2014

A LIFE SPAN APPROACH TO THE RELATIONSHIP BETWEEN CHOLESTEROL, LATE ONSET ALZHEIMER’S DISEASE, AND COGNITIVE FUNCTIONING AMONG OLDER ADULTS

Brian Downer

University of Kentucky, brian.downer27@gmail.com

Right click to open a feedback form in a new tab to let us know how this document benefits you.

Recommended Citation

Downer, Brian, "A LIFE SPAN APPROACH TO THE RELATIONSHIP BETWEEN CHOLESTEROL, LATE ONSET ALZHEIMER’S DISEASE, AND COGNITIVE FUNCTIONING AMONG OLDER ADULTS" (2014). Theses and Dissertations--Gerontology. 7.
https://uknowledge.uky.edu/gerontol_etds/7

This Doctoral Dissertation is brought to you for free and open access by the College of Public Health at UKnowledge. It has been accepted for inclusion in Theses and Dissertations--Gerontology by an authorized administrator of UKnowledge. For more information, please contact UKnowledge@lsv.uky.edu.
STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student’s advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student’s thesis including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Brian Downer, Student

Dr. John Watkins, Major Professor

Dr. John Watkins, Director of Graduate Studies
A LIFE SPAN APPROACH TO THE RELATIONSHIP BETWEEN CHOLESTEROL, LATE ONSET ALZHEIMER’S DISEASE, AND COGNITIVE FUNCTIONING AMONG OLDER ADULTS

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Gerontology at the University of Kentucky

By

Brian G. Downer

Lexington, Kentucky

Co-Directors: John F. Watkins, Professor of Gerontology and David W. Fardo, Assistant Professor of Biostatistics

Copyright © Brian Gregory Downer, 2014
ABSTRACT OF DISSERTATION

A LIFE SPAN APPROACH TO THE RELATIONSHIP BETWEEN CHOLESTEROL, LATE ONSET ALZHEIMER’S DISEASE, AND COGNITIVE FUNCTIONING AMONG OLDER ADULTS

There is evidence that cholesterol presents an important risk factor for Alzheimer’s disease (AD), but the direction of this relationship is modified by age. High cholesterol during midlife and low cholesterol during late life are both associated with an increased risk for AD. This dissertation research engaged a life span approach to study the relationship between cholesterol, AD and cognitive functioning among older adults. The purpose of this research was to determine if trajectories of cholesterol from midlife through late life differ according to AD status and if these trajectories are associated with cognitive functioning during old age.

This research employed a secondary analysis of cognitive, phenotypic and genetic data collected from subjects of the Framingham Heart Study (FHS) Original and Offspring Cohorts. Aim One involved creating three summary scores of the FHS neuropsychological battery. ROC analysis was used to determine which score best differentiated between cognitively normal, impaired and dementia subjects. Aim Two used generalized additive mixed models to examine trajectories of total, HDL and total/HDL cholesterol ratio according to AD status in the Original Cohort. Aim Three used mixed-effects models to examine the relationship between subject-specific trajectories of total cholesterol and cognition during old age.

Aim One determined that a summary score that provided equal weight to each assessment in the FHS neuropsychological battery best differentiates between subjects classified as cognitively normal, cognitively impaired and dementia. The findings from Aim Two indicated that there are subtle differences in the longitudinal trajectories of total, HDL and total/HDL ratio according to AD status. The findings from Aim Three provide limited evidence for a relationship between subject-specific trajectories of total cholesterol and cognitive functioning later in life. Older adults in the highest quartile for cognitive functioning had lower total cholesterol at approximately 55 years of age, but there were no differences in the mean trajectories of total cholesterol according to cognitive functioning later in life.

The findings from this research suggest that older adults with high cognitive functioning have lower total cholesterol during midlife, but life span cholesterol trajectories do not appear to be associated with AD status or cognitive function.

KEYWORDS: Life span, Cholesterol, Alzheimer’s Disease, Cognition, Older Adults
A LIFE SPAN APPROACH TO THE RELATIONSHIP BETWEEN CHOLESTEROL, LATE ONSET ALZHEIMER’S DISEASE, AND COGNITIVE FUNCTIONING AMONG OLDER ADULTS

By

Brian Gregory Downer

David Fardo, PhD
Co-Director of Dissertation

John Watkins, PhD
Co-Director of Dissertation

John Watkins, PhD
Director of Graduate Studies

June 2, 2014
DEDICATION

To My Grandparents
ACKNOWLEDGMENTS

This dissertation would not have been possible without the support and guidance of a countless number of individuals. I first want to thank my dissertation committee, Drs. John Watkins, David Fardo, Frederick Schmitt, Steven Estus, and Wayne Sanderson, as well as Dr. Glen Mays who served as outside examiner, for their mentorship throughout this entire process. I especially want to acknowledge the efforts of my dissertation co-chairs, Dr. Watkins and Dr. Fardo. First, John Watkins who challenged me intellectually and pushed my thinking to a level a never thought was possible. Second, David Fardo who patiently guided me throughout the duration of my research and who made himself available at a moments notice. I also want to thank Dr. Faika Zanjani who served as my primary advisor and mentor. Dr. Zanjani exemplifies what it means to be an advisor and mentor, and I will be forever grateful for the opportunities she provided me while a student in her lab.

I also need to acknowledge the unending encouragement that I received from my friends and family. First, my girlfriend Paige Birkelbach, who supported me through all of the ups and downs of my research, and often times had more confidence in my abilities than I did. Next, my friend, Jared Neumann, who I could always count on too distract me from the stress of trying to complete my dissertation. Also, I need to recognize my classmates and colleagues who supported me in immeasurable ways throughout my time at the University of Kentucky. Finally, my parents, Jane and Greg Downer, and my brother, Ben, and sister, Lorraine, who gave me unconditional love and support through this entire process.
TABLE OF CONTENTS

Acknowledgements ................................................................................................................................................ iii
List of Tables .......................................................................................................................................................... vii
List of Figures ....................................................................................................................................................... viii

Chapter One: Introduction and Background ........................................................................................................ 1
  Alzheimer’s Disease Research: A Brief Historical Review ................................................................. 3
  Understanding Plaques and Tangles .............................................................................................................. 7
  Do Plaques and Tangles Cause Alzheimer’s Disease? .............................................................................. 8
  An Increase in Public Awareness of Alzheimer’s Disease ........................................................................ 10
  The Future of Alzheimer’s Disease Research ............................................................................................ 14
  Purpose and Objectives of Dissertation Research ..................................................................................... 17

Chapter Two: Review of the Literature .................................................................................................................. 25
  Background ..................................................................................................................................................... 25
  Types of Cholesterol ..................................................................................................................................... 26
  Maintaining Cholesterol Homeostasis ......................................................................................................... 26
    Effects of Diet on Cholesterol Homeostasis ............................................................................................ 27
    Absorption and Excretion of Cholesterol ................................................................................................. 27
    Genetic Contributions to Cholesterol Homeostasis ................................................................................... 28
    Cholesterol-Lowering Medications ........................................................................................................... 29
  Age Related Changes to Cholesterol ........................................................................................................... 31
  Cholesterol and Cardiovascular Health ..................................................................................................... 32
  Cholesterol and the Brain ............................................................................................................................... 33
  Epidemiology of Cholesterol and Alzheimer’s Disease .............................................................................. 35
    Midlife Total, LDL, and HDL Cholesterol ............................................................................................... 36
    Late Life Total, LDL, and HDL Cholesterol ............................................................................................. 36
    Change in Total, LDL, and HDL Cholesterol ............................................................................................ 39
  Summary .......................................................................................................................................................... 40

Chapter Three: A Life Span Approach to the Epidemiology of Alzheimer’s Disease ..................................... 55
  Review of the Life Span Research Framework .............................................................................................. 56
  Concepts of Developmental Psychology and the Life Span Framework ............................................... 58
  Socially Constructed Stages of the Life Span ................................................................................................. 59
  Defining Age Boundaries for Midlife and Late Life According to Trends in Total Cholesterol ................... 60
  Methods ......................................................................................................................................................... 61
  Results ............................................................................................................................................................ 62
    Age Ranges for Midlife in the Original and Offspring Cohorts .............................................................. 62
    Age Cutoffs for Late Life in the Original and Offspring Cohorts ............................................................ 64
  Summary .......................................................................................................................................................... 66
  Contributions of the Life Span Framework to Alzheimer’s Disease Research ............................................. 68
  Differences between the Life Span and Life Course ...................................................................................... 71
Chapter Four: Research Design and Methodology ................................................................. 79
   Overview of Specific Aims .................................................................................................. 79
   The Framingham Heart Study .......................................................................................... 80
   Aim One: Summary Score for the FHS Neuropsychological Battery .......................... 81
      Sample Population ....................................................................................................... 81
      The FHS Neuropsychological Battery ........................................................................... 82
      Case Definitions for Dementia and Cognitive Impairment ......................................... 83
      Generating Summary Scores for the FHS Neuropsychological Battery .................... 84
         Composite Subtests Summary Score ...................................................................... 84
         Learning and Memory Summary Score .................................................................. 84
         Composite Domains Summary Score .................................................................... 84
      Statistical Analysis ..................................................................................................... 85
   Aim Two: Differences in the Longitudinal Trajectories of Cholesterol from Midlife to Late Life According to Alzheimer’s Disease Status ........................................... 86
      Sample Population ......................................................................................................... 86
      Diagnosis of Dementia in the FHS Original Cohort .................................................... 86
      Measures of Cholesterol .............................................................................................. 87
      Statistical Analysis ....................................................................................................... 88
      Covariates ....................................................................................................................... 89
   Aim Three: Subject-Specific Trajectories of Cholesterol According to Cognitive Functioning ............................................................. 91
      Sample Population ......................................................................................................... 91
      Measure of Cognitive Functioning ............................................................................... 92
      Measures of Cholesterol .............................................................................................. 92
      Statistical Analysis ....................................................................................................... 92
      Covariates ....................................................................................................................... 95

Chapter Five: Results ............................................................................................................ 99
   Specific Aim One ............................................................................................................... 99
      Sample Characteristics ................................................................................................. 99
      Effects of Age, Sex, and Education on Cognitive Function ........................................ 99
      Ability of Summary Scores to Differentiate Between Cognitive Groups .................... 100
         NC and Dementia ....................................................................................................... 100
         NC and ILM_{TB} ....................................................................................................... 100
         NC and MDI_{TB} ....................................................................................................... 100
         Dementia and ILM_{TB} .......................................................................................... 101
         Dementia and MDI_{TB} ......................................................................................... 101
         ILM_{TB} and MDI_{TB} .......................................................................................... 101
   Specific Aim Two ............................................................................................................... 102
      Sample Population ......................................................................................................... 102
      Trajectories of Cholesterol According to Alzheimer’s Disease Status ...................... 103
      Trajectories of Cholesterol According to APOE e4 Allele Status ............................. 104
      Trajectories of Cholesterol According to Alzheimer’s Disease and APOE e4 Allele Status .......................................................................................................................... 105
      Trajectories of Cholesterol According to Alzheimer’s Disease Status and Sex .......... 105
**LIST OF TABLES**

