth loss within stroke strata
No stroke (incident or prevalent)	1.000	1.147 (0.888-1.481)	1.147 (0.888-1.481)
Stroke (incident or prevalent)	1.061 (0.941-1.196)	1.340 (0.953-1.883)	1.263 (0.891-1.790)

Measure of effect modification on additive scale: RERI (95% CI) = 0.109 (-0.266-0.485)

Measure of effect modification on multiplicative scale: ratio of HRs (95% CI) = 1.102 (0.717-1.693); $P = 0.659$

Hazard ratios are adjusted for gender, age, income, education, population density, alcohol consumption, smoking status, exercise, diabetes, hemoglobin count, hyperlipidemia, history of heart disease, depression level, and stress level.

*Type 3 analysis of results indicated a p-value of 0.902 for overall interaction between tooth loss and stroke on effect on cognitive decline on the multiplicative scale.

$$\begin{aligned}
 \text{Log}(h(t)) = & 0.14244(\text{tooth loss}_{1-16}) + 0.16837(\text{tooth loss}_{17-32}) + 0.06763(\text{stroke}) - \\
 & 0.52349(\text{female}) - 0.45323(\text{age}_{45-54}) + 0.63001(\text{age}_{65-74}) + 1.25191(\text{age}_{75-84}) + \\
 & 1.57322(\text{age}_{85+}) - 0.18643(\text{income}_{\$20K-\$34K}) - 0.23141(\text{income}_{\$35K-\$74K}) - \\
 & 0.35435(\text{income}_{\$75K+}) - 0.29058(\text{income}_{\text{refused}}) - 0.34720(\text{education}_{\text{high school}}) - \\
 & 0.50907(\text{education}_{\text{some college}}) - 0.54645(\text{education}_{\text{college grad}}) - 0.00881(\text{urban}_{\text{mixed}}) + \\
 & 0.12815(\text{urban}_{\text{rural}}) - 0.07703(\text{alcohol}_{\text{heavy}}) - 0.12369(\text{alcohol}_{\text{moderate}}) + \\
 & 0.1466(\text{smoke}_{\text{current}}) + 0.05582(\text{smoke}_{\text{past}}) - 0.01280(\text{exercise}_{1-3/\text{week}}) - \\
 & 0.01459(\text{exercise}_{4+/\text{week}}) + 0.15463(\text{diabetes}) - 0.07665(\text{hemoglobin}) -
 \end{aligned}$$

0.01341(hyperlipidemia) + 0.06039(heart disease) – 0.0001757(depression) +
0.02459(stress)

Table 4.13 Effect of Tooth Loss on Cognitive Impairment (White)

	Hazard Ratio (95% CI)	P-Value
Test for Trend	1.097 (0.996-1.209)	0.0607
1-16 Teeth Lost*	1.153 (0.916-1.452)	0.2260
17-32 Teeth Lost*	1.183 (0.960-1.459)	0.1151

Hazard ratios adjusted for gender, age, income, education, population density, alcohol consumption, smoking status, exercise, diabetes, hemoglobin count, hyperlipidemia, history of heart disease, depression level, stress level, and stroke.

*0 teeth lost as reference category

After adjusting for gender, age, income, education, population density, alcohol consumption, smoking status, exercise, diabetes, hemoglobin count, hyperlipidemia, history of heart disease, depression level, and stress level, stroke was not found to be an effect modifier to the relationship between tooth loss and cognitive decline on the additive or the multiplicative scale, among white Americans. Overall, it was found that those who lost teeth due to gum disease were not at a significantly elevated risk of cognitive decline compared to those who did not.

4.3 Testing Proportional Hazards Assumptions

We computed Kaplan Meier curves and plotted log cumulative hazards to assess whether proportional hazards assumptions were met for categorical variables, and determined that this assumption was, in fact, met for all categorical variables. We constructed Schoenfeld residual curves to assess proportionality of hazards for continuous variables and found that this assumption was also met for all continuous variables.

CHAPTER V

DISCUSSION

5.1 Study Findings

Tooth loss was positively associated with cognitive decline among African Americans only in the model adjusted for age and gender, while in white Americans, tooth loss and cognitive decline were positively associated in models adjusted for age and gender and age, gender, and demographic traits. In other models, further adjustment for lifestyle variables, and/or health characteristics, the associations were attenuated, but remained positive. The association between tooth loss and cognitive decline was stronger among whites than African Americans in all models. Interaction between tooth loss and stroke was not significant in any model, on the multiplicative scale or the additive scale. No previous studies have examined stroke as an effect modifier to the relationship between tooth loss and cognitive decline, but many studies have assessed the relationship between tooth loss and cognitive decline and found a positive association.

Tooth loss was inversely associated with mean learning score, and delay recall score after multivariable adjustment in a cross-sectional analysis conducted among participants of the REGARDS study (Matthews et al, 2011). Batty et al found that having no teeth was associated with 1.48 times the risk of dementia and 1.39 times the risk of cognitive decline, among patients with type II diabetes (Batty et al, 2013). Ide et

al found an increased risk of cognitive decline associated with periodontitis among individuals with Alzheimer's disease (Ide et al, 2016). A systematic review and a meta-analysis both demonstrated a positive association between periodontal disease and Alzheimer's disease (Kalakonda et al, 2016; Leira et al, 2017). Several case-control studies found a positive association between markers of periodontal disease and Alzheimer's disease (Farhad et al, 2014; Noble et al, 2014; de Souza Rolim et al, 2014; Cestari et al, 2016). Using a cross-sectional design, Martande et al found that in patients with Alzheimer's disease, periodontal disease was linked to level of cognitive functioning, and Kamer et al uncovered an association between periodontal disease and brain amyloid load (Martande et al, 2014; Kamer et al, 2015). This study did not find sufficient evidence to suggest a positive relationship between tooth loss and cognitive decline, contrary to evidence in the literature. In the previous analysis conducted among REGARDS study participants relating cognition and tooth loss, cognition was assessed as mean learning and delay recall scores, both of which are continuous variables. This would give good power to indicate differences across tooth loss categories (Matthews et al, 2011). In contrast, the binary outcome was incident cognitive impairment assessed by the 6-item screener, which would provide lower power. The screener is also more subject to misclassification than the mean learning and delay recall scores. Lower specificity would result in more false positives, which could attenuate the results. However, the direction of the associations in the present analysis, though not statistically significant, were qualitatively consistent with the findings in the earlier analysis. Matthews et al used a cross-sectional analysis as well, compared to the longitudinal design used in this study. Cognitive decline may result in changes to lifestyle or diet which lead to tooth loss,

which could contribute to the positive association found in many case-control and cross-sectional studies (Matthews et al, 2011; Farhad et al, 2014; Noble et al, 2014; de Souza Rolim et al, 2014; Cestari et al, 2016; Martande et al, 2014; Kamer et al, 2015). It is also possible that the relationship between tooth loss and cognitive decline is non-linear. Linear regression would then mischaracterize the relationship and categorizing tooth loss would result in a loss of power. Other studies examined the relationship between tooth loss and cognitive decline among high-risk groups, such as those with Type II diabetes or Alzheimer's disease (Batty et al, 2013; Ide et al, 2016; Cestari et al, 2016; Martande et al, 2014). This study examined the relationship between tooth loss and cognitive decline among a sample more representative of the general population, where the association may not be as strong as it is among high-risk groups. Other longitudinal studies did not examine the relationship between tooth loss and cognitive specifically, but other similar exposures, such as periodontal disease and dental interventions, and other similar outcomes, such as Alzheimer's disease and brain amyloid load (de Souza Rolim et al, 2014; Kamer et al, 2015; Sochocka et al, 2017; Ide et al, 2016). While there may be a link between periodontal infections and risk of cognitive impairment, the link between tooth loss (categorized as no teeth lost, 1-16 teeth lost, and 17 or more teeth lost) due to periodontal disease and cognitive decline (defined as score < 5 on the six-item cognitive screener used in this study) may not be significant. Periodontal infection can be present without resulting in tooth loss, and score of 4 or less on the six-item cognitive screener used in the REGARDS study does not necessarily mean that an individual has Alzheimer's or dementia.

