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Effects of Family History of Alzheimer's Disease on Glucose Metabolism (FDG-PET) among Mild Cognitive Impaired Patients: a Longitudinal Study.

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ABSTRACT

EFFECTS OF FAMILY HISTORY OF ALZHEIMER'S DISEASE ON GLUCOSE METABOLISM (FDG-PET) AMONG MILD COGNITIVE IMPAIRED PATIENTS: A LONGITUDINAL STUDY.

By

NERLINE JACQUES

05/19/2017

As life expectancy is increasing, the prevalence of Alzheimer's disease (AD) is expected to escalate. However, there are still no specific markers to confirm AD diagnosis, nor effective treatment for AD, nor an established way to slow down the rate of degeneration.

This study aims to first examine the effect of positive AD family history (FH+) on cerebral metabolic rate of glucose (CMRglc) over a 5-year period among Mild Cognitive Impaired (MCI) subjects. It also assesses whether there are parent gender effects on CMRglc when the groups negative family history (FH-) vs paternal family history (FHp) vs maternal family history (FHm) are compared. Finally, this paper tests whether there is effect modification with APOE4 allele interaction.

Data are drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. A sample size of 177 subjects with a maximum of 30 observations was used. Wilcoxon rank-sum test and Chi-square test had been used to test for baseline differences between FH+ and FH- groups for the continuous and categorical variables respectively. To analyze the effects of FH on CMRglc, multivariate generalized linear mixed-effects models were used.

The results showed that, compared to subjects who are FH-, FH+ participants presented greater CMRglc decline over the 5-year period after controlling for the other covariates. After adding APOE4 in the model, FH+ subjects showed significantly lower glucose metabolism rate

compared to FH- participants. The sample did not have enough statistical power to detect any parental FH differences. Heritability from FH status for explaining CMRglc decline in MCI people is small but statistically significant.

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LONGITUDINAL STUDY.

by

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APPROVAL PAGE

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Author's Statement Page

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Nerline Jacques
Signature of Author

LIST OF ABBREVIATIONS

$A\beta$: β -amyloid

AD: Alzheimer's disease

ADNI: Alzheimer's Disease Neuroimaging Initiative

ANCOVA: Analysis of covariance

APOE (ϵ 4): Apolipoprotein E E4 Genotype

APOE4+: APOE ϵ 4 carriers

APOE4-: APOE ϵ 4 non-carriers

CMR_{glc}: cerebral metabolic rate for glucose

CSF: cerebrospinal fluid

FDG-PET: PET scans with flurodeoxy glucose

FAD: familial AD

FH: family history

FH+: positive AD family history

FH-: negative AD family history

FHp: paternal family history

FHm: maternal family history

ICC: intra-class correlation

NFT: neurofibrillary tangles

MTL: temporal lobes

MRI: magnetic resonance imaging

MMSE score: Mini-Mental State Examination score

OLS: Ordinary least squares

PET: positron emission tomography

PIB: Pittsburgh Compound B

ROI: regions of interest

SPM: Statistical parametric mapping

USA: United States of America

WHO: World Health Organization

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CHAPTER 1

INTRODUCTION

1.1 Background

Alzheimer's disease (AD) is a progressive degenerative disorder that harms the brain's nerve cells resulting in loss of memory and cognitive decline. This disease accounts for around 70 % of all dementia cases (Liu et al., 2016), and leads to death generally within seven to ten years after diagnosis (Villemagne & Chételat, 2016). This type of neurodegenerative dementia has traumatic effects on not only the person suffering and his relatives, but also it has considerable economic impacts on the health care system. Financial cost for AD screening, health care, hospice care and research are substantial. The World Health Organization (WHO) estimated the total costs of AD in the United States (USA) to be \$ 1.75 billion for the year of 2000 ("WHO | Chapter 2," 2001). Analogously, it is projected that the total payments for AD and other dementias will escalate from \$ 259 billion in 2017 to \$ 1.1 trillion by 2050 ("Latest Alzheimer's Facts and Figures," 2013).

As life expectancy is increasing, the number of individuals living with this disorder is expected to soar. In 2000, the worldwide prevalence of AD for the 60-years-old and older population was 5% for men and 6% for women ("WHO | Chapter 2," 2001). Comparably, this prevalence for the same population is estimated at 10 % in 2017 for the USA. Nonetheless, the prevalence of AD for the whole US population was 4.5 million in 2000, and this estimate is expected to rise to 13.2 million by 2050 (Andrawis et al., 2012).

Currently, there are still no specific markers to confirm AD diagnosis, nor effective treatment for AD, nor an established way to slow down the rate of degeneration. Progress in technology allow positron emission tomography (PET) and magnetic resonance imaging (MRI)

scan to determine the extent of brain impairment. Nonetheless, the need for continuing efforts to slow down the progression, to cure, or to prevent AD is still crucial. This paper attempts to further explore the role of positive family history in glucose metabolism among at risk AD subjects.

1.2 Alzheimer's disease description

The term Alzheimer's disease has its origin back in 1906, when a German physician named Dr. Alois Alzheimer presented the case of a rare brain disorder to a meeting. He reported the case of a 50-year-old woman whom he had followed from her admission for memory loss, language problems, and unpredictable behavior, until her death 5 years later. The plaques and tangles identified from brain autopsy characterized what we call nowadays Alzheimer's disease (Hippius & Neundörfer, 2003).

Clinically, AD is characterized by continuing decline in memory, thinking and reasoning ability, disrupting daily activities. This disease is usually associated with two types of abnormal lesions found in the cerebral cortex: amyloid plaques and neurofibrillary tangles (NFT). Amyloid plaques, located between the neurons, are small and dense residues of a certain protein called beta-amyloid ($A\beta$), while neurofibrillary tangles, located inside the neurons, are insoluble twisted fibers of a protein called tau. Depositions of protein from both amyloid plaques and NFT are part of normal aging process, but individuals with AD have far larger amount of these protein depositions. Evidence suggests that plaques and tangles are necessary but not sufficient cause for developing AD, because both are also found in other dementia cases and in non-demented people. Large amount of $A\beta$ depositions obstruct the brain and break connection with other nerve cells that play a critical role in memory and learning functions, leading to neural death.

Amyloid starts accumulating several years before the onset of AD clinical symptoms. It is estimated that neurodegeneration in AD starts around 20 to 30 years before clinical indication of its presence (Jagust, William, 2009). It is also documented that the regions of the brain most affected by the disease are found in the temporal lobes (MTL), specifically the hippocampus, entorhinal cortex, and subiculum (Jagust, William, 2009). Brain imaging can help detect and measure plaque and tangle load.