Table 1.1, FDA Approved Symptomatic Treatments for Alzheimer’s Disease ........................................... 21
Table 1.2, Disease Modifying Therapies for Alzheimer’s Disease ............................................................. 22
Table 2.1, Cholesterol Lowering Medications ......................................................................................... 45
Table 2.2, Midlife Cholesterol and Alzheimer’s Disease ........................................................................ 46
Table 2.3, Late Life Cholesterol and Alzheimer’s Disease .................................................................. 47
Table 2.4, Change in Cholesterol and Alzheimer’s Disease .................................................................. 52
Table 2.5, Covariates ............................................................................................................................. 53
Table 4.1, Cognitive Assessments in FHS Neuropsychological Battery .............................................. 96
Table 4.2, Effects of Age, Sex and Education on Assessments in FHS Neuropsychological Battery (Univariate Model) ......................................................................................................................... 97
Table 4.3, Effects of Age, Sex and Education on Assessments in FHS Neuropsychological Battery (Multivariable Model) ......................................................................................................................... 98
Table 5.1, Demographic Characteristics ............................................................................................... 110
Table 5.2, Differentiating Between Normal and Dementia .................................................................... 110
Table 5.3, Differentiating Between Normal and ILM\textsubscript{TB} ............................................................. 110
Table 5.4, Differentiating Between Normal and MDI\textsubscript{TB} ............................................................. 111
Table 5.5, Differentiating Between Dementia and ILM\textsubscript{TB} ........................................................... 111
Table 5.6, Differentiating Between Dementia and MDI\textsubscript{TB} ........................................................... 111
Table 5.7, Differentiating Between ILM\textsubscript{TB} and MDI\textsubscript{TB} ...................................................... 111
Table 5.8, Demographic Characteristics according to Alzheimer’s Disease Status ............................... 112
Table 5.9, EDF and Adjusted R\textsuperscript{2} for Trajectories of Total, HDL and Total/HDL According to Alzheimer’s Disease Status ................................................................................................. 113
Table 5.10, EDF and Adjusted R\textsuperscript{2} for Trajectories of Total, HDL and Total/HDL According to \textit{APOE} e4 Allele Status ...................................................................................................................... 114
Table 5.11, EDF and Adjusted R\textsuperscript{2} for Trajectories of Total, HDL and Total/HDL Stratified by Alzheimer’s Disease and \textit{APOE} e4 Allele Status ...................................................................................................................... 114
Table 5.12, EDF and Adjusted R\textsuperscript{2} for Trajectories of Total, HDL and Total/HDL Stratified by Alzheimer’s Disease Status and Sex ........................................................................................................... 115
Table 5.13, Demographic Characteristics of Final Sample According to Cognitive Quartile .................. 116
Table 5.14, Association Between Total Cholesterol Trajectory and Cognitive Quartile ...................... 117
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>The Flow of Calcium and Sodium Through and Ion Channel</td>
<td>23</td>
</tr>
<tr>
<td>1.2</td>
<td>Effects of Memantine on Flow of Calcium and Sodium Through Ion Channels</td>
<td>23</td>
</tr>
<tr>
<td>3.1</td>
<td>Scatter Plot of Total Cholesterol According to Chronological Age, Original Cohort</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Scatter Plot of Total Cholesterol According to Chronological Age, Offspring Cohort</td>
<td>74</td>
</tr>
<tr>
<td>3.3</td>
<td>Cross-Sectional Trends in Total Cholesterol, Original Cohort</td>
<td>74</td>
</tr>
<tr>
<td>3.4</td>
<td>Cross-Sectional Trends in Total Cholesterol, Offspring Cohort</td>
<td>75</td>
</tr>
<tr>
<td>3.5</td>
<td>Cross-Sectional Trends in Total Cholesterol Stratified by Sex, Original Cohort</td>
<td>75</td>
</tr>
<tr>
<td>3.6</td>
<td>Cross-Sectional Trends in Total Cholesterol Stratified by Sex, Offspring Cohort</td>
<td>75</td>
</tr>
<tr>
<td>3.7</td>
<td>Scatter Plot of Cholesterol According to Chronological Age, Offspring Cohort (Exam 2)</td>
<td>76</td>
</tr>
<tr>
<td>3.8</td>
<td>Cross-Sectional Trends in Total Cholesterol, Offspring Cohort (Exam 2)</td>
<td>76</td>
</tr>
<tr>
<td>3.9</td>
<td>Cross-Sectional Trends in Total Cholesterol Stratified by Sex, Offspring Cohort (Exam 2)</td>
<td>76</td>
</tr>
<tr>
<td>3.10</td>
<td>Longitudinal Trends in Total Cholesterol, Original Cohort</td>
<td>77</td>
</tr>
<tr>
<td>3.11</td>
<td>Longitudinal Trends in Total Cholesterol Stratified by Sex, Original Cohort</td>
<td>77</td>
</tr>
<tr>
<td>3.12</td>
<td>Longitudinal Trends in Total Cholesterol, Offspring Cohort</td>
<td>77</td>
</tr>
<tr>
<td>3.13</td>
<td>Longitudinal Trends in Total Cholesterol Stratified by Sex, Offspring Cohort</td>
<td>78</td>
</tr>
<tr>
<td>5.1</td>
<td>ROC Curves, Normal Cognition and Dementia</td>
<td>118</td>
</tr>
<tr>
<td>5.2</td>
<td>ROC Curves, Normal Cognition and ILM&lt;sub&gt;TB&lt;/sub&gt;</td>
<td>118</td>
</tr>
<tr>
<td>5.3</td>
<td>ROC Curves, Normal Cognition and MDI&lt;sub&gt;TB&lt;/sub&gt;</td>
<td>118</td>
</tr>
<tr>
<td>5.4</td>
<td>ROC Curves, Dementia and ILM&lt;sub&gt;TB&lt;/sub&gt;</td>
<td>119</td>
</tr>
<tr>
<td>5.5</td>
<td>ROC Curves, Dementia and MDI&lt;sub&gt;TB&lt;/sub&gt;</td>
<td>119</td>
</tr>
<tr>
<td>5.6</td>
<td>ROC Curves, ILM&lt;sub&gt;TB&lt;/sub&gt; and MDI&lt;sub&gt;TB&lt;/sub&gt;</td>
<td>119</td>
</tr>
<tr>
<td>5.7</td>
<td>Trajectories of Total Cholesterol Stratified by Alzheimer’s Disease Status</td>
<td>120</td>
</tr>
<tr>
<td>5.8</td>
<td>Trajectories of HDL Cholesterol Stratified by Alzheimer’s Disease Status</td>
<td>120</td>
</tr>
<tr>
<td>5.9</td>
<td>Trajectories of Total/HDL Ratio Stratified by Alzheimer’s Disease Status</td>
<td>121</td>
</tr>
<tr>
<td>5.10</td>
<td>Trajectories of Total, HDL, and Total/HDL Ratio Stratified by APOE&lt;sub&gt;e4&lt;/sub&gt; Allele Status</td>
<td>121</td>
</tr>
<tr>
<td>5.11</td>
<td>Trajectories of Total, HDL, and Total/HDL Ratio Stratified by Alzheimer’s Disease and APOE&lt;sub&gt;e4&lt;/sub&gt; Allele Status</td>
<td>122</td>
</tr>
<tr>
<td>5.12</td>
<td>Trajectories of Total, HDL, and Total/HDL Ratio Stratified by Alzheimer’s Disease and Sex</td>
<td>123</td>
</tr>
<tr>
<td>5.13</td>
<td>Trajectories of Total, HDL, and Total/HDL Ratio Among Women Adjusted for Supplemental Estrogen Use Stratified by Alzheimer’s Disease Status</td>
<td>124</td>
</tr>
<tr>
<td>5.14</td>
<td>Subject-Specific Trajectories of Total Cholesterol Stratified by Cognitive Quartile</td>
<td>124</td>
</tr>
<tr>
<td>5.15</td>
<td>Total Cholesterol Trajectories Stratified by Cognitive Quartile</td>
<td>125</td>
</tr>
</tbody>
</table>
Chapter One: Introduction and Background

On November 25, 1901, a 51-year-old woman named Auguste D was admitted to a German hospital with symptoms of impaired comprehension, memory, language and psychosocial skills, along with unpredictable behavior, paranoia and hallucinations (Maurer, Volk, & Gerbaldo, 1997). An autopsy following her death in 1906 revealed that her brain was filled with abnormal proteins that had aggregated into plaques and tangles. Auguste D’s physician from 1901 until her death was Dr. Alois Alzheimer, a psychiatrist and neuropathologist who documented the progression of her disease and, postmortem, observed the plaques and tangles in her brain.

Over a century has passed since Alois Alzheimer first described the clinical and neuropathological characteristics of what would become known as Alzheimer’s disease (AD). Alzheimer’s initial reports, at first, attracted limited interest within the scientific community, but the past fifty years have included landmark discoveries on the biological underpinnings of AD, clinical and neuropathological characteristics of the disease, potential treatments, and genetic and environmental risk factors for AD. These discoveries coincided with population aging and influential social and political events, such as the National Alzheimer’s Project Act (United States National Plan to Address Alzheimer’s Disease, 2012), which have collectively contributed to increased public awareness of AD.

Alzheimer’s disease is a complex disease with genetic, physiological, behavioral, social, and cultural factors all apparently contributing to the onset and progression of the disease. Declines in memory and difficulty recalling recently learned information are among the earliest observable symptoms of AD (Perry & Hodges, 1999). However, biomarkers that signal changes in biological processes that likely play a causal role in the development of AD begin to deviate from normal many years before the onset of cognitive symptoms (Jack et al., 2013). The declines in memory and other cognitive domains, such as language and decision making, are followed by declines in physical functioning and behavioral changes (Mega, Cummings, Fiorello, &
Gornbein, 1996) that substantially reduce a person’s quality of life. Older adults in the advanced stages of AD require assistance from family members or professional caregivers to perform routine activities such as bathing, eating, and dressing. The increasing dependence on caregivers as the disease progresses has a substantial impact on the health of the individual who is providing care, and family caregivers are at an increased risk for depression (Pinquart & Sorensen, 2003), anxiety (Mahoney, Regan, Katona, & Livingston, 2005) and chronic stress (Russo, Vitaliano, Brewer, Katon, & Becker, 1995). Alzheimer’s disease also has a significant impact at the societal level. The estimated financial value of care provided by family members in 2010 for the U.S. was $202.6 billion (Thies & Bleiler, 2011) and the estimated total health care costs in 2010 for persons diagnosed with AD was between $157 billion and $215 billion (Hurd, Martorell, Delavande, Mullen, & Langa, 2013).

The overall poor health of middle aged adults in the United States has received considerable media attention because the resources that are required to treat and manage chronic conditions, such as diabetes, hypertension and high cholesterol, have placed considerable strain on our healthcare system. Medical advances have increased the life expectancy of people with chronic vascular conditions, but this may have significant implications during old age because poor vascular health during middle age has been linked with an increased risk for AD (Duron & Hanon, 2008). Cholesterol is a marker and risk indicator for cardiovascular disease (Anderson, Odell, Wilson, & Kannel, 1991; Castelli et al., 1986), but cholesterol may also be an important risk factor for AD. There is increasing evidence that supports the hypothesis that cholesterol is an important risk factor for AD. Observational studies indicate that high cholesterol during midlife\(^1\) increases the risk for AD (Kivipelto et al., 2001; Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009) and several genes involved in cholesterol transport and metabolism are

---

\(^1\) Midlife is typically defined as between the ages of 35 and 55 and late life is often defined as older than 65 years of age, but these definitions vary slightly from study to study. The definitions of midlife and late life that will be used in the dissertation research are described in more detail in chapter three.
associated with AD, most notably the apolipoprotein E (APOE) gene (Corder et al., 1993; Crean et al., 2011; Olgiati, Politis, Papadimitriou, De Ronchi, & Serretti, 2011). However, low cholesterol during late life and a decline in cholesterol from midlife to late life are both associated with an increased risk for AD (Reitz, Tang, Luchsinger, & Mayeux, 2004; Siest et al., 2000; Stewart, White, Xue, & Launer, 2007). These seemingly conflicting findings suggest an age dependent relationship between cholesterol and AD. This relationship can be further explored by examining longitudinal trajectories of cholesterol from midlife through late life.