5.2 Study Strengths

There were several advantages to this particular study. The REGARDS cohort is very large and fairly representative of specific regional (stroke-belt, stroke-buckle, and non-stroke-belt) and racial (African-American and white) groups in the United States. This study used a cohort design, and thus far, few other studies have done so to assess the relationship between periodontal disease and cognition in a non-disease-specific population. The longitudinal nature of the study allows us to establish temporality. We adjusted for a comprehensive set of confounders and made sure to examine the effects of certain sets of confounders separately, beginning with the most obvious confounders (age and gender), followed by demographic traits, then lifestyle factors, then health characteristics, which were the most likely set of potential confounders to lie upon the causal pathway. The assessment of cognitive impairment used was found to have a high sensitivity and specificity when compared to clinical diagnoses. Incident stroke was validated using medical records, and the questionnaire used to assess prevalent stroke was found to have a high positive predictive value and negative predictive value when compared with clinical diagnoses. Participants also identified proxies at baseline, in order to limit loss to follow-up due to stroke, cognitive impairment, or any other event that could influence the participant's ability to complete a telephone interview.

5.3 Study Limitations

Information bias was possible for assessment of outcome, exposure, and stroke at baseline in this study. Participants are likely to know how many teeth they have lost, but they may not necessarily know whether or not they have lost teeth due to gum disease or some other cause. Similarly, stroke at baseline is classified at present if participants have

ever suffered a stroke or any of a number of stroke symptoms. Participants are unlikely to misreport a stroke but may be unsure whether or not they have experienced stroke symptoms. Participants have the potential to cheat on the cognitive screener by writing words that they are asked to recall down, and if they are not feeling well on the day of the screening, this could also influence their cognitive score. The cognitive screener used was found to have a high specificity and sensitivity compared with clinical diagnoses when cognitive impairment was defined as a score less than or equal to 3, but we used a score less than or equal to 4 as our cutoff point in this study, as this is consistent with the cutoff used in other REGARDS studies. While a number of confounders were adjusted for, residual confounding is still possible. We did not adjust for diet, as it was not found to substantially modify the relationship between tooth loss and stroke, is very difficult to validly assess, and could potentially lie on the causal pathway between tooth loss and cognitive decline (Joshipura et al, 2003).

5.4 Study Implications

These findings indicate that, for both African Americans and white Americans, there is not sufficient evidence to suggest that stroke is an effect modifier of the relationship between tooth loss and incident cognitive impairment. The results suggested that tooth loss at baseline was not associated with incident cognitive impairment after controlling for potential confounders among African Americans. Among white Americans the point estimates of the measures of association were consistent with a positive relationship between tooth loss and cognitive decline, and the confidence intervals consisted of mostly positive values. Possible reasons for failing to observe a clear significant association could be that tooth loss is a poor measure of periodontal

disease, which has been related to diminished cognition in other longitudinal studies. It is also possible that measurement error in the definition of the outcome attenuated the association. As tooth loss was found to be linked to cognitive impairment in those with type II diabetes, and other markers of periodontal disease were found to be linked to cognitive decline and related conditions including Alzheimer's disease and dementia, it is still possible that stroke could be an effect modifier in these studies (Batty et al, 2013; de Souza Rolim et al, 2014; Kamer et al, 2015; Sochocka et al, 2017; Ide et al, 2016). For future research, we recommend that stroke be examined as an effect modifier to the relationship between periodontal disease and cognitive decline, dementia, and Alzheimer's disease, particularly in high-risk populations, such as those with type II diabetes. There was also much stronger evidence to support a positive relationship between tooth loss and cognitive decline for white Americans than there was for African Americans, indicating that race may modify this association. Prevention of periodontal disease and tooth loss may pose a potential benefit to preventing cognitive decline among white Americans, while other protective factors, or factors in combination with prevention of periodontal disease, could be more important among African Americans.

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APPENDIX A

COGNITIVE SCREENER

Six item cognitive screener added on 12/18/03

Q: Q11_9

Now I would like to ask you some questions that ask you to use your memory.

- 11.9 I am going to name three objects. Please wait until I say all three words, then repeat them. Remember what they are because I am going to ask you to name them again in a few minutes, but please do not write anything down. Please repeat these words for me:
apple, table, penny.

INTERVIEWER: Did respondent correctly repeat all three words?

1. Yes
2. No

INTERVIEWER: You may repeat the three words, apple, table and penny up to three times if necessary.

CogScore = 0

Q: Q11_10

- 11.10 Now, without looking at a calendar or watch, what year is this?

INTERVIEWER: Current year = CATI SHOWS CURRENT

DAY

1. Respondent answered correctly
2. Respondent answered incorrectly

IF (ANS = 1) CogScore = CogScore + 1

IF (ANS = 2) CogScore = CogScore + 0

Q: Q11_11

- 11.11 Without looking at a calendar or watch, what month is this?

INTERVIEWER: Current month = CATI SHOW CURRENT

MONTH

1. Respondent answered correctly
2. Respondent answered incorrectly

IF (ANS = 1) CogScore = CogScore + 1

IF (ANS = 2) CogScore = CogScore + 0

Q: Q11_12

11.12 Without looking at a calendar or watch, what is the day of the week?

INTERVIEWER: Today is CATI SHOW CURRENT DAY

1. Respondent answered correctly
2. Respondent answered incorrectly

IF (ANS = 1) CogScore = CogScore + 1

IF (ANS = 2) CogScore = CogScore + 0

Q: Q11_13

11.13 What were the three objects I asked you to remember?

Items = Apple, Table, Penny Any order is acceptable

1. Respondent able to remember 1 item
2. Respondent able to remember 2 items
3. Respondent able to remember all 3 items
4. Respondent unable to remember any of the items

INTERVIEWER: Any order is acceptable. Do not prompt

If respondent remembers 0 items CogScore = CogScore + 0

If respondent remembers 1 item CogScore = CogScore + 1

If respondent remembers 2 items CogScore = CogScore + 2

If respondent remembers 3 items CogScore = CogScore + 3

APPENDIX B

STROKE-FREE PHENOTYPE

Q: Q1_1 ++++++

The first set of questions asks about whether you have had a stroke or a mini stroke.

Were you ever told by a physician that you had a stroke?

- 1. Yes
- 2. No
- 8. Don't Know/Not Sure
- 9. Refused

IF (ANS <> 1) SKP Q1_2

Q: Q1_1a ++++++

How many strokes have you had?

___ Enter number of strokes

- 888 Don't Know/Not Sure
- 999 Refused

IF (ANS > 10 AND < 888) REASK

Q: Q1_1b ++++++

IF (Q1_1a = 1) How old were you when you had your stroke?

IF (Q1_1a > 1) How old were you when you had your first stroke?