1.3 Detection of Alzheimer's disease with Positron Emission Tomography (PET)

Research advancements in AD, specifically in neuroimaging, in the past decades made it possible to visualize the human brain during life using positron emission tomography (PET). The modality PET offers the capability to monitor AD-related changes in the brain in many views. However, the most widely used are Pittsburgh Compound B (PIB-PET) by tracking the burden of $A\beta$ deposition in the brain, and flurodeoxy glucose (FDG-PET) by providing estimates of the cerebral metabolic rate of glucose (CMR_{glc}). Those views are effective in depicting brain functional abnormalities.

Amyloid PET scan helps identify both fibrillar amyloid detected in blood vessels (cerebral amyloid angiopathy) and interstitial fibrillar amyloid in plaques. Nevertheless, amyloid PET is limited in helping diagnose AD because of the prevalence of normal older individuals in whom amyloid deposition is found is high. The estimates for age-specific positivity rates for amyloid PET are less than 5 adults for every 100 adults aged between 50 and 60 years, 10 adults for every 100 adults aged between 60 to 70 years, 25 adults for every 100 adults aged between 70 and 80 years, and more than 50 adults for every 100 adults aged between 80 to 90 years (Johnson et al., 2013). These high prevalences suggest that, although clinical symptoms of $A\beta$

are a risk factor for AD, they are not a sufficient cause of AD. Besides, these age-related prevalences provide evidence that amyloid detection may be related to age or other medical conditions.

Conversely, FDG-PET studies have shown significant correlation between CMRglc reductions and AD symptoms severity. Thus, although normal aging is also characterized by CMRglc decline, hypo-metabolism is widely considered as a consistent in vivo AD biomarker (Jagust, William, 2009). Importantly, as glucose is known as the main source of energy for the brain, FDG-PET tool help depict medial temporal lobe (MTL) glucose metabolism at pre-symptomatic stages of AD.

1.4 Purpose

In this study, I will examine the longitudinal effect of family history on cerebral metabolic rate of glucose in Mild Cognitive Impaired individuals.

First degree family history is considered as the most conspicuous risk factor for developing AD, after advanced age (Jagust, William, 2009). However, researchers and clinicians still rely on subject self-report FH to ascertain this variable because the biological mechanism underlying the effects of FH on AD biomarkers are still not fully established (Lampert et al., 2014). Besides, several studies suggest that AD brain changes have a lengthy period before clinical symptoms manifestations. Therefore, identifying how family history (FH) of Alzheimer's disease affects the brain function through AD biomarker abnormalities will contribute to a better understanding and interpretation of those biomarkers. It will help better understand the brain change mechanisms at pre-symptomatic stages of AD, which will greatly improve clinical interventions regarding the disease.

Although considerable research has been devoted to evaluating the effects of positive family history on AD hallmarks, those studies are limited in several ways. First, most of those studies are cross-sectional, and do not assess the temporal effect of a positive family history and hypo-metabolism. Second, the few studies that used longitudinal analysis are limited by the relatively short period of subjects' follow-up (less than 4 years). Finally, most of those studies used relatively small samples. Therefore, the purpose of this study is first to examine the effect of positive AD family history (FH+) on cerebral metabolic rate of glucose (CMRglc) over a period of 5 years on specific brain regions. Additionally, this study attempts to test whether there are parent gender effects on FDG-PET when the groups negative family history (FH-) vs paternal family history (FHp) vs maternal family history (FHm) are compared. This paper will also examine whether there is effect modification with Apolipoprotein E E4 Genotype (APOE4) interaction.

1.5 Research Questions

This study research questions are: Are there significant CMRglc differences between FH- and FH+ (maternal and paternal combined) groups? Does the interaction with APOE4 allele modify these results? Are the effects of maternal family history on CMRglc different from the effects of paternal family history on CMRglc when the groups FH- vs FHp vs FHm are compared? To answer these questions, it is hypothesized that:

- 1) A positive FH would be associated with greater reduction of CMRglc in specific brain areas (Left and right Angular Gyrus, Bilateral Posterior Cingular, Left and right Inferior Temporal Gyrus).
- 2) Positive APOE4 allele has effect modification on the association of positive family

history with CMRglc.

- 3) Maternal history of AD would be associated with greater reduction of CMRglc in specific brain areas relative to that seen in groups of subjects with paternal or no parental history of AD.

The remainder of this paper is organized as follows. Chapter 2 presents a literature review related to AD risk factors, and the association between positive AD family history and CMRglc. Chapter 3 describes the methods and procedures for the analyses. Chapter 4 reports the main findings and chapter 5 discusses the results and conclude.

CHAPTER 2

LITERATURE REVIEW

2.1 Alzheimer's disease risk factors

It has been proven that the most common factors that increase the risk of developing Alzheimer's are age, family history, and genetics. Nonetheless, recent advances suggest that there are other factors that need to be investigated.

- Age

Known as a gradual decline in cognitive functions, AD is mostly common among those who are 65 years old and more. The age-specific incidence rates for AD double for every six years of added life (Tanna, 2004). This implies that the more advanced in age an individual is, the higher is the risk for this person to develop AD. This effect is consistent across the literature (Adluru et al., 2014; Xiong et al., 2011; Honea, Swerdlow, Vidoni, & Burns, 2011).

- Family history

Xiong et al., (2011) defined a person with positive FH for AD as someone with one or both biological parents with AD onset below 80 years old, and a person with negative FH as someone with both biological parents living to age 70 or greater without AD.

Studies report that early onset familial AD (FAD) represents less than 5 % of all AD cases (Jagust, William, 2009). Interestingly, Lampert and colleagues (2013) speculated that AD FH status is associated with earlier onset of AD pathology. Kennedy and colleagues (1995) reinforced these observations by reporting that global CMRglc reductions worsens along the course of the disease for individuals with positive AD family history. Importantly, first degree family history is largely recognized as the second demographic AD risk factor. The risk for a

normal individual with an AD-affected parent is 4 to 10 times higher than a normal individual with no family history (FH-).

- Apolipoprotein E E4 Genotype

Known to provide lipids throughout the central nervous system, APOE allele has three common isoforms which are APOE-2, APOE-3, and APOE-4. Every individual inherits a copy of the isoform from each of his/her parent. Individuals who inherit the APOE-4 ($\epsilon 4$) genotype have an increased risk of developing AD, even at a younger age than normal. Studies revealed that 40 out of every 100 AD persons have at least one APOE-4 allele (Jagust, William, 2009). In 2013, Fleisher and colleagues examined the effects of APOE-4 gene and aging on florbetapir F18-PET. Their study demonstrated that cortical amyloid deposits start accumulating 20 years earlier in cognitively healthy APOE-4 carriers compared to non-carriers (Fleisher et al., 2013).