The remainder of this chapter first presents a broad overview of the modern history of AD research. This review is meant to provide readers who are not familiar with AD research with sufficient background knowledge to appreciate the purpose and significance of this dissertation research. This review includes a summary of landmark scientific discoveries that have shaped the current scientific understanding of AD, important social and political events that have increased the public awareness of AD, as well as research on the etiology, treatment and prevention of AD. This chapter then introduces the life span research perspective, which served as the conceptual framework for the dissertation research, and summarizes the dissertation research by outlining the organization of the subsequent chapters of this dissertation.

Alzheimer’s Disease Research: A Brief Historical Review

By the start of the 20th century, the term dementia was fairly well established in the scientific literature and several case reports of patients with the cognitive, behavioral, and neuropathological characteristics associated with dementia had been described (Berrios, 1990). The term Alzheimer’s disease, first used by Alois Alzheimer’s mentor Emil Kraepelin, would suggest that Alois Alzheimer had discovered a new disease. However, Alzheimer did not make this claim and there is debate as to if Kraepelin chose the term for purely scientific reasons and believed Alzheimer’s had in fact identified a new disease or if there were personal motivations behind his decision [see Berrios (1990) for a historical review of Kraepelin’s potential motivations for crediting Alois Alzheimer with discovering a new disease). What made Auguste
D a unique case were the combination of clinical and neuropathological characteristics and the unusually young age of onset (Berrios, 1990).

Alzheimer’s disease has been subdivided into early and late onset based on the age of diagnosis. Early onset AD refers to cases that are diagnosed before 65 years of age, whereas late onset AD refers to cases that are diagnosed after 65 years of age or older. Mutations in the APP (Nilsberth et al., 2001), PSEN1 (Uttner et al., 2010), and PSEN2 (Marchani et al., 2010) genes are known causes of early onset AD. These genetic mutations are rare and early onset AD accounts for less than 5% of all cases of AD (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). Unlike early onset AD, there is no single gene or set of genes that ensures a person will develop late onset AD, but the APOE e4 allele is a genetic risk factor that has consistently been observed to increase the risk for AD (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007). Auguste D’s young age of onset makes it likely that she had early onset AD, but there is no definitive evidence that Auguste D carried a genetic mutation for early onset AD. In 2010, Yu et al. (2010) identified a modern-day German family residing in the Hesse region of Germany, the same region that Auguste D lived, with a family history of early onset AD and who carried a mutation in the PSEN2 gene. This circumstantial evidence, along with the cognitive and neuropathological characteristics and the relatively young age in which her symptoms were observed, make it possible that Auguste D had early onset AD.

Relatively little research on AD was conducted in the decades following the initial discoveries by Alois Alzheimer in the early 1900s. This was due largely in part to the limited funding for AD research and a lack of scientific interest in AD and aging research in general prior to the 1970s (Hodges, 2006; Morley, 2004). The 1970s and 1980s marked a significant change in the scientific interest and public awareness of AD in possible response to the founding of the National Institute on Aging (NIA), the Alzheimer’s Association, and Alzheimer’s Disease Centers (ADC) at select academic institutions in the United States. The NIA was founded in 1974 with the purpose of studying the biological mechanisms of aging and aging related diseases
Soon after, in 1980, the Alzheimer’s Association was founded with support from the NIA. The Alzheimer’s Association was started in an effort to compliment the mission of the NIA by focusing research on AD, educating the public about AD and giving support to families who were providing care for someone with AD. Finally, in 1984 the NIA granted funding to Harvard University, Johns Hopkins University, Mount Sinai Medical School, the University of California San Diego and the University of Southern California to allow each institute to start an ADC. One year later, five more institutions, which included Duke University, the University of Kentucky, Washington University at St. Louis, the University of Pittsburgh, and the University of Washington, were provided funding for ADCs. There are currently twenty-nine ADCs in the United States and these Centers conduct focused research on understanding the etiology, progression, prevention and treatment of AD and other neurodegenerative diseases. These Centers also make significant contributions to their respective communities by providing patients and their families with educational resources about dementia, family and patient support groups, and other resources (additional information can be accessed at the Alzheimer’s Disease Education and Referral Center http://www.nia.nih.gov/alzheimers).

The substantial increase in funding for research brought on by the founding of the NIA, Alzheimer’s Association, and ADCs, as well as an expected increase in dementia prevalence (Plum, 1979), all contributed to significant scientific discoveries in the 1970s and 1980s that have advanced scientific understanding of the biological underpinnings of AD. Extensive research in the 1980s focused on determining the biological processes that allow humans to form new memories, and how these processes may be altered in older adults diagnosed with AD. One of the most significant discoveries was reported in 1974 by Drachman & Levit, who determined that a chemical in the brain called acetylcholine plays an important role in the formation and retrieval of memories (Drachman & Leavitt, 1974). In their study, Drachman & Leavitt examined healthy adults to determine if blocking acetylcholine in the brain impairs a person’s ability to form and retrieve recently learned information. Healthy adults who received a drug that blocked
acetylcholine performed worse on a series of memory tests compared to those who did not receive the drug. Furthermore, the memory performance of subjects who received the drug were consistent with the memory performance of older adults who received the same series of memory tests (Drachman & Leavitt, 1974). These findings provided strong evidence that acetylcholine plays a crucial role in the formation and retrieval of memories and that a decrease in acetylcholine may contribute to the decline in memory that is observed to occur with age (Bartus, Dean, Beer, & Lippa, 1982). Subsequent research revealed that the brains of older adults diagnosed with AD have significantly fewer neurons that produce and release acetylcholine compared to older adults without dementia (Lehericy et al., 1993; Whitehouse et al., 1982; Wright, Geula, & Mesulam, 1993). Collectively, these findings made acetylcholine an early target for drugs designed to treat patients with AD. Early therapeutic treatments for AD were designed to target the decrease in acetylcholine by inhibiting the activity of the enzyme acetylcholinesterase, which breaks down acetylcholine (Soreq & Seidman, 2001). Drugs that target this enzyme are called acetylcholinesterase inhibitors (AChEI). This class of drugs makes up the majority of therapeutic treatments for AD that are currently approved by the Food and Drug Administration (FDA). An example of an AChEI is tacrine, which was the first AD drug to enter large scale clinical trials in the United States (Summers, Majovski, Marsh, Tachiki, & Kling, 1986) and was the first pharmaceutical treatment to be approved by the FDA for the symptomatic treatment of mild to moderate AD (Summers, 2006). There are currently five medications approved by the FDA that treat the symptoms of AD (Table 1.1). Four of these medications (donepezil, galantamine, rivastigmine, and tacrine) are acetylcholinesterase inhibitors.

The medication memantine targets a different chemical in the brain called glutamate. Glutamate plays an integral role in learning and memory (Riedel, Platt, & Micheau, 2003), but the presence of too much glutamate is harmful to neurons (Choi, 1992). Under normal physiological conditions, glutamate and another chemical in the brain called glycine open a structure called an ion channel by binding to specific receptors on the channel. Once the ion
channel has been opened, calcium and sodium are able to enter into the neuron. The flow of sodium and calcium into the neuron is stopped once glycine and glutamate are removed from their receptors on the ion channel (Figure 1.1). Neurons may become damaged in the presence of too much glutamate because the ion channels remain open for an extended period of time, which allows for calcium and sodium to over-stimulate the neuron. This over-stimulation increases activity of specialized enzymes that breakdown structural proteins within a neuron and production of free radicals that break down the cell membrane, which ultimately leads to early death of neurons (Choi, 1988). Memantine limits the amount of calcium and sodium that enters into the neuron by creating a physical barrier inside the ion channel (Figure 1.2). Memantine has been shown to temporarily improve physical and cognitive functioning of patients diagnosed with severe AD (Reisberg et al., 2003; Winblad & Poritis, 1999). Until recently, memantine was the only FDA approved medication for older adults in the advanced stages of AD (Cosman, Boyle, & Porsteinsson, 2007), but high doses of donepezil and rivastigmine have both shown efficacy for severe AD (Farlow, Grossberg, Sadowsky, Meng, & Somogyi, 2013; Farlow et al., 2010).

Understanding Plaques and Tangles

Alois Alzheimer described the characteristic plaques and tangles in 1906, but it was not until eighty years later that scientists were able to determine the composition of these two hallmark pathologies of AD. In 1984, Glenner & Wong reported that they were able to successfully isolate and identify the amyloid beta (Aβ) protein, which aggregates to form neuritic plaques in the brain (Glenner & Wong, 1984). Insoluble Aβ2 is produced when the amyloid precursor protein (APP) is cut sequentially by the enzymes β-secretase and γ-secretase (Pike et al., 2007). In AD, there is an increase in β-secretase activity, which leads to an over production of insoluble Aβ in the brain. These proteins stick together to form neuritic plaque (Sinha et al., 1999), which is hypothesized to play a direct role in the decline in cognitive functioning.

A soluble form of Aβ that does not aggregate into neuritic plaques is produced when APP is cut by α-secretase and γ-secretase.
consistent with AD because the build up of neuritic plaque disrupts neuronal function and leads, ultimately, to cell death (Geula et al., 1998).

Soon after it was determined that neuritic plaques form from the aggregation of Aβ, scientists successfully identified the protein that makes up neurofibrillary tangles. Several research groups published findings between 1986 and 1989 that indicated neurofibrillary tangles as comprised mostly of the protein tau (Grundke-Iqbal et al., 1986; Kosik, Joachim, & Selkoe, 1986; J. G. Wood, Mirra, Pollock, & Binder, 1986). Tau is an important protein that maintains the structural integrity of microtubules (Weingarten, Lockwood, Hwo, & Kirschner, 1975). In AD, tau becomes saturated with the chemical phosphate in a process called phosphorylation (Goode, Drubin, & Barnes, 2000). This causes tau to dissociate from microtubules (Ballatore, Lee, & Trojanowski, 2007) and bind together to form neurofibrillary tangles inside of neurons (Santa-Maria et al., 2012). Microtubules are involved in the transportation of nutrients, molecules, and other materials within neurons (Goode et al., 2000) and neurons are unable to maintain normal physiological functioning once microtubules lose their structural integrity.

**Do Plaques and Tangles Cause Alzheimer's Disease?**

Neuritic plaques and neurofibrillary tangles must both be present along with cognitive impairment to warrant a diagnosis of AD (Murayama & Saito, 2004). However, there is debate among scientists as to if an abnormality in Aβ or tau is the primary cause of AD. The amyloid cascade hypothesis proposes that changes in the processing of APP triggers the initial deposition of neuritic plaques and subsequent deposition of neurofibrillary tangles that both contribute to the loss of neurons in the brain and, ultimately, cognitive decline (Hardy & Higgins, 1992). There is a large body of research that has produced evidence supporting the amyloid cascade hypothesis. First, mutations in genes that regulate the processing of APP are associated with early onset AD (Nilsberth et al., 2001; Rogaev et al., 1995; Sherrington et al., 1995). Second, changes in the processing of APP and the accumulation of Aβ both occur before tau becomes phosphorylated and forms neurofibrillary tangles (Jack, Vemuri, et al., 2011; Jack et al., 2012). Finally, there is
evidence that the presence of Aβ in the brain directly contributes to the phosphorylation of tau and subsequent formation of neurofibrillary tangles (Gotz, Schild, Hoerndli, & Pennanen, 2004; M. E. King et al., 2006), but the biological mechanisms that drive this relationship are not well understood (Armstrong, 2011; Ittner & Gotz, 2011). The evidence for the amyloid cascade hypothesis has made Aβ and neuritic plaque a primary target of pharmaceutical treatments and preventions.