___ Enter age in years

If not sure, ask for best guess. If not possible to guess exact age use:

- 770 Less than 10 years old
- 771 Between 10 and 19
- 772 Between 20 and 29

773 Between 30 and 39
 774 Between 40 and 49
 775 Between 50 and 59
 776 Between 60 and 69
 777 Between 70 and 79
 778 Between 80 and 89
 779 Between 90 and 99
 780 Over 99
 888 Don't Know/Not Sure
 999 Refused

IF (ANS > RESPAGE) AND IF (ANS < 769) REASK
 IF (Q1_1a = 1) SKP Q1_2

Q: Q1_1c ++++++

How old were you when you had your last stroke?

___ Enter age in years

If not sure, ask for best guess. If not possible to guess exact age use:

770 Less than 10 years old
 771 Between 10 and 19
 772 Between 20 and 29
 773 Between 30 and 39
 774 Between 40 and 49
 775 Between 50 and 59
 776 Between 60 and 69
 777 Between 70 and 79
 778 Between 80 and 89
 779 Between 90 and 99
 780 Over 99
 888 Don't Know/Not Sure
 999 Refused

IF (ANS > RESPAGE) AND IF (ANS < 769) REASK
 SKP Q2_1

Q: Q1_2 ++++++

Were you ever told by a physician that you had a mini stroke or TIA, also known as a
 transient
 ischemic attack?

1. Yes
2. No
8. Don't Know/Not Sure
9. Refused

IF (Q1_1 = 1) SKP Q2_1

Q: Q1_3 ++++++

Have you ever had sudden painless weakness on one side of your body?

1. Yes
2. No
8. Don't Know/Not Sure
9. Refused

Q: Q1_4 ++++++

Have you ever had sudden numbness or a dead feeling on one side of your body?

1. Yes
2. No
8. Don't Know/Not Sure
9. Refused

Q: Q1_5 ++++++

Have you ever had sudden painless loss of vision in one or both eyes?

1. Yes
2. No
8. Don't Know/Not Sure
9. Refused

Q: Q1_6 ++++++

Have you ever suddenly lost one half of your vision?

1. Yes
2. No
8. Don't Know/Not Sure
9. Refused

Q: Q1_7 ++++++

Have you ever suddenly lost the ability to understand what people were saying?

- 1. Yes
- 2. No
- 8. Don't Know/Not Sure
- 9. Refused

Q: Q1_8 ++++++

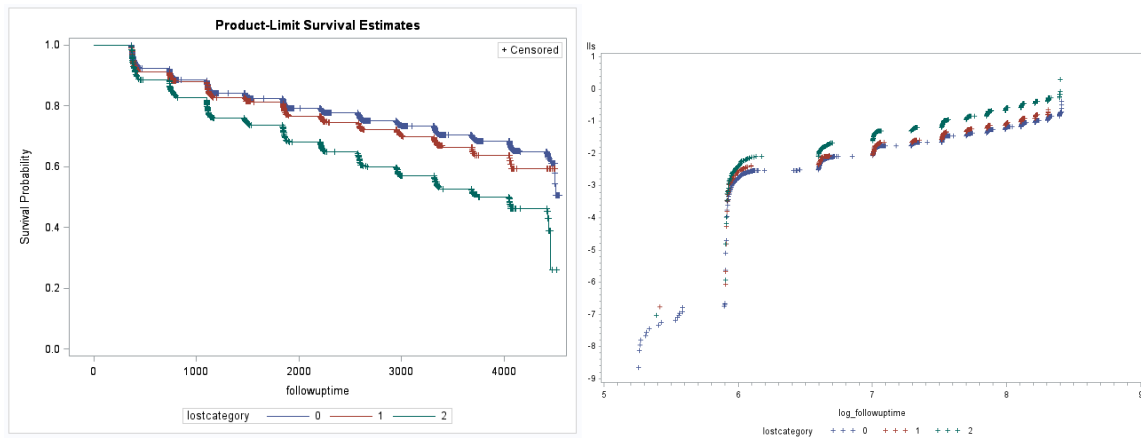
Have you ever suddenly lost the ability to express yourself verbally or in writing?

- 1. Yes
- 2. No
- 8. Don't Know/Not Sure
- 9. Refused

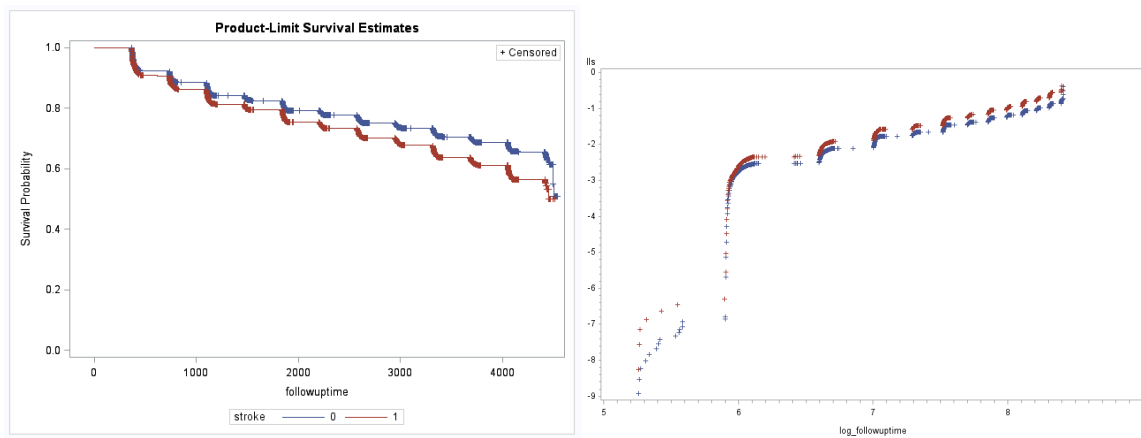
APPENDIX C

ASSESSMENT OF PROPORTIONAL HAZARDS

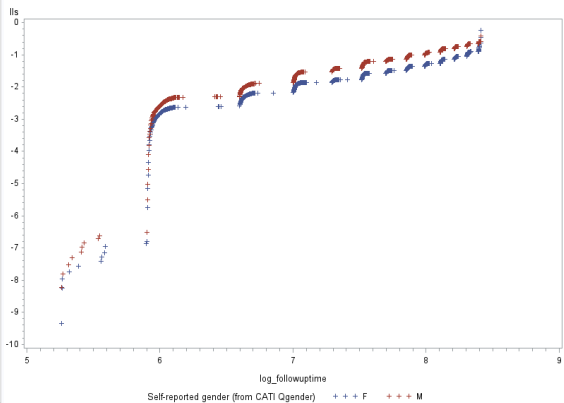
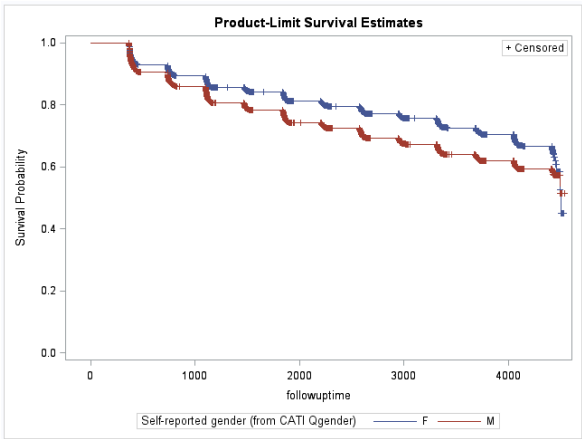
Tooth Loss