2.2 CMRglc from FDG-PET and family history

The literature on the effects of family history on CMRglc is sparse.

To describe the metabolic features of 3 AD-affected subjects and 1 unaffected individuals, all subjects having positive AD family history, A. M. Kennedy et al., (1995) used Statistical parametric mapping (SPM), and analysis of covariance (ANCOVA). The investigators discovered that all cases showed hypo-metabolism in the parieto-temporal regions. These observations even were greater for the two severely affected patients. These findings indicate that deficit in CMRglc aggravates along the course of the disease. Nonetheless, the use of a small sample size of 4 patients detract the relevance of these findings.

Kennedy et al., (1995) attempted to determine whether FDG-PET can help detect changes in CMRglc in a population of 24 cognitively normal individuals with positive AD family history

and 16 age-matched with no AD family history. For the at-risk group, Kennedy and colleagues found significant CMRglc reductions in the areas of parietal, temporal, and frontal cortices. This study provides evidence that asymptomatic individuals who are FH+ have metabolic deficit on PET. However, this study did not control for partial volume correction of glucose metabolism values. Normally, patients with AD show significant brain shrinkage on magnetic resonance imaging (MRI). Thus, the CMRglc reductions could be an effect of brain volume losses, or the effect of cerebrospinal fluid (CSF) in certain region of the brain.

In 2006, Mosconi and colleagues addressed this limitation by comparing CMRglc and volumes in several regions of the brain for FH+ subjects and age-matched controls (Mosconi, Sorbi, de Leon, Li, & al, 2006). They considered the whole brain in their analysis. This study reports that asymptomatic FH+ individuals present global CMRglc reductions, and these effects of CMRglc on FDG-PET remain significant after correcting for partial volume from MRI. However, the authors used a cross-sectional analysis. This limits the study power in finding a significant difference because AD has a lengthy period of onset. Moreover, the investigators used a small sample size of 7 at risk individuals and 7 healthy controls.

In another study, Mosconi et al., (2007) examined the FDG-PET of cognitively healthy elderly, comparing those with maternal, paternal and no AD family history. This study revealed that, compared to those with an AD-affected father and those who are FH-, individuals with maternal FH have greater CMRglc reductions in the same brain regions of affected AD subjects. These regions are posterior cingulate cortex/precuneus, parieto-temporal and frontal cortices, and medial temporal lobes. Nevertheless, the authors recommended longitudinal investigations to determine whether the observed results predispose those with maternal FH to develop the disease. Another limitation of this study was the relatively small sample size.

Remarkably, through a longitudinal study, Mosconi et al., (2008) evaluated the effect of maternal history of AD on CMRglc using FDG-PET on 121 cognitively intact subjects. From the 121 participants, 61 of them were considered in the longitudinal analysis (2 years of follow-up). This population was categorized as 35 with FH-, 8 with paternal FH+, and 18 with maternal FH+. There was no difference of CMRglc between paternal FH group and negative FH group. Conversely, the maternal FH group had greater CMRglc reductions when compared with paternal FH group and negative FH group. The researchers concluded that progressive CMRglc decline happens at middle age for those with maternal history of AD, and is even more severe for those crossing two generations of maternal grandmother AD history. The results of this study suggest that there is a transmitted maternal factor that impacts the brain pathophysiology of the offspring. Nevertheless, the relatively short period of subjects' follow-up weakens the relevance of this study.

A much more recent study evaluated the effects AD family history on glucose metabolism with FDG-PET using a population of 153 cognitively normal individuals among whom 29 were FH+ (Lee et al., 2016). Comparing the FH+ group with the FH- group, the authors did not find any differences in CMRglc in any cortical region of the brain, even after controlling for the effect of APOE ϵ 4.

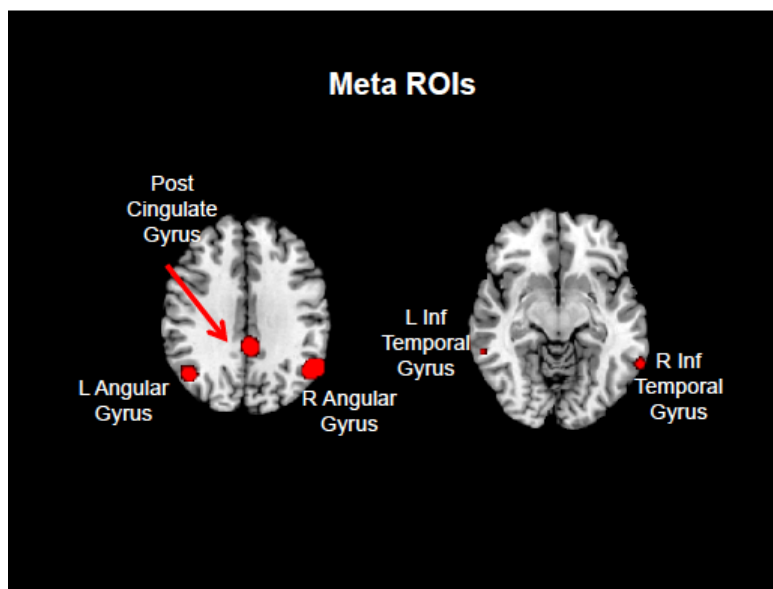
CHAPTER 3

METHODS AND PROCEDURES

3.1 Data source

Data were drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI is a continuing multisite imaging longitudinal study across the U.S. and Canada currently with three phases: ADNI-1, ADNI-GO and ADNI-2. Starting on October 2004, the first phase last 5 years with 200 cognitively normal control, 400 MCI, and 200 mild AD subjects. Participants were recruited by using advertisements and clinical referrals. More information regarding ADNI phase one study is provided in the procedures and protocol manual (Alzheimer's Disease Neuroimaging Initiative, 2010).

Figure 1: Regions of interest



(Landau & Jagust, 2009)

This study's outcome of interest (FDG-PET) is the mean glucose metabolism drawn for five different brain regions: Left and right Angular Gyrus, Bilateral Posterior Cingular, Left and

right Inferior Temporal Gyrus. The choice of these regions were based on the literature review as they demonstrated hypo-metabolism in AD patients (Landau & Jagust, 2009).