Despite the strong support for the amyloid cascade hypothesis, there are important limitations that suggest the accumulation of Aβ may not be the primary cause of AD. First, the severity of neuritic plaque accumulation in the brain is not a strong predictor of the degree of cognitive impairment among older adults diagnosed with AD (Giannakopoulos et al., 2003). Furthermore, it has been reported that in some instances older adults who exhibit normal cognitive functioning have Aβ accumulation in the brain consistent with AD (Bennett et al., 2006; Knopman et al., 2003), while other investigators have reported severe cognitive impairment despite relatively low plaque accumulation among the oldest old\(^3\) (Haroutunian et al., 2008). The second major limitation of the amyloid cascade hypothesis is that several therapies meant to decrease the amount of Aβ produced in the brain and prevent neuritic plaques from forming have not been shown to reverse or halt the progression of AD symptoms (Green et al., 2009; Siemers et al., 2010; Wilcock et al., 2008).

An alternative explanation to the amyloid cascade hypothesis is that structural changes to tau and subsequent formation of neurofibrillary tangles is the primary cause of AD (Parihar & Hemnani, 2004). This hypothesis has been referred to as the tau and tangle hypothesis (Mudher & Lovestone, 2002). The tau and tangle hypothesis has received considerably less support from the scientific community compared to the amyloid cascade hypothesis, but tau plays an important role in the development of AD. During the early stages of AD, neurofibrillary tangles begin to accumulate in regions of the brain involved in memory (Arriagada, Growdon, Hedley-Whyte, &

\(^3\) Oldest old was defined by Haroutunian et al. (2008) as subjects greater than 90 years of age.
Hyman, 1992; E. Braak, Braak, & Mandelkow, 1994) and spread to other regions of the brain as the disease progresses (H. Braak & Braak, 1991, 1995). One of the strongest pieces of evidence for the tau and tangle hypothesis is there is a much stronger relationship between the severity of cognitive impairment and accumulation of neurofibrillary tangles compared to the amount of neuritic plaque in the brain (Arriagada et al., 1992; Ghoshal et al., 2002; Guillozet, Weintraub, Mash, & Mesulam, 2003; Mitchell et al., 2002; Nagy et al., 1995). The tau and tangle hypothesis is not without its limitations; most notably that genetic mutations to the tau protein do not lead to AD. Instead, genetic mutations in tau are known to cause frontotemporal dementia, which is characterized by damage to the frontal and temporal lobes of the brain and severe changes to personality, behavior, and language (McKhann et al., 2001).

Causal relationships between the accumulation of neuritic plaques and neurofibrillary tangles and onset of cognitive and behavioral symptoms of AD have been difficult to establish and disappointing findings from clinical studies that have employed therapies that remove neuritic plaques and neurofibrillary tangles among older adults who are in the mild to moderate stages of AD have motivated criticism towards some AD hypotheses. The collective strengths and limitations of both the amyloid cascade and tau and tangle hypothesis suggest that changes in an unknown biological pathway or pathways cause both the increased production of Aβ and phosphorylation of tau (Small & Duff, 2008). The next steps for scientists are to identify biological pathways that when altered lead to an increased production of both Aβ and phosphorylated tau, and then determine if these biological pathways are potential therapeutic targets. Current research is also focused on the pre-clinical stages of AD and investigating if administering disease modifying therapies to older adults who may be in the pre-clinical stages of AD have efficacy in delaying or preventing progression of AD.

An Increase in Public Awareness of Alzheimer’s Disease

Biomedical research attention along with growing federal funding targeting AD came at a time when population aging was becoming increasingly recognized as a social issue. Retirement
migration was having profound impacts on the age structure of such places as Florida and Arizona (Bohland & Rowles, 1988; Litwak & Longino, 1987; A. Rogers & Watkins, 1987), and even the local population aging as a result of labor outmigration (Wiseman & Roseman, 1979) attracted public attention. An increase in fertility following World War II, along with public health advances that dramatically affected mortality and life expectancy, brought elders into the public spotlight. This lead to elders becoming a larger part of what the population saw each day and their unique needs also became more visible, and more contentious, to the American public.

By the 1990’s, demographic changes in the United States had brought significant attention to the social implications of AD and the anticipated increase in AD prevalence during the coming decades was alarming to scientists and the general public. A significant event in the public awareness of AD occurred on November 4, 1994 when President Ronald Reagan wrote a letter to the American public that announced he had been diagnosed with AD. Even before his announcement, President Reagan had worked hard to increase awareness of AD. In 1982 he, along with the Alzheimer’s Association, established the week of Thanksgiving as National Alzheimer’s Disease Awareness Week. While President Reagan’s announcement immediately increased the awareness of AD among the general public, the disease was already widely recognized as a significant public health concern within the scientific community due to the anticipated increase in the prevalence of AD as the baby boomer generation advanced towards old age.

In 1980, an estimated 2.88 million adults 65 years of age or older were living with AD (D. A. Evans, 1990). This was approximately 11.3% of adults who were 65 years of age and over, but only 3.9% of adults between 65 and 74 years of age were estimated to have AD, whereas 16.4% of adults between the ages of 75 and 84, and 47.6% of adults 85+ were estimated

---

4 Prevalence is a measure that indicates the total number of people in a population with a specific disease.
to have AD. Several studies that examined secular trends in the prevalence and incidence rate\(^5\) of dementia during the 1980’s, 1990’s and early 2000’s have provided evidence for a decline in dementia during this time period. In one of the first studies to examine trends in AD incidence rate over time, Kokmen et al., (1993) observed a U shaped trend in the age and sex adjusted five year cumulative incidence\(^6\) of AD over a twenty-five year period beginning in 1960. In this study, Kokmen and colleges observed that the cumulative incidence rate of AD from 1960-64 was 74.8 cases per 100,000 people, which declined from 1965-69 to 59.6 cases/100,000 people. The decline in the cumulative incidence was followed by a steady increase from 1970-74 (75.2 cases/100,000 people), 1975-79 (87.4 cases/100,000 people), which continued from 1980-84 (94.8 cases/100,000 people). A follow-up analysis conducted by Rocca et al., (2011), which included data collected from 1985-94 detected a small but statistically significant 3% decline per year in the cumulative incidence of AD during this period. These findings (Rocca et al., 2011) are consistent with an earlier study conducted by Manton, Gu, and Ukraintseva (2005) in which the estimated prevalence of dementia in the U.S. decreased from 5.7% in 1982 to 2.9% in 1999. Finally, there is also evidence for a decreasing trend in the prevalence of mild cognitive impairment (MCI), which is often described as a transitional stage between normal cognitive aging and AD (Petersen, 2000, 2004), in the United States during the 1990’s and early 2000’s. Utilizing data from the Health and Retirement Study, Langa et al. (2008) observed that the prevalence of MCI from 1993 to 2002 among two different cohorts of adults 70 years of age and older declined from 5.2% (1993 cohort) to 3.5% (2002 cohort), and that the prevalence of older adults with cognitive impairment consistent with dementia declined from 7.0% (1993 cohort) to 5.2% (2002 cohort). Collectively, the decreasing trends for dementia, AD and cognitive

\(^5\) An incidence rate reflects the number of new cases of a disease per person in the at risk population over a specified period of time, typically ranging from days to a year.

\(^6\) Cumulative incidence accounts for the number of new cases of a disease (i.e. incidence) reported in the at-risk population over a rather long period of time compared to the common incidence rate. Whereas the incidence rate allows examination of immediate disease trends, the cumulative incidence addresses overall impact of a disease and its spread.
impairment from 1980 to 2000 have been attributed to a greater proportion of older adults with high educational attainment, improved vascular health, increased physical activity and greater access to medical resources (Langa et al., 2008; Manton et al., 2005; Rocca et al., 2011). The number of adults 65 years of age and older living with AD in the U.S. has increased during the past decade from approximately 4.5 million in 2000 (Hebert et al., 2003) to 4.7 million in 2010 (Hebert, Weuve, Scherr, & Evans, 2013). The increase in the number of older adults with AD is due largely in part to the growing segment of the population that is living well into old age.

According to the U.S. Census, the number of adults 65 years of age and older increased from 35 million in 2000 (Meyer, 2001) to 40 million in 2010 (Werner, 2011). When the 2000 and 2010 estimates for the number of AD cases reported by Hebert et al. are divided by the number of older adults living in the U.S. in 2000 and 2010, the percentage of adults 65 years of age and older with AD actually decreased slightly from 12.9% in 2000 to 11.8% in 2010.

Since AD risk increases with advancing age, the aging of the baby boomers all but guarantees that the number of older adults diagnosed with AD will increase in the coming decades. Many studies that have projected the future prevalence of AD estimate the number of older adults living with AD by 2050 will approach or exceed 10 million people (Brookmeyer, Gray, & Kawas, 1998; D. A. Evans et al., 1989; Hebert et al., 2003; Hebert et al., 2013).

However, it is important to take into account changes in the secular trends of AD risk factors and how these changes may influence the future prevalence and incidence of AD. Compared to previous generations, there is higher prevalence for obesity, diabetes and hypertension among baby boomers (D. E. King, Matheson, Chirina, Shankar, & Broman-Fulks, 2013), but the higher educational attainment (Day & Bauman, 2000), decreased prevalence of smoking (D. E. King et al., 2013) and better access to medical care (Freid & Bernstein, 2010) may make baby boomers less susceptible to AD. There is concern, however, that the continued increase in obesity (Wang & Beydoun, 2007), diabetes (Mokdad et al., 2001) and hypertension (Ford, Giles, & Mokdad, 2007).
The Future of Alzheimer’s Disease Research

Memantine and other FDA approved medications are designed to lessen the severity of AD symptoms but do not change the progression of the disease because these medications do not target the biological mechanisms believed to cause AD (Golde, Schneider, & Koo, 2011; Huang & Mucke, 2012). Several disease-modifying therapies for AD that target Aβ or phosphorylated tau are currently in development (Table 1.2). The majority of these therapies target Aβ by either: (1) altering the function of the enzymes that cut APP (Best et al., 2005; Eriksen et al., 2003); (2) preventing Aβ from aggregating into neuritic plaques (Gervais et al., 2007; McLaurin et al., 2006); or (3) removing Aβ from the brain (Bard et al., 2000; DeMattos et al., 2001; Escribano et al., 2010). There are other disease-modifying therapies that focus on other biological mechanisms that are believed to cause AD. Two of these therapies are designed to target the tau protein. The first prevents tau from becoming phosphorylated (Hong, Chen, Klein, & Lee, 1997) and the second prevents phosphorylated tau from aggregating into neurofibrillary tangles (Wischik, Edwards, Lai, Roth, & Harrington, 1996). A third therapy is designed to maintain mitochondrial function in neurons (S. Zhang, Hedskog, Petersen, Winblad, & Ankarcrona, 2010). Mitochondria are structures found inside of cells that produce the main energy source used by cells (Freeman, 2008). It has been hypothesized that a decrease in mitochondrial functioning with age contributes to the onset of AD and that maintaining mitochondrial functioning may prevent the cascade of biological events that culminate in AD (Swerdlow, Burns, & Khan, 2010; Swerdlow & Khan, 2004).