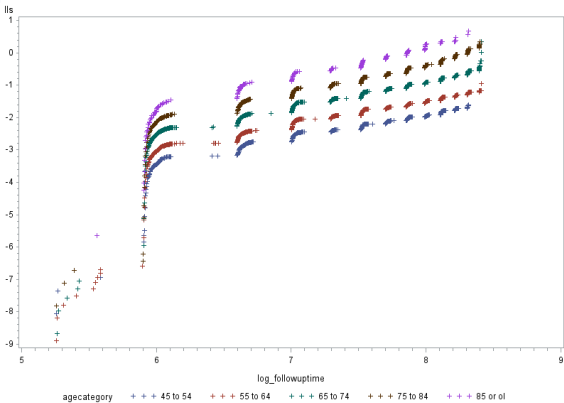
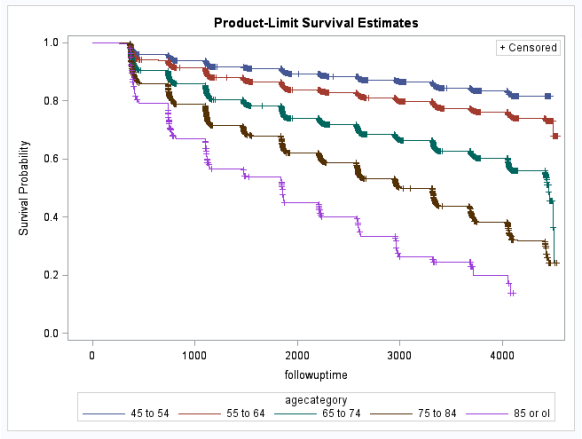
Stroke



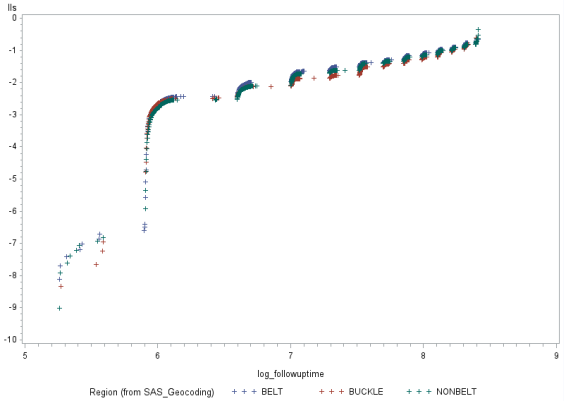
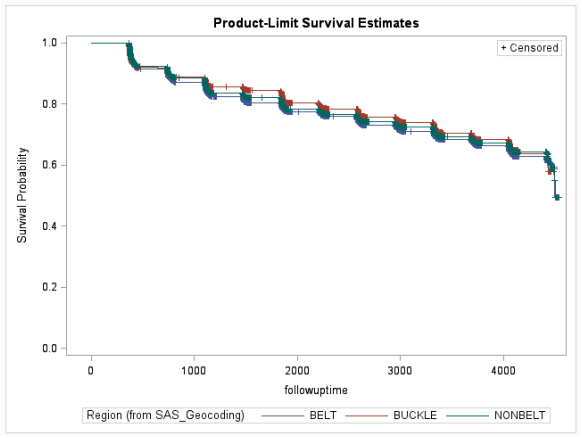
Gender