3.2 Study design and population

The analyses in this paper refer to ADNI phase-1 with the MCI population only. The choice of MCI population is justified by the fact that neurodegeneration starts several years before memory symptoms manifest, and MCI subjects is widely considered as being at higher risk of developing AD. Consequently, since MCI is recognized as a transitional phase into AD, it is expected that the MCI group near to the anticipated age at onset will provide a greater number of subjects in a pre-symptomatic stage of the disease which, in turn, will increase the power of the study to detect an effect. ADNI classified subjects as Mild Cognitive Impaired if they had subjective memory complaint, objective evidence of abnormal memory function, Mini-Mental State Examination (MMSE) score between 24 and 30, and Clinical Dementia Rating of at least 0.5.

Subjects' exclusion criteria were: important neurologic disease other than AD; psychiatric disorder; alcohol dependency within the last 2 years; and clinical illnesses that could impair cognition or protocol compliance. An exhaustive list of inclusion and exclusion criteria is provided in the procedures and protocol manual (Alzheimer's Disease Neuroimaging Initiative, 2010).

At the time the data were gathered, February 22nd 2017, a sample size of 177 subjects with a maximum of 30 observations per subject met the study inclusion criteria, establishing a total of 952 observations. Not all subjects had the same number of follow-ups and only 124 subjects had baseline information available. All missing observations for the independent variables were excluded in the study. Age and education are measured in years, and FH, APOE4

and gender are dichotomous variables. These covariates were chosen based on the literature. Participants included in the study had a MMSE score between 24 and 30, aged between 57 and 90 years old, with education level ranging from 8 to 20 years. 40 % were female and 49 were APOE4 carriers. There was a total of 8 observation time-points: the baseline interview and seven follow-up measurements (6, 12, 18, 24, 36, 48, and 60 months from baseline).

3.3 Statistical Analyses

For all analyses, significance level is set at 0.05, unless stated otherwise. To test for baseline difference between FH+ and FH- groups for the continuous independent variables, the Wilcoxon rank-sum test had been used, because these variables are not normally distributed. To examine if there is baseline difference between FH+ and FH- groups for the categorical variables, the Chi-square test was used. Additionally, to analyze the effects of FH on CMRglc, multivariate generalized linear mixed-effect models were used. This statistical approach will help assess factors influencing longitudinal glucose metabolism reduction in AD while accounting for variability in individual initial points. This approach also accounts for both within-subject variations and between-subject variability. Statistical analyses were carried out using SAS PROC MIXED (version 9.4). Three sets of mixed effects models were carried out. Model 1 assess if there are CMRglc differences between FH+ and FH- groups over time. Model 2 tests if APOE4 effects modifies the results. Finally, model 3 examine if the effects of maternal family history on CMRglc are different from the effects of paternal family history on CMRglc when the groups FH- vs FHp vs FHm are compared.

Model specification:

In the analyses, random intercept with random slope coefficient of Time models are estimated based on the assumption that subjects have different CMRglc lines with different starting points and CMRglc change over time. We also assume that the individual background variables (Age and Gender) may influence CMRglc, but their effects will not change over time. Only the effects of region and family history will change over time.

Model 1: Effects of FH on CMRglc

The level-one or the within-subject model is described as:

$$\text{CMRglc}_{ijt} = \beta_{0ij} + \beta_{1ij} (\text{Time})_{it} + \varepsilon_{ijt}$$

and the level-two or the between-subject model takes the following form:

$$\beta_{0ij} = \beta_0 + \beta_{\text{Region}j}(\text{Region})_{ji} + \beta_{\text{Age}}(\text{Age})_i + \beta_{\text{Gender}}(\text{Gender})_i + \beta_{\text{FH}}(\text{FH})_i +$$

$$\beta_{\text{Age}*\text{Region}j}(\text{Age}*\text{Region})_{ji} + \beta_{\text{Gender}*\text{Region}j}(\text{Gender}*\text{Region})_{ji} + \gamma_{0i}$$

and

$$\beta_{1ij} = \beta_{\text{Time}} + \beta_{\text{Time}*\text{Region}j}(\text{Region})_{ji} + \beta_{\text{Time}*\text{FH}}(\text{FH})_i + \beta_{\text{FH}*\text{Region}j}(\text{FH}*\text{Region})_{ji} + \gamma_{1i}$$

The combined equation is:

$$\text{CMRglc}_{ijt} = \beta_0 + \beta_{\text{Region}j}(\text{Region})_{ji} + \beta_{\text{Age}}(\text{Age})_i + \beta_{\text{FH}}(\text{FH})_i + \beta_{\text{Gender}}(\text{Gender})_i +$$

$$\beta_{\text{Time}}(\text{Time})_{it} + \beta_{\text{Age}*\text{Region}j}(\text{Age}*\text{Region})_{ji} + \beta_{\text{Gender}*\text{Region}j}(\text{Gender}*\text{Region})_{ji} +$$

$$\beta_{\text{Time}*\text{Region}j}(\text{Time}*\text{Region})_{jit} + \beta_{\text{FH}*\text{time}}(\text{FH}*\text{Time})_{it} + \beta_{\text{FH}*\text{Time}*\text{Region}j}(\text{FH}*\text{Time}*\text{Region})_{ijt}$$

$$+ \gamma_{1i}(\text{Time})_t + \gamma_{0i} + \varepsilon_{ijt}$$

CMRglc_{ijt} designates the t^{th} occasion ($t= 0, 6, \dots 60$ months) of glucose metabolism measure for the j^{th} region ($j=1, 2, \dots 5$) of the brain for the i^{th} individual ($1, 2, \dots 177$). β_{0i} and β_{1i} are respectively intercept coefficient and slope coefficient of $(\text{Time})_{it}$. They are both random regression coefficients suggesting that the initial level and the rate of change of glucose

metabolism measures will differ by subject. $(\text{Time})_{it}$ is the time measurement occasion and ε_{ijt} refers to the within-subject error coefficient. This error term accounts for variation in each subject's repeated measurements over time. ε_{ijt} is assumed to follow a Gaussian distribution with mean zero and variance σ^2 .

In level-two, β_0 denotes the grand mean initial level of glucose metabolism for “Cingulum Post Bilateral” region for a 75 years old male with no FH of AD. β_{Time} represents the average rate of change of glucose metabolism for the subjects with positive family history adjusting for individual-level covariates. $\beta_{\text{Region}j}$ represents the fixed effects of region j on glucose metabolism with “Cingulum Post Bilateral” as reference. β_{FH} is the difference in the average initial level of glucose metabolism between FH+ group and FH- group. $\beta_{\text{FH}*\text{time}}$ represents the difference in rate of change of glucose metabolism between FH+ group and FH- group. β_{Age} and β_{Gender} are respectively fixed-effect of the individual-level predictors Age and Gender. γ_{0i} and γ_{1i} account for unknown error of the i^{th} individual on the level-1 random regression coefficients (β_{0i} and β_{1i}). Thus, they represent between-subjects error coefficients accounting for cross-individual variations in the effects of predictors' rate-of-change on CMRglc. It is assumed that γ_{0i} and γ_{1i} are normally distributed with means zero and variances $\sigma_{\gamma_0}^2$ and $\sigma_{\gamma_1}^2$ respectively, and covariance $\sigma_{\gamma_{01}}^2$.