A limited number of studies have reported that disease-modifying therapies improve cognitive functioning among patients diagnosed with mild to moderate AD. Encouraging results
from animal models\(^7\) of AD for treatments that inhibit the aggregation of phosphorylated tau have been reported (Deiana, Harrington, Wischik, & Riedel, 2009) and a Phase II clinical trial demonstrated that patients with moderate AD who received the treatment had slower disease progression compared to patients who were given a placebo (Gura, 2008). The findings from a randomized clinical trial of the drug nilvadipine, which is designed to modify the processing of APP and remove Aβ (Paris et al., 2011), indicated that mild AD patients in the treatment group exhibited less declines in overall cognitive functioning and executive functioning\(^8\) compared to AD patients who received a placebo (Kennelly et al., 2012). A point must be made that this was an open-label study, which means that both the study investigators and participants were aware of which participants were in the control group and which were in the treatment group (Kennelly et al., 2012). Finally, a Phase II\(^9\) clinical trial of the drug dimebon, which is designed to maintain mitochondrial function, indicated that treatment was associated with improved cognitive performance over a 26-week period among participants diagnosed mild to moderate AD relative to those who received a placebo (Doody et al., 2008). While initial reports for the benefits of dimebon were promising, later clinical trials did not support these findings and dimebon did not move past phase III clinical trials.

Despite the encouraging results from some clinical trials and animal models of AD, the majority of Phase III clinical trials\(^10\) have produced discouraging results, with little to no observable benefits for cognitive functioning or overall quality of life (Extance, 2010; Gold et al., 2010; Hampel et al., 2009; Salloway et al., 2009; Salloway et al., 2011; Siemers et al., 2010).

\(^7\) Scientists often use animals, such as mice or rats, when conducting research on biological mechanisms of disease or when developing new therapies. These animals mimic the symptoms or pathologies of a particular disease and are used to eliminate the risk of harming human subjects.

\(^8\) Executive functioning is the ability to manage several different cognitive tasks, such as memory, judgment, and decision-making.

\(^9\) Phase II clinical trials include a large sample of patients to determine the effectiveness of the treatment and identify harmful side effects.

\(^10\) Phase III clinical trials include a large sample of patients to confirm the effectiveness of the treatment and further identify harmful side effects.
The limited benefit of disease modifying therapies may be due to therapies being administered too late in the disease process when irreversible damage to the brain has already occurred (Roh & Holtzman, 2012). Such results from drug trials suggest an urgency to develop methods to accurately identify older adults who may be in the preclinical stages of AD. Identifying older adults in the pre-clinical stages of AD may increase the effectiveness of pharmaceutical interventions, and allow a longer time period for people to engage in behavioral changes and to begin planning for potential care needs. But there are significant ethical implications that need to be considered. An argument can be made that disclosing information to a person that they may be in the pre-clinical stages of AD could cause more harm than good because of the anxiety and fear brought on by the knowledge they will develop a disease that has no known cure. Therefore, employing biomarkers to identify older adults with pre-clinical AD has valuable implications in research settings, but is unlikely to have significant clinical value until a cure for AD, or therapy that significantly slows or delays AD progression, is developed.

There are five established biomarkers for AD that reflect AD pathology in the brain (Jack et al., 2010). The accumulation of Aβ in the brain is indicated by a decrease of Aβ in cerebrospinal fluid (CSF; Andreasen et al., 1999) and detection of Aβ in the brain using imaging techniques (Klunk et al., 2004). The loss of neurons in the brain is indicated by an increase in total and phosphorylated tau in the CSF (Andreasen, Vanmechelen, Vanderstichele, Davidsson, & Blennow, 2003), a decrease in glucose metabolism in the brain (Lowe et al., 2009), and cerebral atrophy (Dickerson et al., 2011). These biomarkers accurately discriminate between older adults who may be in the preclinical stages of AD and older adults who maintain normal cognitive function (Shaw et al., 2009), but cost and physical discomfort are potential barriers to collecting these biomarkers. These limitations have motivated research into detecting other biomarkers that may identify older adults who are in the preclinical stages of AD. In a recent study (Mapstone et al., 2014), older adults who transitioned from normal cognition to impaired memory during a five-year period had lower concentrations for ten different phospholipids compared to older
adults who maintained normal cognition. When an independent sample of older adults was examined, this biomarker profile was highly accurate in identifying older adults who went on to convert from normal cognition to impaired memory over a five-year period. These results suggest that a biomarker profile obtained through a simple blood draw may be able to identify older adults who develop memory impairment before any cognitive impairment is observed. The full implications of these findings will not become clear until additional research is conducted, but these findings are an important step forward in developing a blood test that accurately identifies older adults who may be in the preclinical stages of AD.

**Purpose and Objectives of Dissertation Research**

There is a clinical need for a marker that can be collected quickly and is relatively non-invasive, such as a blood draw, that can be used to assess a person’s risk for AD long before cognitive symptoms are observed. Mounting evidence for a relationship between cholesterol and AD strongly suggest that continued research in this area is warranted because cholesterol is routinely measured in clinical settings. This dissertation research utilized data from the Framingham Heart Study (FHS) Original and Offspring Cohorts and engaged a life span approach to study how cholesterol trajectories relate to both AD diagnosis and cognitive functioning. The purpose of this research was to determine if longitudinal trajectories of cholesterol from midlife through late life differ between older adults diagnosed with AD and those without dementia and, further, if these cholesterol trajectories are associated with cognitive functioning among older adults without dementia. Participants in the FHS have received a comprehensive neuropsychological battery comprised of twelve cognitive assessments. The ability of three different summary scores of the FHS neuropsychological battery to differentiate between subjects classified as having normal cognition, impaired cognition, and dementia was therefore investigated.

The life span research approach emphasizes human development as an ongoing process from birth until death (Baltes, 1987). The dissertation research focused on examining continuous
changes in cholesterol with age as opposed to treating midlife and late life as discrete life stages as has been frequently done in previous studies. This allowed for potentially important changes in the trajectories of total cholesterol, HDL cholesterol and total/HDL ratio to be detected. The FHS is a multigenerational study and this research utilized data from the Original and Offspring Cohorts. The Offspring Cohort is comprised of subjects, and their spouses, who had at least one parent who participated in the Original Cohort. Subjects recruited to participate in the FHS Original Cohort were between 28 and 74 years of age during the first clinical examination. The FHS Offspring Cohort does include subjects who were as young as five years of age during the first clinical exam, but this Cohort has not been followed for a long enough period of time to allow for these subjects to reach what would be considered an old age. Therefore, this research is limited in that only a segment of the life span can be studied at the individual level and potentially significant factors prior to middle age are unable to be examined. This limitation needs to be acknowledged because childhood, adolescence and young adulthood are potentially important life stages that may influence AD risk and cognitive functioning later in life. An analysis of biographies written by Catholic Nuns during their early 20’s conducted by Snowdon et al. (1996), for example, revealed that low idea density and low grammatical complexity were both associated with poor cognitive functioning nearly 60 years later. Idea density and grammatical complexity were both positively correlated with educational attainment (Snowdon et al., 1996), which makes it plausible that educational experiences during childhood and adolescence may influence cognitive functioning during old age. This explanation is supported by the findings from other studies that have identified low socioeconomic status during childhood to be associated with poor cognitive functioning during old age (Moceri et al., 2001; R. S. Wilson et al., 2005). Childhood and adolescence play a significant role in health outcomes among middle-aged adults, and these early life stages may have lasting consequences for cognitive functioning during old age. Subsequent research is necessary to examine how genetic, physiological, behavioral and social
factors during childhood and young adulthood influence cholesterol during adulthood and if these early life factors modify the relationship between cholesterol and AD.

Cholesterol is a vital molecule for healthy brain function (Mauch et al., 2001; Pfrieger, 2003), but excess cholesterol has been hypothesized to be harmful to the brain by altering APP processing and increasing production of insoluble Aβ (Frears, Stephens, Walters, Davies, & Austen, 1999). Furthermore, variations in genes that regulate cholesterol balance in the brain, such as *CYP46A1* (Combarros, Infante, Llorca, & Berciano, 2004), *ABCA1* (Katzov et al., 2004) and *APOE* (Corder et al., 1994; Corder et al., 1993) have all been observed to modify the risk for AD. The blood brain barrier effectively prevents the exchange of cholesterol between the brain and the periphery (Bjorkhem & Meaney, 2004), which makes it unlikely that peripheral cholesterol (i.e. cholesterol outside of the brain) directly contributes to AD neuropathology.

While clear biological mechanisms that explain the apparent relationship between peripheral cholesterol and AD remain unknown, there are several reasons why it is important to conduct research on longitudinal trajectories of cholesterol, AD and cognitive functioning. First, the anticipated findings from the dissertation research may generate evidence that patterns of change in cholesterol from midlife to late life differ according to AD status and cognitive functioning later in life. Second, the anticipated findings of the dissertation research may provide insight into the approximate age in which physiological changes associated with AD begin to occur. Finally, the anticipated findings may open new avenues of research to determine if longitudinal trajectories of cholesterol can be used to identify individuals who are at an increased risk for AD before symptoms are observed.