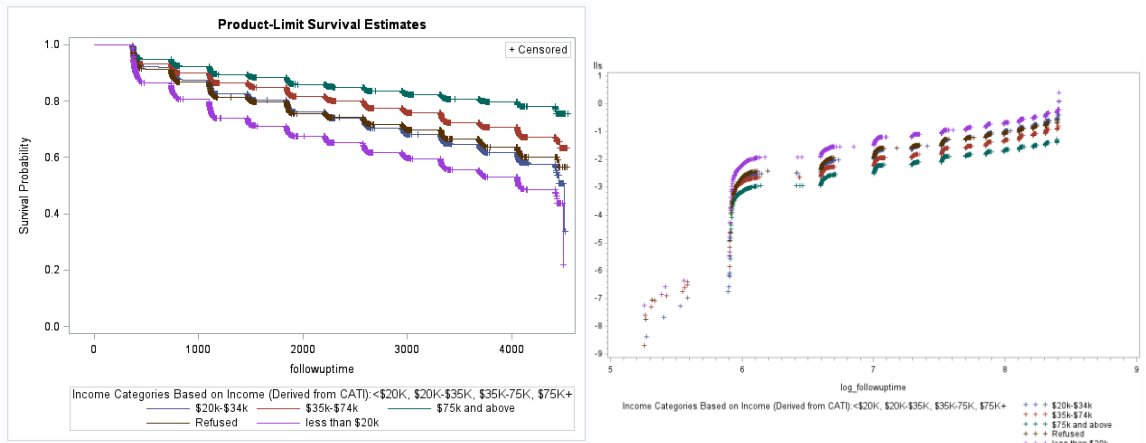
Age



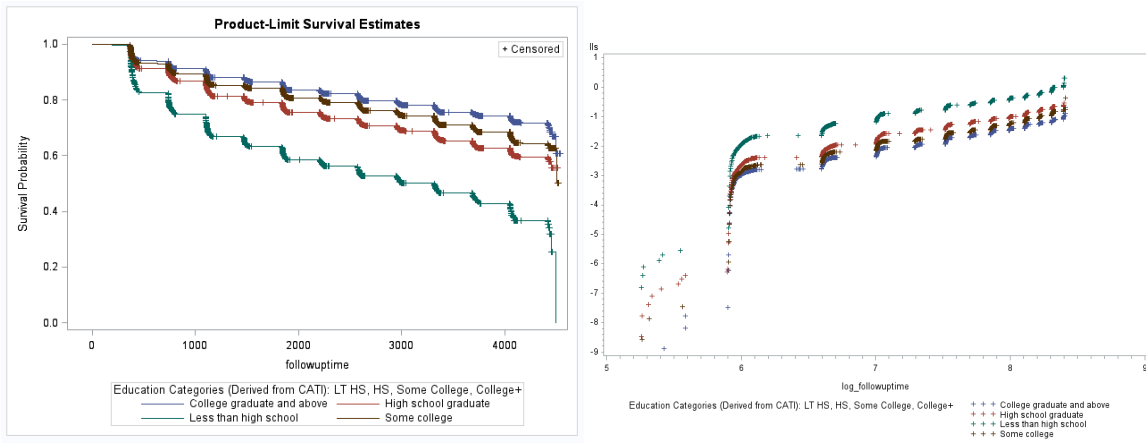
Region



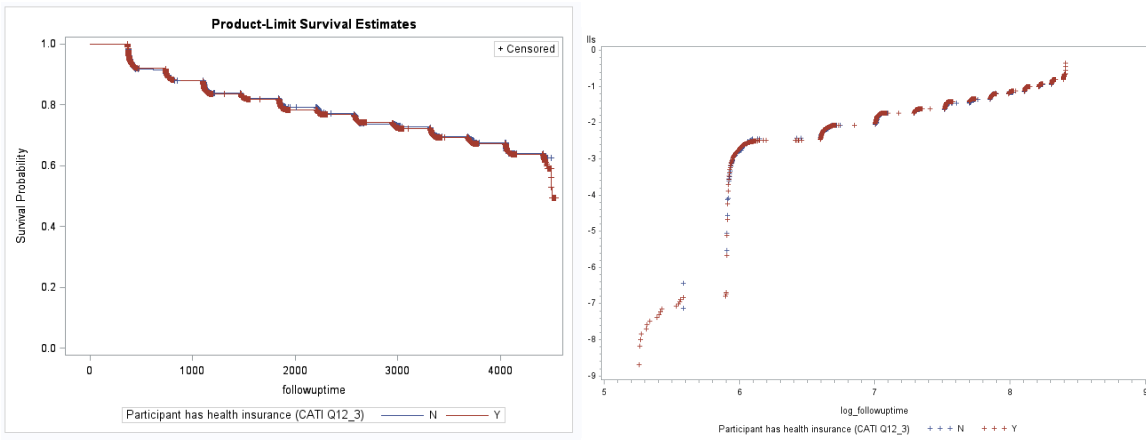
Income



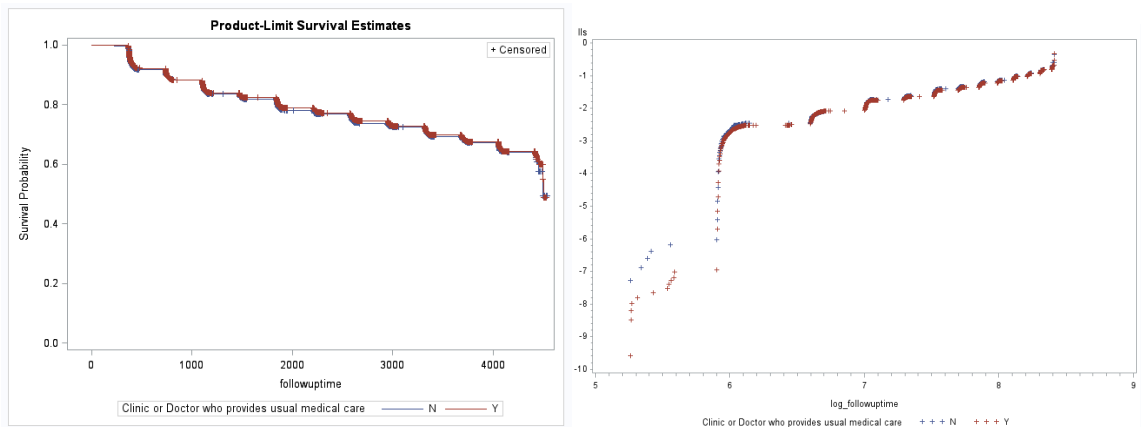
Education



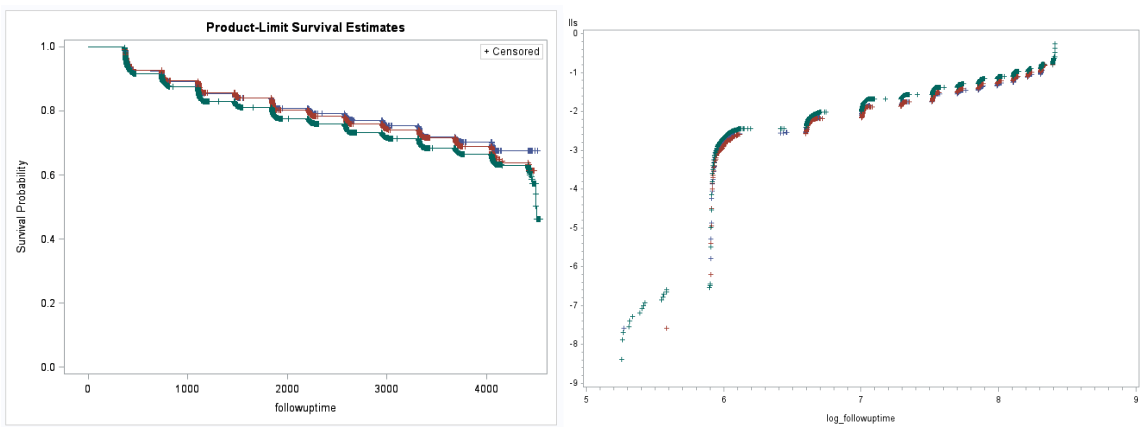
Insurance



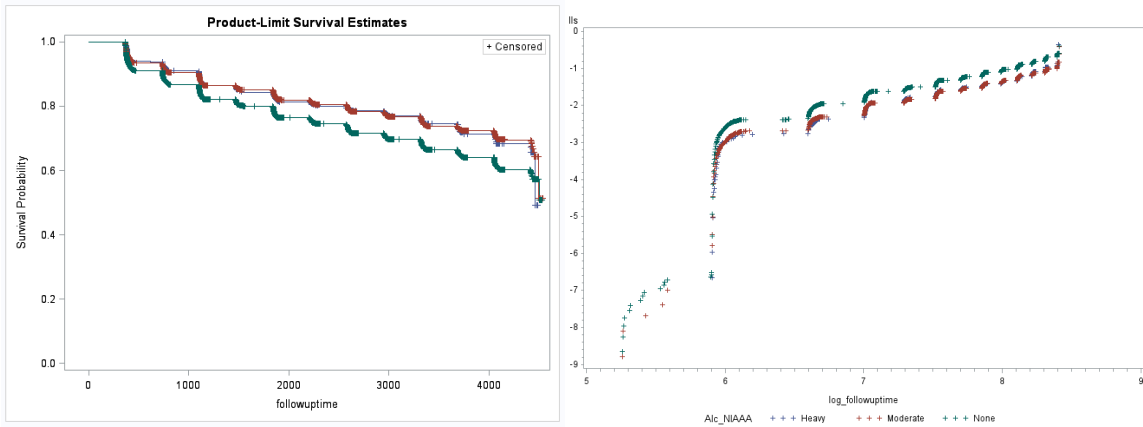
Medical Care