Model 2: Controlling for APOE4

$$\begin{aligned} \text{CMRglc}_{ijt} = & \beta_0 + \beta_{\text{Region}j}(\text{Region})_{jit} + \beta_{\text{Age}}(\text{Age})_{it} + \beta_{\text{Gender}}(\text{Gender})_i + \beta_{\text{FH}}(\text{FH})_i + \beta_{\text{Time}}(\text{Time})_{it} \\ & + \beta_{\text{APOE4}}(\text{APOE4})_i + \beta_{\text{Age}*\text{Region}j}(\text{Age}*\text{Region})_{jit} + \beta_{\text{Gender}*\text{Region}j}(\text{Gender}*\text{Region})_{ji} + \\ & \beta_{\text{Time}*\text{Region}j}(\text{Time}*\text{Region})_{jit} + \beta_{\text{APOE4}*\text{Time}}(\text{APOE4}*\text{Time})_{it} + \beta_{\text{FH}*\text{time}}(\text{FH}*\text{Time})_{it} + \\ & \beta_{\text{FH}*\text{Time}*\text{Region}j}(\text{FH}*\text{Time}*\text{Region})_{ijt} + \beta_{\text{APOE4}*\text{Time}*\text{Region}j}(\text{APOE4}*\text{Time}*\text{Region})_{ijt} \\ & + \gamma_{1i}(\text{Time})_t + \gamma_{0i} + \varepsilon_{ijt} \end{aligned}$$

In model 2, the common terms have the same meaning as in model 1, except that baseline subject additionally possesses APO4- allele. The term β_{APOE4} indicates additional baseline effect of APOE4+. $\beta_{APOE4*Time}$ denotes the difference in rate of change of glucose metabolism between APOE4+ group and APOE4- group. $\beta_{APOE4*Time*Region}$ represents the difference in rate of change of glucose metabolism between APOE4+ group and APOE4- group by brain region.

Model 3: Effects of FH parenting on CMRglc

$$\begin{aligned}
CMRglc_{ijt} = & \beta_0 + \beta_{Regionj}(Region)_{ji} + \beta_{Age}(Age)_i + \beta_{FH}(FH)_i + \beta_{Gender}(Gender)_i + \\
& \beta_{Time}(Time)_{it} + \beta_{Age*Regionj}(Age*Region)_{ji} + \beta_{Gender*Regionj}(Gender*Region)_{ji} + \\
& \beta_{Time*Regionj}(Time*Region)_{jit} + \beta_{FH*time}(FH*Time)_{it} + \beta_{FH*Time*Regionj}(FH*Time*Region)_{ijt} \\
& + \gamma_{1i}(Time)_t + \gamma_{0i} + \varepsilon_{ijt}
\end{aligned}$$

In model 3, the common terms have the same meaning as in model 1 as well. The only difference is that the variable FH has three categories: FH-, FHp, and FHm.

CHAPTER 4

RESULTS

4.1 Subject characteristics

As summarized in table 1, there was not enough evidence to reject the null hypothesis regarding no differences between the FH+ and FH- in terms of age, gender, education, MMSE score and percent of APOE4. Thus, it is assumed that demographic and clinical factors do not differ between FH groups. Patients who had a parent with AD represent 25.8 % of the baseline sample. Of the participants with parental family history of AD, 65 % were APOE4 carriers. Among those who had no AD family history, 51 % were APOE4 carriers. For both groups, the mean MMSE score was approximately 27, the mean years of education was around 16 and the mean age was roughly 75 years. The percent of females in the group with no FH is slightly higher than those in the other group, 34 % compared to 28 %.

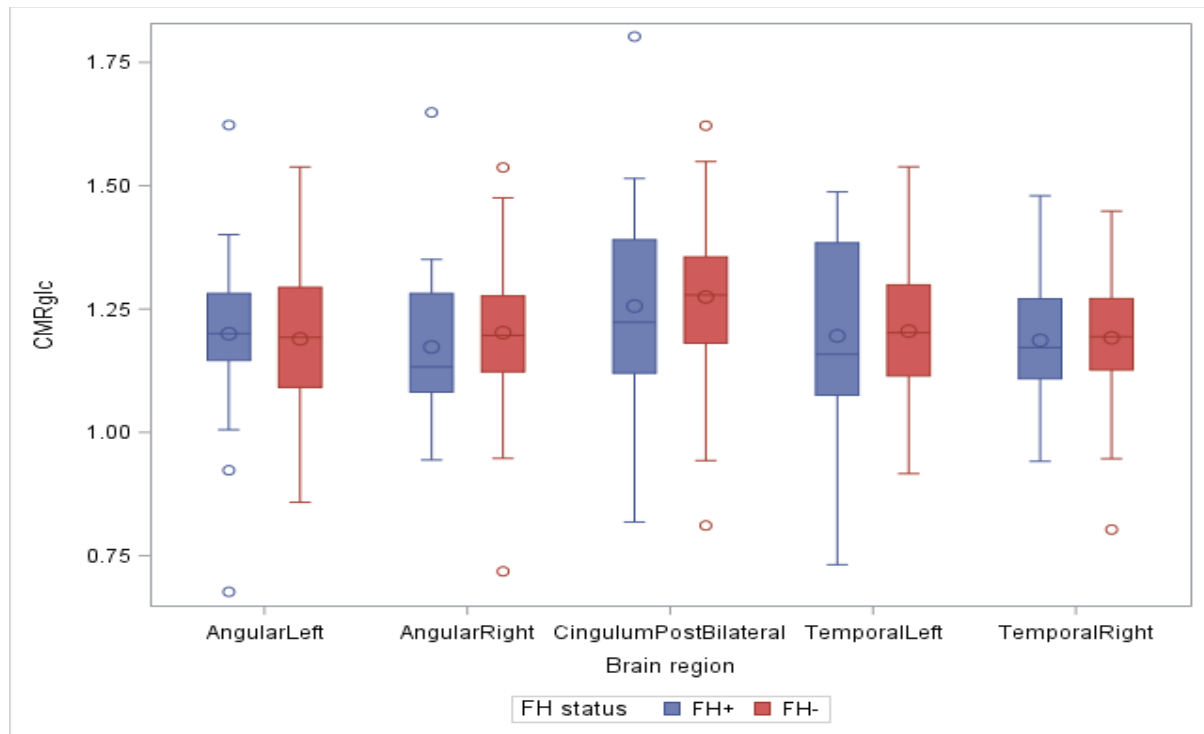
Table 1: MCI Subjects' demographic and clinical characteristics at baseline by Family History status

Characteristics	FH+	FH-	p-value
n	32	92	
Age (mean)	74.96	75.86	0.3943
Female %	0.28	0.34	0.4905
Education (mean)	16.31	15.75	0.4460
MMSE Score (mean)	27	27.25	0.5121
APOE4 %	0.65	0.51	0.1761

It worth noticing that while the baseline sample size is 124, subjects were allowed to leave and enter the study at any time. Therefore, the total sample size in this analysis

is 177. Figure A1 illustrates the trend¹ for CMRglc measurement occasions. On the other hand, figure 2 compares baseline CMRglc with FH status by brain region.