This dissertation is comprised of six chapters. Chapter Two offers a comprehensive literature review from areas of research that influenced the dissertation research. This literature review is meant to establish the background knowledge on the relationship between cholesterol and AD to establish necessary context for this study’s specific aims. Chapter Three describes the life span as a conceptual research framework and how this framework was engaged in the
dissertation research. Chapter Four describes in detail the methods utilized for each of the three specific aims, and Chapter Five presents the results of each specific aim. Finally, Chapter Six summarizes the results generated by the dissertation research and discusses these findings within the context of previous research. This chapter also describes the life course perspective and how applying this perspective to the study of AD and cognitive functioning later in life can contribute to future research.
Table 1.1: FDA Approved Symptomatic Treatments for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept™)</td>
<td>Cholinesterase inhibitor</td>
<td>Evidence that treatment slows the progression of cognitive impairment and physical decline for up to a year or more.</td>
<td>Increased occurrences of adverse events, such as falls, urinary tract infection, pneumonia, and aggression, among patients who received 23 mg/d dose versus standard 10 mg/d dose.</td>
</tr>
<tr>
<td>Galantamine (Reminyl™)</td>
<td>Cholinesterase inhibitor</td>
<td>Evidence that treatment maintains/improves behavioral changes associated with AD, which contributes to a decrease in self-reported caregiver burden.</td>
<td>Treatment does not appear to be more effective for mild to moderate AD compared to previously FDA approved cholinesterase inhibitors (Mintzer &amp; Kershaw, 2003).</td>
</tr>
<tr>
<td>Rivastigmine (Exelon™)</td>
<td>Cholinesterase inhibitor</td>
<td>Treatment has been shown to be effective in moderately severe cases of AD.</td>
<td>Side effects such as nausea and vomiting can be severe in some patients (Mimica &amp; Presecki, 2009).</td>
</tr>
<tr>
<td>Tacrine (Cognex™)</td>
<td>Cholinesterase inhibitor</td>
<td>Treatment has been shown to be beneficial for cognitive functioning, ability to perform ADL, and overall quality of life.</td>
<td>Treatment can be harmful to the liver (Watkins et al. 1994) due to multiple daily doses being required (Bentue-Ferrer, Tribut, Polard, &amp; Allain, 2003).</td>
</tr>
<tr>
<td>Memantine (Ebixa™, Namenda™)</td>
<td>Prevents NMDA receptors from functioning</td>
<td>Treatment is able to delay/slow progression of cognitive decline, behavioral changes, and loss of ability to perform ADL.</td>
<td>Side effects include incontinence, diarrhea, difficulty sleeping, and agitation.</td>
</tr>
</tbody>
</table>
Table 1.2: Disease Modifying Therapies for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>Increases removal of Aβ from the brain.</td>
<td>Evidence for a decline of Aβ in specific regions of the brain of mouse models of AD. Effectiveness of treatment in humans may depend upon APOE genotype. Improvement in cognitive functioning among APOE e4- AD patients, but no observable benefits for APOE e4+ AD patients.</td>
</tr>
<tr>
<td>Semagacestat</td>
<td>Decreases γ-secretase activity.</td>
<td>Evidence that treatment significantly decreases Aβ production among patients with AD. However, Eli Lilly halted the development of semagacestat because of significantly worse cognitive performance among AD patients compared to AD patients who received placebo.</td>
</tr>
<tr>
<td>Tarenflurbil (Flurizan™)</td>
<td>Decreases γ-secretase activity.</td>
<td>Limited to no evidence that treatment is able to delay or slow cognitive decline among patients with mild to moderate AD.</td>
</tr>
<tr>
<td>Tramiprosate (Alzhemed™)</td>
<td>Prevents Aβ from forming neuritic plaques.</td>
<td>Evidence that treatment has short-term benefits for cognition, but treatment was not successful in a Phase III clinical trial. Evidence that treatment may increase the deposition of phosphorylated tau in the brain.</td>
</tr>
<tr>
<td>Scyllo-inositol</td>
<td>Prevents Aβ from forming neuritic plaques.</td>
<td>Findings from a Phase II clinical did not support that Scyllo-inositol had a significant benefit for cognition compared to placebo in patients diagnosed with mild to moderate AD. The two highest doses of Scyllo-inositol were terminated due to an increased risk of death in the treatment group.</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>Increases removal of Aβ from the brain.</td>
<td>Evidence for a slower rate of cognitive decline among patients with mild to moderate AD who were APOE e4-, but not for patients who were APOE e4+. Two Phase II clinical trials did not find bapineuzumab to be effective for patients with mild to moderate Alzheimer’s disease.</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Increases removal of Aβ from the brain.</td>
<td>No observed benefit for cognitive functioning among patients with mild to moderate Alzheimer’s disease.</td>
</tr>
</tbody>
</table>
Charged particles pass through the lipid bilayer via protein structures called ion channels. Calcium and sodium cannot pass through the lipid bilayer when an ion channel is closed (1). An ion channel opens when glutamate and glycine bind to specialized receptors (2). Once the magnesium “cork” leaves the ion channel, calcium and sodium are able to enter the neuron (3). Eventually, glutamate and glycine are removed from their binding sites on the ion channel and the flow of calcium and sodium into the neuron is stopped (4).

During Alzheimer’s disease, it is hypothesized that excess glutamate causes the ion channel to remain open for too long. This leads to an increase in the amount of sodium and calcium that enters into the neuron, which causes the neuron to become damaged or destroyed due to over stimulation. Memantine prevents neurons from becoming damaged from over stimulation by blocking sodium and calcium from passing through an ion channel and into the neuron. Sodium and calcium are able to pass through the ion channel once glycine and glutamate bind to their receptors on the ion channel (1). However, memantine blocks sodium and calcium from entering into the neuron by creating a physical barrier in the ion channel (2).
Chapter Two: Review of the Literature

This chapter comprehensively reviews literature from the areas of scholarship that contributed to this dissertation research. Chapter Two is divided into three major sections. Section one is a broad overview of the exogenous and endogenous sources of cholesterol, how the body uses cholesterol, how the body maintains cholesterol homeostasis, age related changes to cholesterol, and the detrimental effects of abnormal levels of cholesterol on health. It is not feasible to review all of these areas of research in detail, and section one is designed to provide only the necessary background knowledge for subsequent sections of this chapter and the dissertation research. Section two is a literature review of epidemiological studies that have examined the relationship between cholesterol and AD. This includes reviews of midlife and late life measures of total, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol and the change in these cholesterol measures with increasing age. Section three is an overall summary of the literature presented in section two and describes how this research will contribute to the current scientific understanding of the relationship between cholesterol and AD, as well as cholesterol and cognitive functioning.

Background

There is a negative connotation associated with cholesterol among the general public due to the established relationship between high cholesterol and adverse health events, such as heart attack and stroke (Pancioli et al., 1998). This perception is somewhat misguided because cholesterol is an essential molecule for healthy functioning of the human body. The liver is the primary source of cholesterol for the body (van der Wulp, Verkade, & Groen, 2013), but animal based food products such as meat, eggs, and cheese are also significant sources of cholesterol (Ford & Capewell, 2013). Cholesterol is necessary for maintaining the structural integrity of cell membranes (de Meyer & Smit, 2009) and is a precursor for several molecules that have important biological functions (Rezen, Rozman, Pascussi, & Monostory, 2011), including testosterone and estrogen, vitamin D, and bile salts, which aid in digestion.
Types of Cholesterol

Cholesterol is transported in the bloodstream by combining with specialized proteins to form lipoproteins. The efficiency in which a lipoprotein travels through the bloodstream depends on the proportion of protein to cholesterol that comprises the lipoprotein. There are three different lipoproteins that are commonly found in the body. Lipoproteins that contain less protein in relation to cholesterol have a low density and do not travel through the bloodstream very efficiently. These lipoproteins are commonly referred to as “bad” cholesterol because it can accumulate on the walls of blood vessels. The primary function of LDL is to transport cholesterol from the liver through the bloodstream to be used by cells throughout the body (Goldstein & Brown, 2009). Conversely, lipoproteins that contain more protein than cholesterol have a high density and travel more efficiently through the bloodstream than LDL. These lipoproteins are commonly referred to as “good” cholesterol because they carry excess cholesterol in the bloodstream back to the liver where it is secreted into bile and eventually delivered to the intestine (C. J. Fielding & Fielding, 1995). HDL and LDL are the two main lipoproteins that transport cholesterol to and from the liver, but a third lipoprotein called very-low density lipoprotein (VLDL) transports triglycerides along with cholesterol to cells where they are used for energy (Hussain, 2000). Once VLDL has transported the triglycerides to a cell, it is converted to LDL (Havel, 1984). Total cholesterol is the sum of HDL, LDL, and VLDL cholesterol that is found in the bloodstream.

Maintaining Cholesterol Homeostasis

Homeostasis is the constant internal state that is maintained by adjusting chemical, biological, and physiological processes in response to changes in the environment. The body maintains cholesterol homeostasis by tightly regulating how much cholesterol the liver produces based on how much dietary cholesterol is consumed, how much cholesterol is removed from the bloodstream, and how much cholesterol is excreted from the body. Cholesterol levels fall out of homeostasis if the biological mechanisms that regulate cholesterol synthesis, removal, or
excretion become disrupted or do not function properly. Normative physiological changes in liver function and cholesterol absorption that occur with age contribute to disruption in cholesterol homeostasis (Schatz et al., 2001; Silbernagel et al., 2010; Strandberg, Gylling, Tilvis, & Miettinen, 2010; Tilvis, Valvanne, Strandberg, & Miettinen, 2011).

**Effects of Diet on Cholesterol Homeostasis:** There is not strong evidence that consuming a high cholesterol diet substantially increases the concentration of cholesterol in the bloodstream (Harman, Leeds, & Griffin, 2008; Katz et al., 2005; Mutungi et al., 2008). This is because complex biological mechanisms regulate cholesterol synthesis and the liver increases or decreases the amount of cholesterol that is produced based on how much cholesterol is consumed in the diet (Brown & Goldstein, 1997). For example, a person whose typical diet contains a lot of animal products will synthesize less cholesterol because the body is able to utilize dietary cholesterol, whereas a person whose typical diet contains a lot of plant based products, which do not contain cholesterol, will synthesize more cholesterol to meet the body’s needs (P. J. Jones et al., 1996; Sundram, French, & Clandinin, 2003). Foods that are high in fat, specifically trans fat and saturated fat, such as red meat, fried and processed foods, and baked goods have a much greater impact on cholesterol levels in the bloodstream (Mensink & Katan, 1990; Mensink, Zock, Kester, & Katan, 2003). Consuming foods that are high in fat increase LDL cholesterol and decrease HDL cholesterol (Mozaffarian, Katan, Ascherio, Stampfer, & Willett, 2006). This means that there is more cholesterol being transported from the liver to cells throughout the body in the form of LDL cholesterol and less cholesterol being transported back to the liver in the form of HDL cholesterol resulting in a net increase in cholesterol.

**Absorption and Excretion of Cholesterol:** The small intestines play an important role in maintaining cholesterol homeostasis because they regulate cholesterol absorption and excretion from the body. Cholesterol that is consumed in the diet is first absorbed by the intestines and is then transported to the liver where it is either used to make bile salts (J. Y. Chiang, 2004) or is distributed throughout the body as VLDL, which is subsequently converted into LDL cholesterol.
There is considerable variability among humans in the percentage of dietary cholesterol that is absorbed by the intestines, which can range between 20 and 80 percent (Bosner, Lange, Stenson, & Ostlund, 1999; Sehayek et al., 1998; Sudhop et al., 2002). Research suggests that genetics accounts for largest source of variability in cholesterol absorption (Berge et al., 2002; Gylling & Miettinen, 2002; Kesaniemi, Ehnholm, & Miettinen, 1987), but age related changes in cholesterol synthesis and absorption and the use of cholesterol-lowering medications also influence how much dietary cholesterol the intestines absorb. These factors are summarized in subsequent sections of this chapter. Cholesterol is removed from the body in feces either in its original form as cholesterol or in its modified form as bile salts (van der Wulp et al., 2013).

Genetic Contributions to Cholesterol Homeostasis: Several genes play an important role in the absorption, transport, and excretion of cholesterol (Bjorkhem & Eggertsen, 2001; Chawla, Repa, Evans, & Mangelsdorf, 2001; Keller et al., 2013). The most pertinent of these genes to the dissertation research is apolipoprotein E (APOE). APOE is located on chromosome 19 (Olaisen, Teisberg, & Gedde-Dahl, 1982) and encodes the apoE protein. APOE includes three different variations or alleles, e2, e3, and e4. All people inherit one allele from each parent resulting in one of six possible genotypes (e2/e2, e2/e3, e2/e4, e3/e3, e3/e4, and e4/e4). Among Caucasians an estimated 78% of the APOE alleles are the e3 allele, whereas 15% are the e4 allele and the remaining 7% are the e2 allele (Plassman & Breitner, 1996). The apoE protein is one of several proteins that transport dietary cholesterol and triglycerides through the bloodstream as VLDL and is also involved in the conversion of VLDL to LDL cholesterol and the absorption of dietary cholesterol by the small intestines (Hauser, Narayanaswami, & Ryan, 2011). The apoE protein plays an important role in cholesterol homeostasis as indicated by the differences in cholesterol concentrations according to APOE genotypes. Adults with the e3/e3 genotype tend to have lower cholesterol than adults with either the e3/e4 or e4/e4 genotypes, but higher cholesterol compared to adults with either the e2/e4, e2/e3 or e2/e2 genotypes (Boerwinkle & Utermann, 1988; Ehnholm, Lukka, Kuusi, Nikkila, & Utermann, 1986; C. E. Tan et al., 2003). When
environmental factors such as high body mass index, high calorie diet and high blood sugar are also present, adults with the APOE e2/e2 genotype often develop type III hyperlipidemia (de Beer et al., 2002; Mahley, Huang, & Rall, 1999); a rare condition that is characterized by abnormally high concentrations of chylomicrons in the bloodstream, which are another lipoprotein that transports triglycerides to cells (Hussain, 2000).