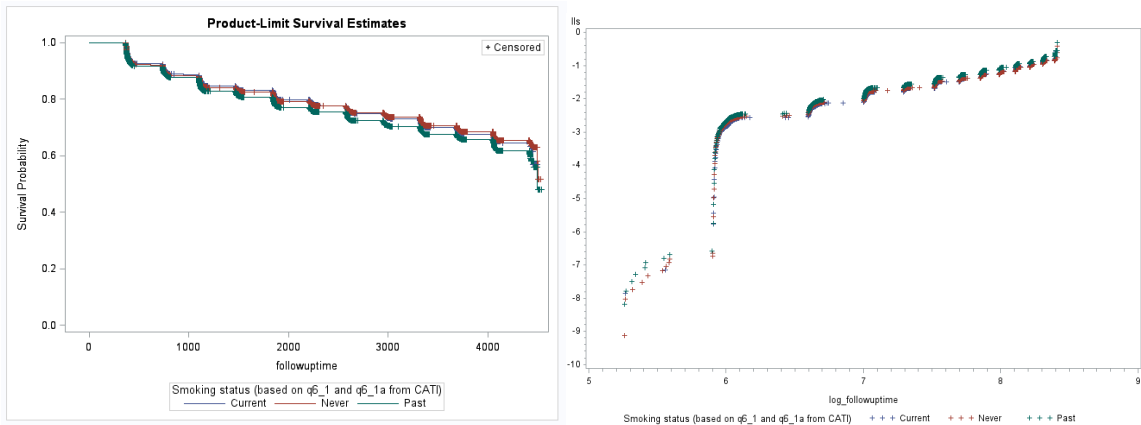
Population Density



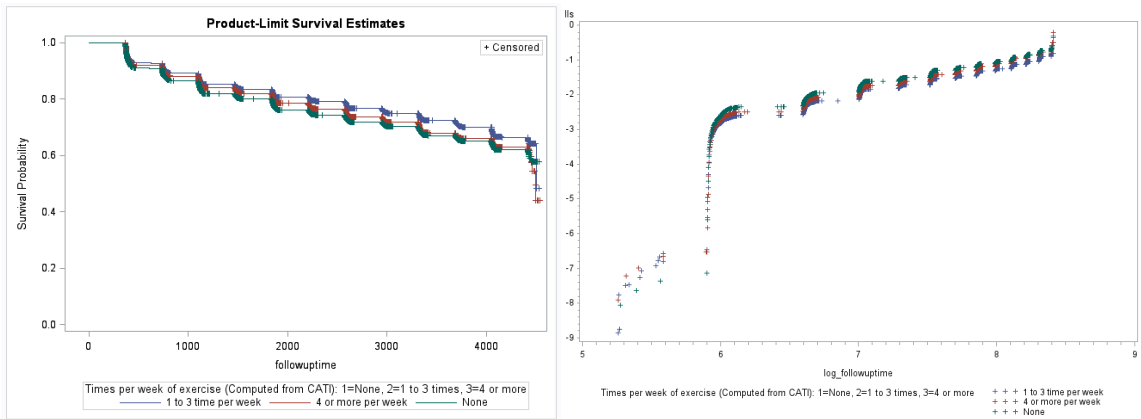
Alcohol Consumption



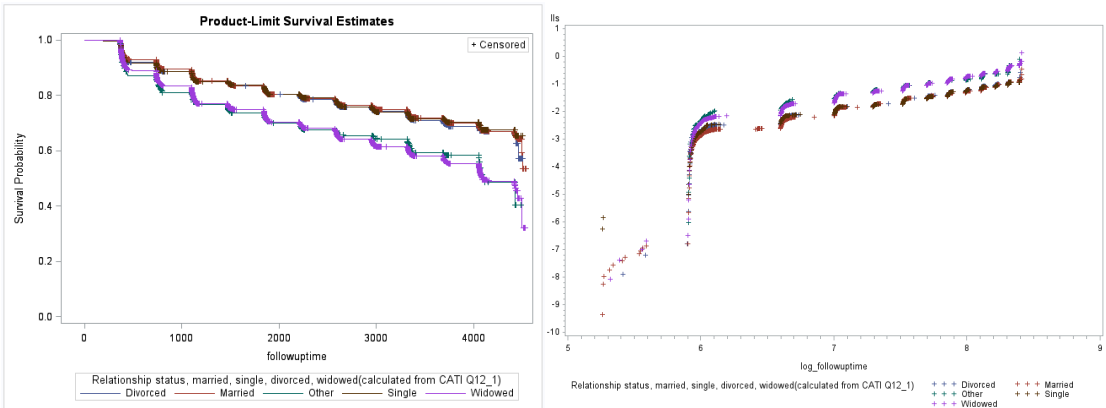
Smoking Status



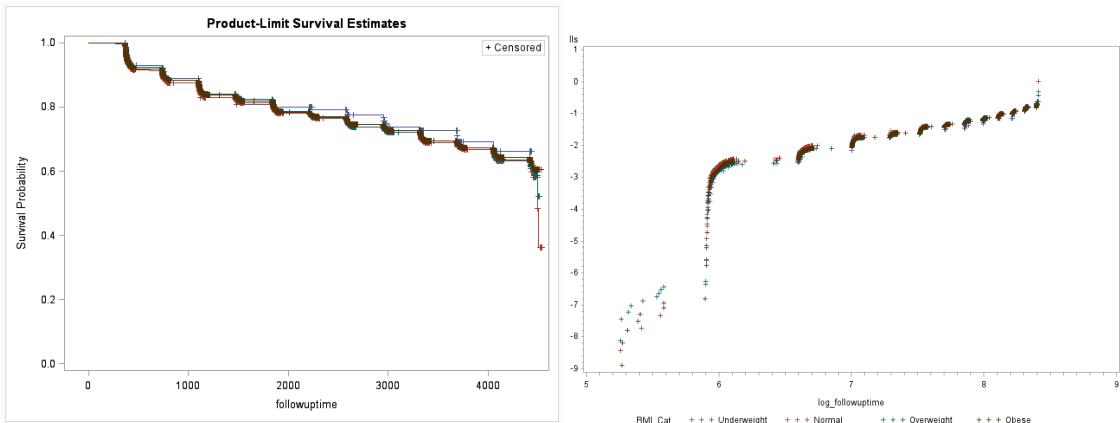
Physical Activity



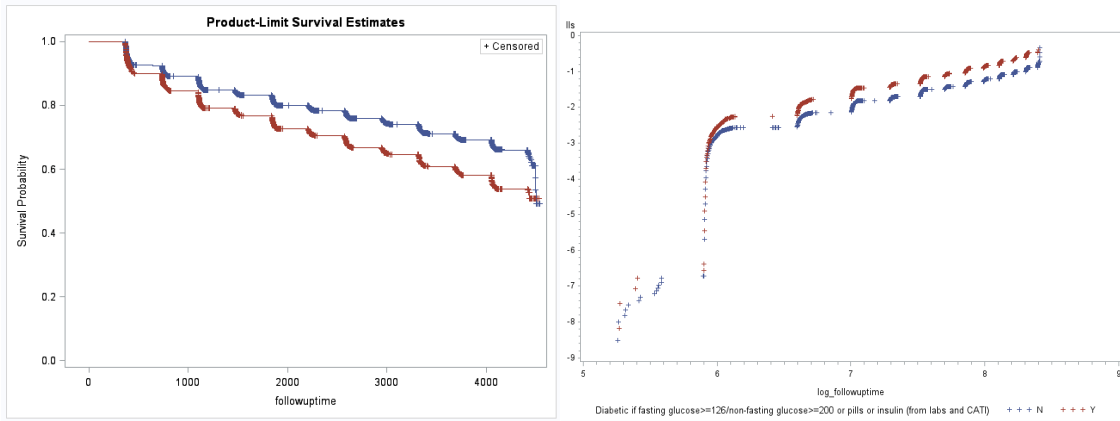
Marital Status



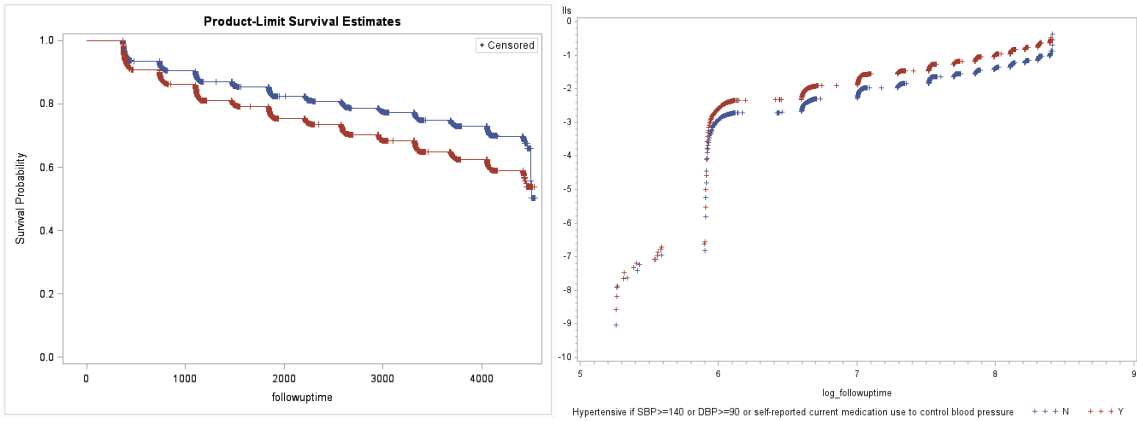
BMI