Figure 2: Baseline Cerebral Metabolic of Glucose by brain region and FH status



Although some differences are modest, overall, subjects with positive FH showed lower CMRglc at baseline.

4.2 Effect of FH on CMRglc

Since having an age of 0 in the study is meaningless, the variable AGE has been centered around its mean (75 years). The intra-class correlation (ICC) for this model is 0.728 which means that 72.8 % of the total deviation is due to between-subject heterogeneity. ICC score also suggests that individual (level-2) variability is a much more important than random variations

¹ See appendices.

between measurement occasions (level-1 variability). The global effect of brain region, time, age, and the interactions age by region, gender by region, and time by FH by region are all statistically significant. However, gender, FH and the interaction terms time by region and time by FH are not statistically significant. The estimated average initial glucose metabolism for the region “Cingulum Post Bilateral” for male subjects aged 75 years old in the FH- group is 1.292 ($p < .0001$), and it is expected to change on average across occasions at a rate of -0.00265 ($p < .0001$). Nonetheless, while decreasing and statistically significant, the main effect of time is very low. The mixed effects model also showed that as age is increasing, total glucose metabolism is decreasing (-0.00896, $p < .0001$) for male with FH-.

Interestingly, the main effect of FH (-0.019, $p = 0.4987$) shows that baseline glucose metabolism was slightly lower for FH+ subjects, compared to FH- participants although this difference is not statistically significant. This result confirms the observations in figure 2. Intriguingly, the rates of change for FH- subjects are positive for all regions, thus they are increasing. Still, this observation is statistically significant only for two regions: Angular Right ($p = 0.0012$) and Temporal Right ($p = 0.008$).

Table 2: Effects of Family History on 5 years Cerebral Metabolic Rate of Glucose

Regions	FH- rate	FH- rate SE	FH- rate p-value	Difference of FH+ rate	FH+ rate difference SE	FH+ rate difference p-value
Angular Left	0.001183	0.000618	0.0559	-0.00127	0.000919	0.1692
Angular Right	0.00215	0.000664	0.0012	-0.00252	0.000989	0.0111
Temporal Left	0.000808	0.000676	0.2325	-0.0022	0.001	0.0281
Temporal Right	0.001858	0.000699	0.008	-0.00306	0.001007	0.0025
Cingulum PostBilateral	ref.			ref.		

Regarding the effects of FH+ on CMRglc, the primary analysis revealed that, after controlling for the other covariates, FH effects for all brain region on glucose metabolism rate is

lower for FH+ participants compared to FH- subjects. These findings are all statistically significant, except for the region Angular Left ($p=0.1692$). The same models were fitted for each brain region separately, this approach led to the same findings. As a result, the mixed effects model shows that FH+ subjects present greater CMRglc decline over time compared to FH- subjects.

4.3 Effect of FH on CMRglc after Adjusting for ApoE4

Mixed effect model results for model 2 are shown in table 3. APOE4+ subjects had smaller glucose metabolism at baseline compared with APOE4- subjects, however these differences failed to reach statistical significance (-0.04705 , $p=0.1263$). Moreover, compared to non-carriers, APOE4 carriers presented smaller CMRglc for all the regions, although statistically nonsignificant. In short, there was not enough evidence to infer that APOE4 is a significant predictor of CMRglc either globally or for specific brain region.

Table 3.- Effect of Family History on 5 years Cerebral Metabolic Rate of Glucose, adjusting for APOE4 allele

Regions	APOE4+ rate	APOE4+ SE	APOE4+ p-value	Difference of FH+ rate	FH+ rate difference SE	FH+ rate difference p-value
Angular Left	-0.00142	0.001195	0.2357	-0.00111	0.001017	0.2767
Angular Right	-0.00041	0.001303	0.7508	-0.00296	0.0011	0.0073
Temporal Left	-0.00258	0.001352	0.0566	-0.00229	0.00112	0.0414
Temporal Right	-0.00117	0.001372	0.3936	-0.00324	0.001121	0.004
Cingulum PostBilateral	ref.			ref.		

As in the previous model, FH+ subjects showed significantly lower glucose metabolism rate compared to FH- participants after additional control for APOE4. However, the model adjusting for APOE4 presented slightly greater decline than the model without APOE4.

Specifically, positive FH is associated with greater CMRglc decline over the 5-year period for all the region under study, except for “Angular Left” (p=0.2767). The results, after adding APOE4 in the model with its interactions with brain region and time, indicates that heritability from FH status for describing CMRglc decline in MCI people is likely to be small but significant.

4.4 Effect of Parental Family History on CMRglc

Table 4 displays the results for model 3. Notably, as noticed in the previous models, FH+ status is associated with a lower decline of CMRglc over time compared to FH- status. However, this result is not statistically significant for any of the brain region when comparing three groups: FH- with maternal FH with paternal FH.

Table 4: Effects of Parental Family History on 5 years Cerebral Metabolic Rate of Glucose

Regions	FHm rate difference	FHm rate difference SE	FHm rate difference p-value	FHp rate difference	FHp rate difference SE	FHp rate difference p-value
Angular Left	-0.00182	0.001378	0.1862	-0.00123	0.001683	0.4644
Angular Right	-0.00172	0.001533	0.2615	-0.00247	0.00176	0.1605
Temporal Left	-0.00032	0.001491	0.8302	-0.00178	0.002031	0.3802
Temporal Right	-0.00241	0.001511	0.1106	-0.00148	0.00204	0.4698
Cingulum PostBilateral	ref.			ref.		