The relationship between the gene APOE and cholesterol is important to the dissertation research because the APOE e4 allele is the most widely recognized genetic risk factor for late onset AD. The APOE e4 allele was first reported to be linked to AD by Pericak-Vance et al. (1988). Subsequent research conducted by Saunders et al., (1993) and Strittmatter et al. (1993) indicated that the APOE e4 allele frequency was significantly higher in AD cases compared to controls. Finally, Corder et al. (1993) reported that compared to subjects with no APOE e4 alleles, those who carried one APOE e4 allele were nearly three times as likely to develop AD and subjects with two APOE e4 alleles were eight times as likely to develop AD. Also, the average age of AD diagnosis decreased with the presence of each APOE e4 allele. The average age of diagnosis for subjects with no APOE e4 alleles was 85 years, those with one APOE e4 allele was 75 years, and subjects with two APOE e4 alleles was 68 years (Corder et al., 1993).

Cholesterol-Lowering Medications: There are several different cholesterol-lowering medications that are commonly prescribed for the treatment of high cholesterol (Table 2.1). The most well known class of these medications is HMG-CoA reductase inhibitors, more commonly known as statins. Statins lower the concentration of cholesterol in the bloodstream by decreasing the amount of cholesterol produced by the liver. Cholesterol is synthesized by the liver through a series of complex steps regulated by the enzyme HMG-CoA reductase (Goldstein & Brown, 1984). Statins lower the concentration of cholesterol in the bloodstream by limiting the function of HMG-CoA reductase to decrease cholesterol synthesis by the liver (Istvan & Deisenhofer, 2001). Statins are an effective therapy for lowering high LDL cholesterol and high triglycerides (P. Jones, Kafonek, Laurora, & Hunninghake, 1998). However, statins are not able to lower
cholesterol to a healthy level in all adults with high cholesterol. In these instances a physician may prescribe another cholesterol lowering medication in addition to a statin and dietary changes, the combination of which is an effective method to lower cholesterol.

Other classes of cholesterol-lowering medications include niacin, resins, fibrates, and selective cholesterol absorption inhibitors. The benefits of niacin for cholesterol levels were first reported in 1955 (Altschul, Hoffer, & Stephen, 1955). Niacin, also known as nicotinic acid, is a type of B vitamin that effectively increases the amount of HDL cholesterol in the bloodstream by decreasing the uptake of HDL cholesterol by the liver (L. H. Zhang, Kamanna, Zhang, & Kashyap, 2008). Resins are a second class of cholesterol lowering medication that increases the synthesis of HDL cholesterol, but also decreases LDL cholesterol (Davidson et al., 1999; Insull et al., 2001). Resins improve LDL cholesterol levels by decreasing the amount of bile that is reabsorbed by the small intestines during the digestive process. This requires the liver to increase the amount of cholesterol that is converted into bile salts (Sheng, Otani, Brown, & Goldstein, 1995). The fourth class of cholesterol lowering medications is fibrates. These therapies lower triglycerides and increase HDL cholesterol (Rubins et al., 1999) by decreasing the liver’s synthesis of triglycerides while increasing HDL synthesis (Staels et al., 1998). The final class of cholesterol lowering medications is selective cholesterol absorption inhibitors. These therapies lower LDL cholesterol by decreasing the amount of dietary cholesterol that is absorbed by the small intestines (Altmann et al., 2004; Ballantyne et al., 2003; Kastelein et al., 2008). All five classes of cholesterol lowering medications are generally well tolerated by patients and common side effects include flushing of the skin, headache, constipation, and dizziness (Beltowski, Wojcicka, & Jamroz-Wisniewska, 2009; Bissonnette et al., 2006; Davidson et al., 1999; Goldberg et al., 2000; Jeng et al., 1997). However, rhabdomyolysis, which is severe muscle inflammation, is a rare but serious side effect of statins (P. H. Jones & Davidson, 2005).
Age Related Changes to Cholesterol

Longitudinal studies indicate that total, HDL, and LDL cholesterol all tend to increase with age among young and middle age adults and decline with age later in life (Carroll et al., 2005; Ferrara, Barrett-Connor, & Shan, 1997; P. W. Wilson, Anderson, Harris, Kannel, & Castelli, 1994). There are several factors that contribute to the age related changes in cholesterol. The most consistent predictors for an increase in total and LDL cholesterol among young and middle aged adults are consuming a high fat diet (Johansson et al., 2012) and weight gain (Ferrara et al., 1997). The decline in cholesterol among older adults coincides with weight loss, a decrease in body fat, and the use of statins and other cholesterol lowering medications (Carroll et al., 2005). Previous studies have reported that the effect of age on cholesterol among older adults remains significant even after adjusting for changes in diet, physical activity and the use of statins and other lipid lowering medications (P. W. Wilson et al., 1994). This indicates that additional factors influence the decline in cholesterol among older adults. One such factor is hormone differences between men and women. Young and middle-aged women tend to have higher HDL cholesterol and lower total and LDL cholesterol compared to men but these differences become less apparent with increasing age (Jousilahti, Vartiainen, Tuomilehto, & Puska, 1999). Women have a more desirable lipid profile earlier in life because the hormone estrogen regulates cholesterol levels (Lundeen, Carver, McKean, & Winneker, 1997). As women age, total and LDL cholesterol tend to increase and HDL cholesterol decreases due to a decline in estrogen production preceding menopause (Matthews et al., 2009; Stevenson, Crook, & Godsland, 1993). Postmenopausal women with other risk factors for cardiovascular disease may begin estrogen replacement therapy (ERT) to improve their cholesterol levels and decrease their risk for cardiovascular disease (Stampfer et al., 1991). Estrogen replacement therapy may be prescribed for men diagnosed with prostate cancer (Ho, Lee, Lam, & Leung, 2011) but ERT is not used to control high cholesterol among men. There is evidence from comparable studies examining the relationship between testosterone and cholesterol levels among men that a decline in testosterone
with advancing age coincides with an increase in triglycerides and decrease in HDL cholesterol (Barrett-Connor, 1995; Zmuda et al., 1997). Supplementation of endogenous testosterone, however, has not been consistently observed to improve the lipid profile among men (Meriggiola, Marcovina, Paulsen, & Bremner, 1995; Zgliczynski et al., 1996).

The decline in cholesterol with increasing age among older adults observed in longitudinal studies may be the result of a survivor effect in which subjects at an increased risk for mortality due to diseases caused by elevated cholesterol die and subjects with healthy cholesterol levels remain in a study into old age (Bilheimer, 1991). While this certainly needs to be taken into consideration, the decline in cholesterol synthesis by the liver and decline in the amount of dietary cholesterol absorbed by the intestines plays a significant part in the decline of cholesterol later in life. This was demonstrated in a study conducted by Tilvis et al. (2011) in which older adults exhibited a decline in the concentrations of lathosterol, which reflects cholesterol synthesis (Kempen, Glatz, Gevers Leuven, van der Voort, & Katan, 1988) and sitosterol, which reflects cholesterol absorption (Miettinen, Tilvis, & Kesaniemi, 1990) along with a decline in total cholesterol with increasing age. These findings replicate those from earlier studies (Schatz et al., 2001; Silbernagel et al., 2010; Strandberg et al., 2010) and may reflect an overall decline in biological functioning with age that decreases the body’s ability to maintain cholesterol homeostasis.

**Cholesterol and Cardiovascular Health**

A lipid profile test is often included as part of a routine medical exam and involves taking a blood sample to estimate how much total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides are in the blood. Current guidelines recommend that a lipid profile test be performed after an eight to twelve hour fast (Grundy et al., 2004) because the concentration of triglycerides in the blood increases after consuming a high fat meal (B. A. Fielding et al., 1996). A physician is able to use the results from a lipid profile test along with additional health information, such as age and family health history, to estimate a person’s risk for different
cardiovascular diseases. According to the National Cholesterol Education Program's Adult Treatment Panel III guidelines, total cholesterol should not exceed 200 mg/dl, LDL cholesterol should not exceed 100 mg/dl, and HDL cholesterol should not be below 40 mg/dl for men and 50 mg/dl for women (Grundy et al., 2004). Triglyceride levels should not exceed 150 mg/dl (Grundy et al., 2004). Based on data from the National Health and Nutrition Examination Survey (NHANES), the percentage of adults between the ages of 40 and 74 with high LDL cholesterol has declined from 59% between 1976-1980 to 27% between 2007-2010 (Kuklina, Carroll, Shaw, & Hirsch, 2013). This decline is due largely to the increasing trend in the number of Americans who have been prescribed cholesterol-lowering medications during the same time period (Kuklina et al., 2013). Maintaining healthy levels of cholesterol is still a significant public health concern because adults with high LDL cholesterol or low HDL cholesterol are at a substantial risk for atherosclerosis (Assmann, Cullen, & Schulte, 2002), condition described by a hardening and narrowing of arteries due to accumulation of fatty deposits inside the arterial wall (Berliner et al., 1995). If left untreated the fatty deposits will increase in size and substantially restrict blood flow, which may lead to a heart attack or stroke (Lloyd-Jones et al., 2009). Maintaining healthy levels of HDL cholesterol decreases the risk for atherosclerosis because HDL is able to remove cholesterol from fatty deposits and bring it back to the liver (von Eckardstein, Nofer, & Assmann, 2001).

### Cholesterol and the Brain

The brain is a cholesterol rich organ and contains up to 30 percent of all the cholesterol found in the human body (Reitz, 2013). Dietary cholesterol and cholesterol that is synthesized by the liver does not contribute to the cholesterol that is found in the brain because the blood-brain barrier prevents the exchange of cholesterol between the bloodstream and the brain (Dietschy & Turley, 2001). Instead, specialized cells in the brain called oligodendrocytes and astrocytes are responsible for synthesizing nearly all of the cholesterol found in the brain (Bjorkhem & Meaney, 2004). Neurons are also capable of synthesizing cholesterol, but in much smaller amounts.
Oligodendrocytes need to synthesize large amounts of cholesterol because they use cholesterol to produce myelin (Jurevics & Morell, 1995), which is essential for the normal functioning of the brain and other parts of the nervous system. Myelin insulates the axons of certain nerve cells similar to the insulating cover that surrounds a wire and allows for electrical impulses to travel quickly along a nerve cell (Sherman & Brophy, 2005). The cholesterol that is synthesized by astrocytes is transported to neurons where it is then incorporated into the cell membrane (Bjorkhem, 2006).

Oligodendrocytes and astrocytes synthesize cholesterol using the same biological pathway as the liver (Maioli et al., 2013). Oligodendrocytes synthesize a limited amount of cholesterol in utero because very little myelination occurs in the brain during the fetal stage of development (Dietschy & Turley, 2004). The rate of cholesterol synthesis in the brain increases following birth and remains high up until young adulthood at which point the rate of synthesis begins to decline as the brain becomes fully developed (Dietschy & Turley, 2004). While the brain needs to synthesize cholesterol to maintain normal physiological functioning, it is important that excess cholesterol is removed from the brain. The brain maintains cholesterol homeostasis by modifying the structure of cholesterol into a form that is able to pass through the blood brain barrier (Lutjohann et al., 1996). The inability to adequately modify the structure of cholesterol and remove it from the brain is linked to several neurodegenerative diseases, including AD (Casserly & Topol, 2004), Parkinson’s disease (Vance, 2012), and Huntington’s disease (Karasinska & Hayden, 2011).