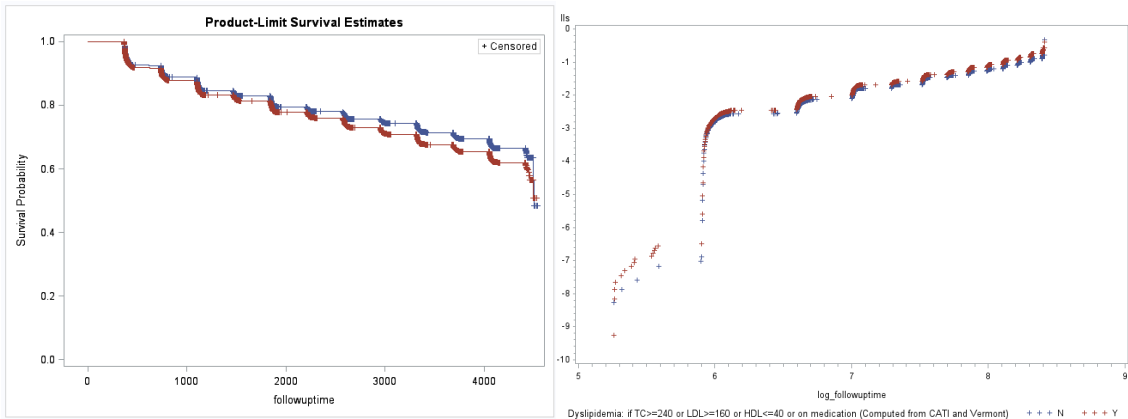
Diabetes



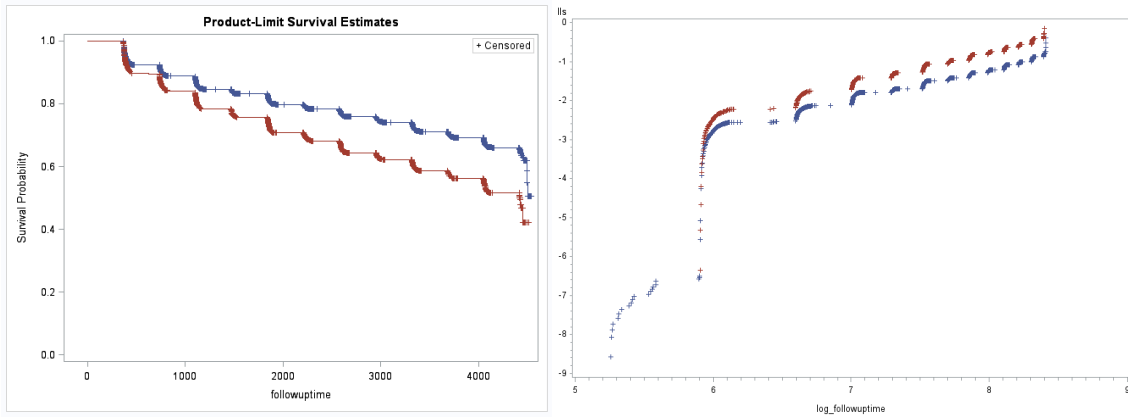
Hypertension



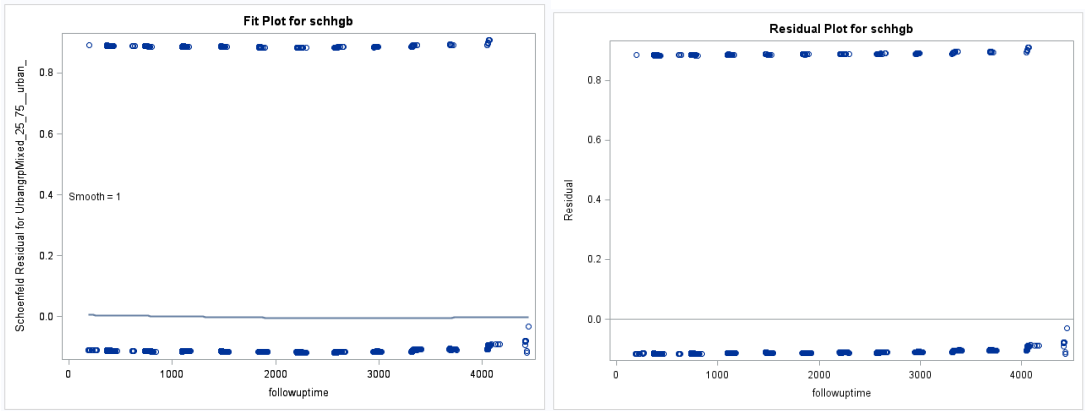
Hyperlipidemia

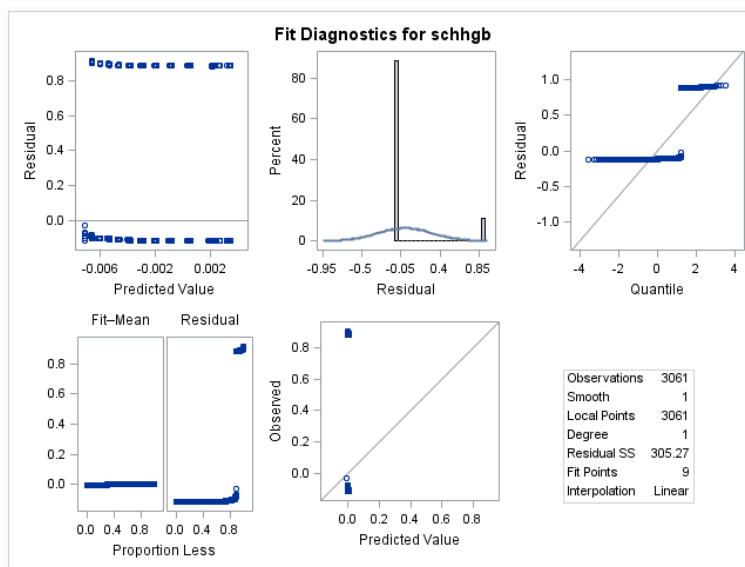
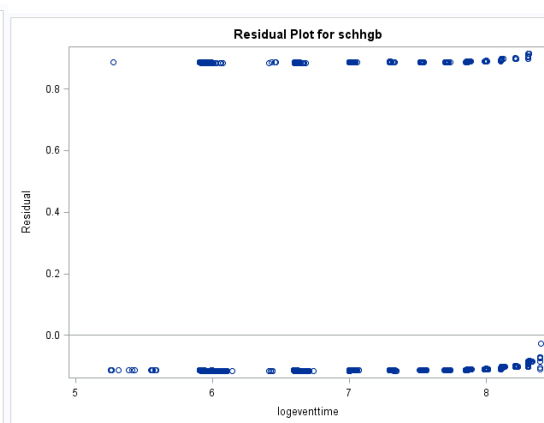
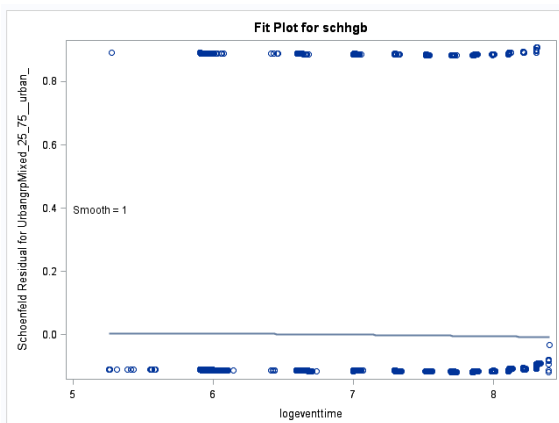
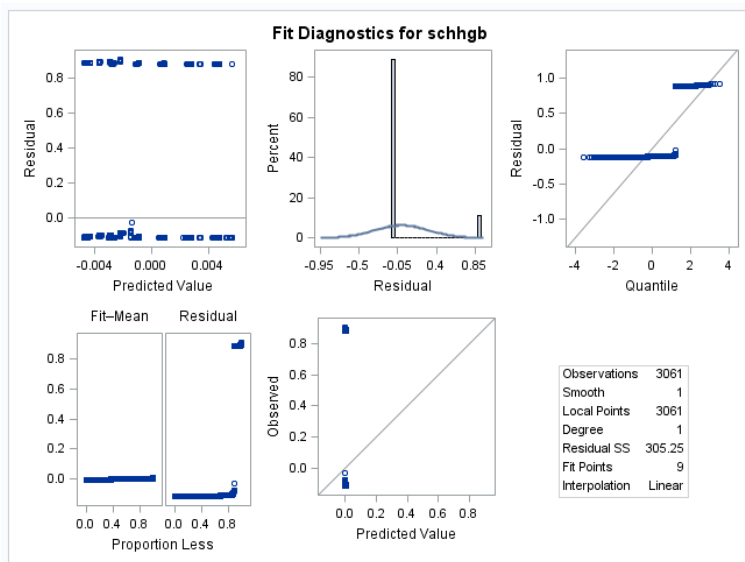