Contrary to what expected, subjects with paternal FH showed greater CMRglc decline when compared with FHm and FH- groups (-0.00246 p= 0.1847) although these differences did not reach statistical significance. Nonetheless, it is worth to remark that this study found no evidence of differences between parental FH groups. This might stem from a lack of statistical power in the sample because, while there were 131 subjects who are FH-, there were only 38

subjects with maternal history and 8 subjects with paternal history in the sample. Thus, this finding regarding parental FH is not reliable.

CHAPTER 5

DISCUSSION AND CONCLUSION

5.1 Discussion of Research Questions

The goal of this study was to assess if there is a difference on glucose metabolism rate from FDG-PET for selected brain regions between FH+ and FH- subjects while controlling for AD risk factors. This study also examined if there were parent gender effects on CMRglc. As hypothesized, there were greater and statistically significant CMRglc decline among FH+ participants compared to FH- subjects. This result aligns with prior studies (Angus M. Kennedy et al., 1995; Mosconi et al., 2006), and implies that neural function of subjects in FH+ group utilizes glucose at a higher rate than neural function of subjects in FH- group.

Similar to previous finding, gender did not have a significant effect on glucose metabolism (Adluru et al., 2014). Conversely, hypo-metabolism was associated with age which is consistent across the literature (Xiong et al., 2011; Adluru et al., 2014). It was assumed that after adjusting for APOE4, effects of FH on CMRglc would be modified. But, the analyses showed that effects of FH on CMRglc remain significant and presented slightly greater decline when controlling for APOE4.

It was hypothesized that participants with maternal history would show greater CMRglc decline compared to participants with paternal and those without FH. Strikingly, the results showed that subjects with paternal history had greater glucose metabolism rate decline than participants with maternal and FH- although nonsignificant. This finding is not in agreement with previous reports (Mosconi et al., 2007; Mosconi et al., 2008). This inconsistency may be due to differences in the type of population considered in the study (healthy subjects, MCI, or

AD), brain regions included, sample size, period of the study, covariates included, etc. This might also result from grouping bias since the groups maternal and paternal history were very small compared to the group of FH-. Nonetheless, it is worth noticing that others have also found no effect of FH on CMRglc (Lee et al., 2016).

5.2 Study Strengths and Limitations

To our knowledge, no previous studies have considered MCI subjects to investigate the effects of FH+ on CMRglc over such a long period. Another strength of this study is the use of a relatively large sample size drawn from a well-established ongoing cohort study (ADNI). Using the multilevel linear regression model present many advantages also. This approach helps account for unbalanced data structures; it allows the use of all available observations from each subject; it has greater statistical power when applied to the same data; and it assess the within-subject variations and the between-subject variability simultaneously.

However, this study presents also some limitations. Firstly, FH status was ascertained via subjects' self-report or their study partners' report. It is thus possible to have report bias in the sample due to uncertainty about parental AD history, denial, or unawareness due to early parental death, etc. Secondly, this study models did not control for partial volume from MRI. It has been established that AD at risk subjects present significant brain volume loss on MRI (Jagust, William, 2009). Therefore, it is possible that CMRglc reductions were an effect of brain shrinkage in the regions under study. Thirdly, the study sample size is limited and lack statistical power to detect the true differences between maternal history and paternal history and negative FH. The groups FHm and FHp might be under represented. Finally, using a multilevel modeling

approach, all subjects with at least one measurement observations were included in the analysis. Considering participants with at least 2 follow-up visits might have improved the model.

5.3 Implications of Findings

The mechanism explaining the effects of FH status is still not completely established and diverge depending of AD biomarkers. Subsequently, the contribution of examining the effect of FH on CMRglc over time is twofold. First, it characterizes the course of glucose metabolism in the brain at asymptomatic AD stages. Second, it shows that heritability from FH status for defining CMRglc decline in MCI people is small but statistically significant. These results extend the findings of previous research and imply that prevention interventions regarding AD could focus on the pre-symptomatic group “MCI subjects with FH+ aged between 57 and 90 years”. Potentially, these findings could also facilitate drug development for AD at risk people.

5.4 Future research direction

Future research could further explore these results comparing, with the same approach, the three groups: Normal Cognitive (NC), MCI and AD subjects. Moreover, further analyses on this topic could test parental versus siblings AD history. Besides, replicating these models while controlling for partial volume correction would be interesting.

5.5 Conclusion

In summary, this study found that subjects with positive FH presented greater CMRglc decline over the 5-year period. Thus, positive FH is associated with higher reduction of glucose metabolism rate. Furthermore, the analyses showed that APOE4 is not a significant predictor of

CMRglc. This suggest that, independent of APOE4, heritability from FH status for explaining CMRglc diminution in MCI people is small but significant. Finally, there was not enough evidence to detect any parental FH differences. Nevertheless, more research is needed to fully characterize the mechanism underlying the effect of FH status on AD biomarkers.

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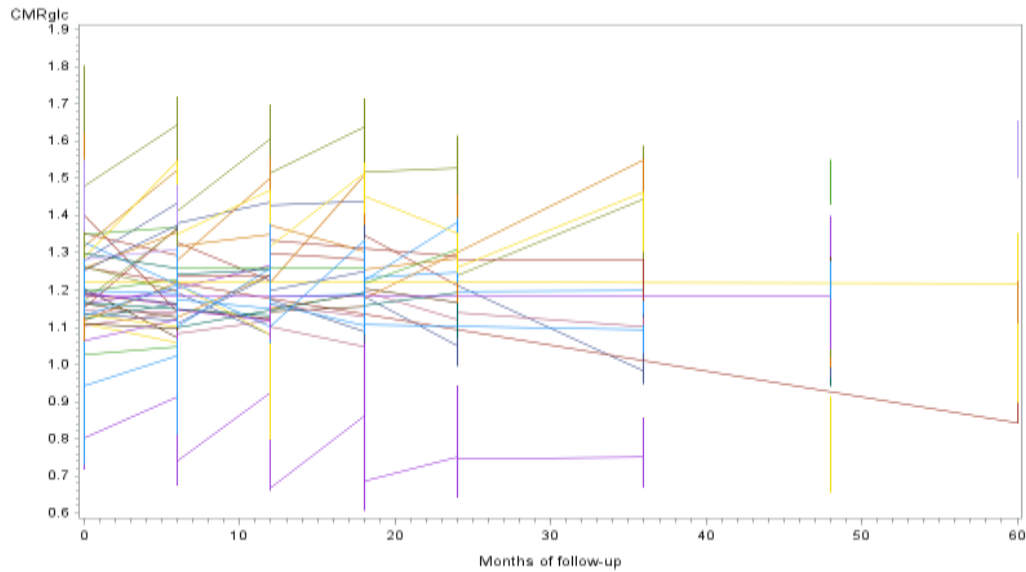
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APPENDICES

Figure A1: Observed individual CMRglc over five years



The linear relationship does not hold across all the subjects and the slopes vary across all the subjects.