History of Heart Disease

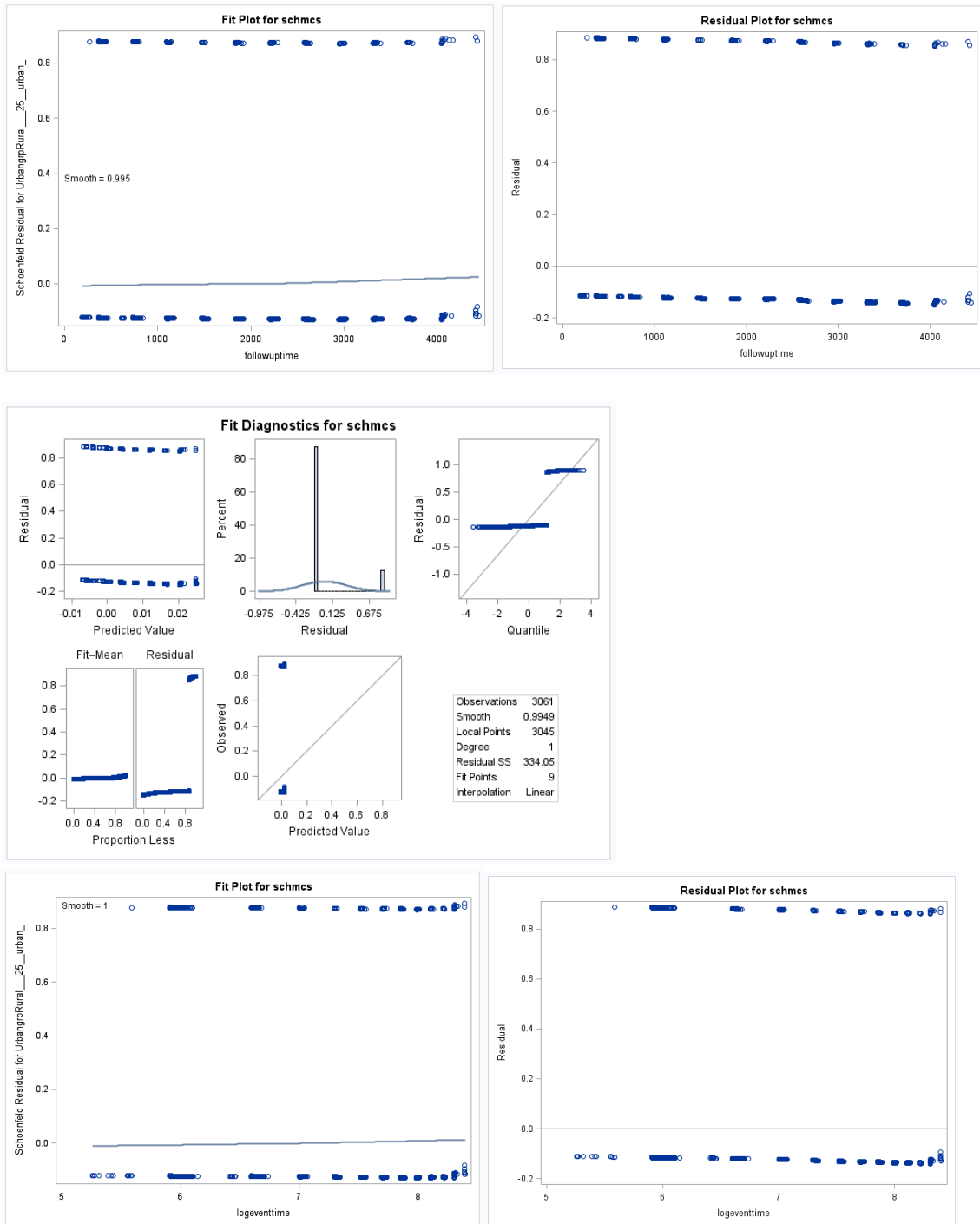


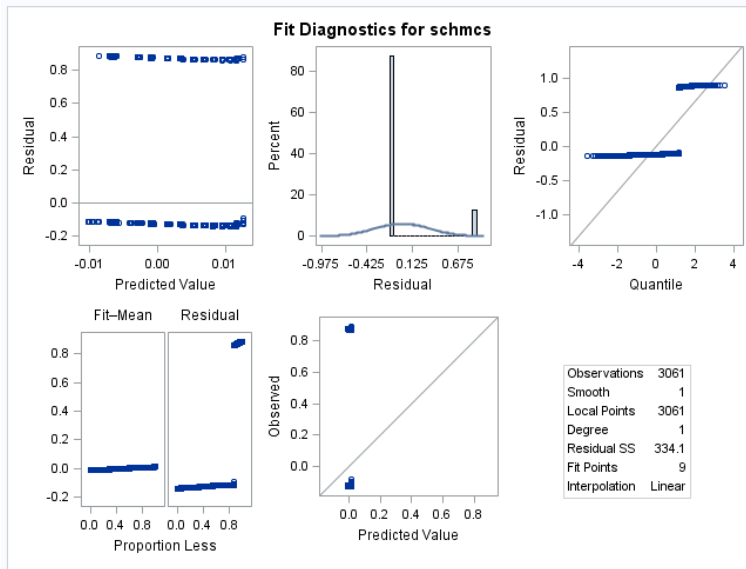
Hemoglobin Count





Depression





Stress Level