Figure A2: Observed individual CMRglc and overall estimated trend of CMRglc over five years by FH status

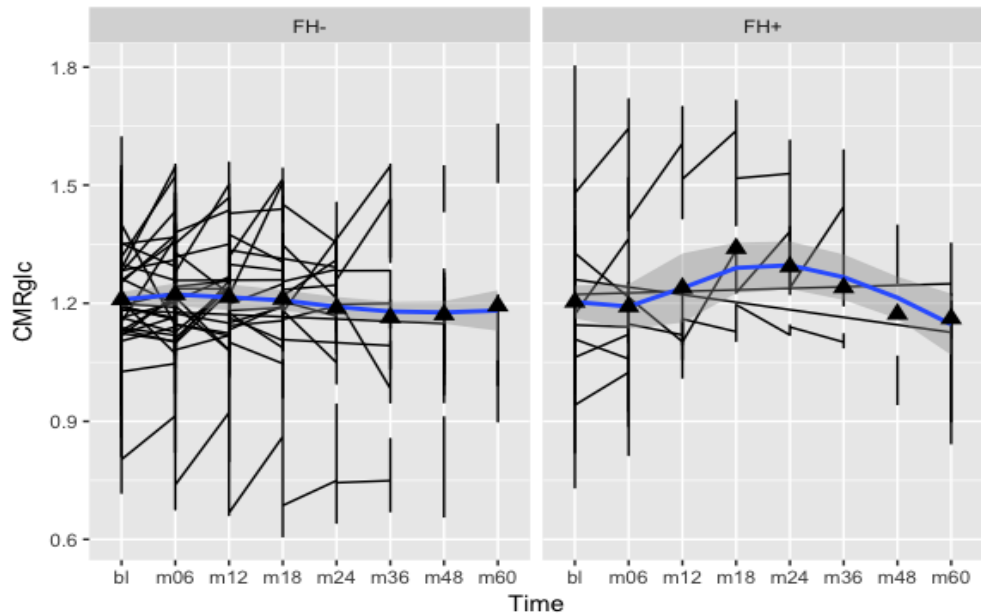


Figure A3: Observed individual glucose metabolism levels and the regression of CMRglc over five years by FH status

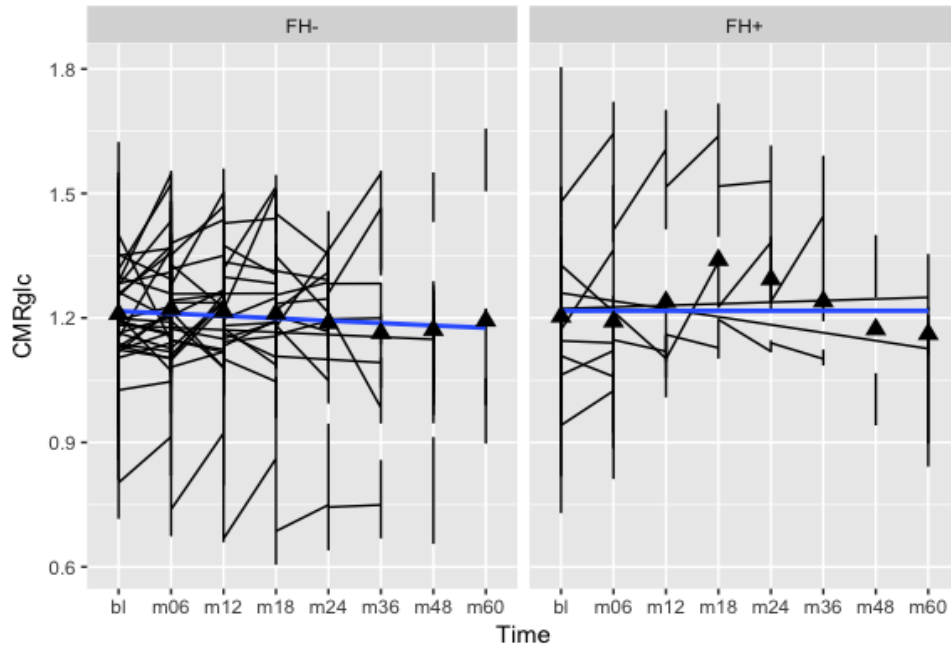
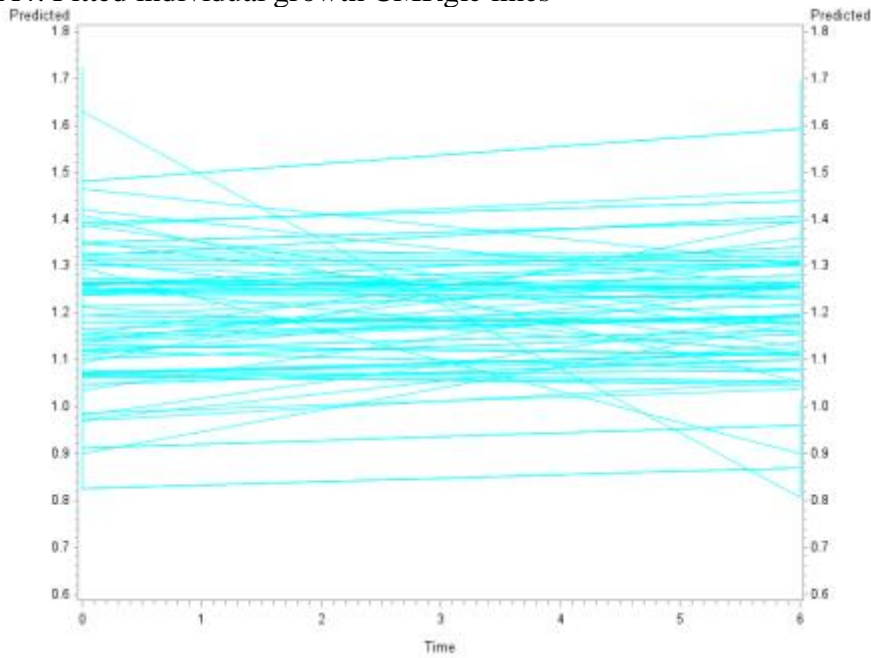


Figure A4: Fitted individual growth CMRglc lines



The individual growth lines vary differently with individual intercepts and slopes.

Some of the individual growth lines slope upwards, some slope downward and others are nearly flat.

Figure A5: Individual and average change trajectory from OLS regression by FH status