Children who do not synthesize an adequate amount of cholesterol by the liver and the brain in utero and during the first few years of life exhibit developmental, physical, and neurological abnormalities. Smith–Lemli–Opitz syndrome (SLOS) is a genetically inherited cholesterol deficiency syndrome that is caused by a defect in the enzyme that converts 7-dehydrocholesterol into cholesterol during the final step of the cholesterol synthesis pathway (Fitzky et al., 1998). The number of live births that are diagnosed with SLOS is estimated to be between 1 in 2,100 and 1 in 19,000 (Battaile, Battaile, Merkens, Maslen, & Steiner, 2001). Children diagnosed with SLOS may be born with physical abnormalities, such as a cleft-palate and small head circumference and exhibit delayed growth and intellectual delays (Tint et al., 1994).
There are many different biological mechanisms proposed to explain the relationship between high total cholesterol during midlife and AD. One potential mechanism is the link between high cholesterol and atherosclerosis. The Circle of Willis is a collection of arteries that supplies blood to the brain and atherosclerosis in these arteries is more prevalent among older adults diagnosed with AD (Roher et al., 2011). The blood-brain barrier significantly limits the exchange of cholesterol between the circulatory system and the brain (Dietschy & Turley, 2001) making it unlikely that cholesterol directly contributes to Aβ production in the brain. While cholesterol may not directly cause AD neuropathology, targeting high cholesterol may disrupt the biological chain of events that triggers the deposition of Aβ and tau pathologies that ultimately lead to neurodegeneration, cognitive decline, and AD. High cholesterol causes inflammation of the brain (Thirumangalakudi et al., 2008) and to the small blood vessels that surround the brain (Granger, Rodrigues, Yildirim, & Senchenkova, 2010). This inflammation has been linked to an increase in Aβ generation (Lee et al., 2008). The accumulation of Aβ in the brain contributes to the deposition of hyperphosphorylated tau (Busciglio, Lorenzo, Yeh, & Yankner, 1995; Takahashi, Capetillo-Zarate, Lin, Milner, & Gouras, 2010), but the biological mechanisms driving this relationship are not fully understood (Armstrong, 2011).

**Epidemiology of Cholesterol and Alzheimer’s Disease**

Epidemiologists primarily study how a disease or other health outcome is distributed within a population and the factors that protect or predispose a population to that disease or outcome. There is increasing evidence from epidemiological studies that indicate concentrations of total, LDL, and HDL cholesterol in the bloodstream modify the risk for AD. This section addresses literature that examines how the relationship between cholesterol and AD varies according to the type of cholesterol that is measured (total, LDL, or HDL cholesterol), the age that cholesterol is measured (midlife versus late life) and the change in cholesterol with age.
Midlife Total, LDL, and HDL Cholesterol

Studies that examine the relationship between midlife measures of cholesterol and AD are summarized in Table 2.2. In general, the findings from these studies indicate that high total cholesterol during midlife is associated with an increased risk for AD during old age. There were no studies identified by the literature review that assessed HDL or LDL cholesterol during midlife. The findings of the three studies that reported a significant relationship between midlife total cholesterol and AD suggest that the concentration of total cholesterol must surpass a specific threshold before the risk for AD is increased. All three of these studies reported that an increased risk for AD was only observed for subjects with total cholesterol that was ≥240 mg/dl whereas subjects with borderline high cholesterol (200 mg/dl - <240 mg/dl) were not at an increased risk compared to subjects with normal total cholesterol (<200 mg/dl). Mielke et al., (2010) did not observe that high midlife total cholesterol increased AD risk but this may have been due to only being able to examine women. None of the other four studies tested for an interaction between total cholesterol and sex, so the potential interactive effects of sex on the relationship between cholesterol and AD could not be determined based on the evidence from the literature review. The age cut-off used to define midlife may also modify the relationship between total cholesterol and AD. Of the three studies that detected a significant relationship, two restricted their sample population to include subjects between 40 and 60 years of age (Kivipelto, Helkala, & Hallikainen, 2000; Notkola et al., 1998) and the third limited their sample to include subjects between 40 and 45 years of age (Solomon, Kivipelto, et al., 2009). C. J. Chiang et al. (2007) excluded subjects who were younger than 30 years of age upon enrollment into the study, but this was the only study identified in the literature to not specify if an upper limit was placed on age. Age was treated as a continuous variable in all four of these studies.

Late Life Total, LDL, and HDL Cholesterol

Studies that examined the relationship between late life measures of cholesterol and AD are summarized in Table 2.3. All of these studies assessed total cholesterol, whereas a limited
number of studies included measures of LDL cholesterol or HDL cholesterol. The relationship between cholesterol measures during late life and AD appears to vary according to total, LDL, or HDL cholesterol. Based on evidence from the available literature, low total cholesterol during late life appears to be a risk factor for AD. Nine studies detected a significant relationship between total cholesterol and AD. Three of these studies reported that total cholesterol was significantly lower in AD cases compared to controls (Lepara, Valjevac, Alajbegovic, Zaciragic, & Nakas-Icindic, 2009; Merched, Xia, Visvikis, Serot, & Siest, 2000; Siest et al., 2000) and four studies observed that higher total cholesterol decreased the risk for AD (R. M. Evans et al., 2000; Kuusisto et al., 1997; Mielke et al., 2005; Reitz et al., 2004). Furthermore, Hayden et al., (2006) reported that older adults with a history of high total cholesterol after the age of 65 had a decreased risk of developing AD three years later. However, Lesser et al. reported that AD cases had significantly higher total cholesterol compared to controls. Two of the seven studies that examined LDL cholesterol found a significant association with AD. Lepara et al., (2009) reported that AD cases had significantly lower LDL cholesterol during late life compared to controls, whereas Lesser et al., (2001) observed that AD cases had higher LDL cholesterol compared to controls. Finally, of the eleven studies that examined late life HDL cholesterol, only three detected a significant association between HDL cholesterol and AD. Merched et al., (2000) reported that AD cases had lower HDL cholesterol during late life compared to non-demented controls. This is consistent with the findings reported by Reitz et al., (2004) in which high HDL cholesterol during late life was protective against AD, but this finding was not replicated when the data were examined using a prospective study design. However, Kalman et al., (1999) observed that older adults diagnosed with AD had higher HDL cholesterol compared to controls.

Close examination of these studies suggests that the age cut-offs to define late life influences the relationship between total cholesterol during late life and AD. Eleven of the seventeen studies that assessed cholesterol during late life reported if the final sample was restricted according to age and the majority of these studies removed subjects who were younger
than 65 years of age. The results of studies that excluded subjects who were not 65 years of age or older were much more consistent and seven of the ten studies reported that low total cholesterol was associated with AD. The only study to contradict the above findings was conducted by Lesser et al. (2001). In this study, Lesser et al. reported that AD cases had significantly higher total cholesterol compared to controls (210.0 mg/dl vs. 194.0 mg/dl P<0.05). There are several explanations as to why the results from this study contradict those reported by the majority of studies. First, the sample population studied by Lesser et al. (2001) was considerably older than the sample populations of the other studies. The median age of the final sample of the Lesser et al. study was 89 years and only twelve of the 106 participants were younger than 80 years of age. This is due to Lesser et al. only including participants in the final sample who had received a postmortem autopsy of the brain to definitively diagnose AD. Second, the control group consisted of subjects who had received a diagnosis of dementia while living but did not meet the neuropathological criteria for possible, probable or definitive AD based on a brain autopsy. The advantage of selecting a control group that consists of subjects who exhibit the outward symptoms of a disease but do not actually have the disease is it can decrease sampling bias. However, this is only the case if the exposure is not related to the observed symptoms (Wacholder, Silverman, McLaughlin, & Mandel, 1992). Lesser et al. may have violated this assumption because there is evidence that low cholesterol during late life is associated with impaired cognitive functioning among non-demented older adults (Solomon, Kareholt, et al., 2009; J. Zhang, McKeown, & Hajjar, 2005). These characteristics of the study by Lesser et al. need to be considered when comparing their findings with those of other studies.

There is little evidence to suggest that there is a significant relationship between late life LDL and HDL cholesterol and AD. Furthermore, the findings from the few studies that detected a significant relationship between LDL, HDL, and AD are inconsistent. Two of the seven studies that examined LDL cholesterol found a significant association with AD. Lepara et al., (2009) reported that AD cases had significantly lower LDL cholesterol during late life compared to
controls (3.51 mmol/L vs. 4.08 mmol/L P<0.05), whereas Lesser et al., (2001) observed that AD cases had higher LDL cholesterol compared to controls (132.5 mg/dl vs. 119.5 mg/dl P<0.05). Eleven studies examined late life HDL cholesterol, but only three studies detected a significant association between HDL cholesterol and AD. Merched et al., (2000) reported that AD cases had lower HDL cholesterol during late life compared to non-demented controls. This is consistent with the findings reported by Reitz et al., (2004) in which high HDL cholesterol during late life was protective against AD, but this finding was not replicated when the data was examined using a prospective study design. However, Kalman et al., (1999) observed that older adults diagnosed with AD had higher HDL cholesterol compared to controls. This conflicting finding may be due to Reitz et al., (2004) and Merched et al., (2000) using fasting measures of HDL cholesterol whereas Kalman et al. did not specify if fasting or non-fasting measures of HDL cholesterol were used in the analysis.

**Change in Total, LDL, and HDL Cholesterol**

A summary of the four studies that examined the change in cholesterol and AD risk is provided in Table 2.4. All four of these studies assessed total cholesterol, but none examined changes in LDL or HDL cholesterol. Notkola et al. (1998) collected a total of six measures of cholesterol over a thirty-year period beginning in 1959 from 444 Finish men. According to the results from repeated measures ANOVA, men diagnosed with AD had higher total cholesterol on average from 1959-1974 and a greater decrease in total cholesterol from 1974 to 1989 compared to men without AD. In a more recent study, Mielke et al. (2010) used Cox proportional hazards regression models to examine the time-dependent change in cholesterol and the onset of dementia and AD among 1,462 Swedish women. Cholesterol change was defined by Mielke et al. (2010) as the difference in cholesterol between consecutive examinations and was analyzed as quartiles. Women in the quartile of greatest decrease in cholesterol (difference > -0.5 mmol/L between examinations) were at an increased risk for all-cause dementia compared to women in the middle two quartiles (cholesterol change of -0.5 mmol/L to 0.75 mmol/L between examinations). When
only cases of AD were examined, women in the quartile of greatest decrease in cholesterol were at a greater risk for AD compared to women in the middle two quartiles, but these results were not statistically significant (Mielke et al., 2010). Tan et al., (2003) calculated the change in total cholesterol using data that had been collected during two observation periods, but did not observe that a greater decrease in cholesterol increased the risk for AD. Finally, there is limited evidence to suggest that subjects who develop AD exhibit a different trajectory of cholesterol over time compared to subjects without dementia. In a study conducted by Stewart et al. (2007), random-effects models were used to estimate the trajectories of cholesterol among Japanese American men over a twenty-six year period. Stewart et al. (2007) did not observe any differences in total cholesterol according to dementia status during the baseline examination, but men who developed AD exhibited a greater non-linear decline in cholesterol with age compared to men who did not develop dementia.

**Summary**

Many studies in this literature review did not detect a significant relationship between late life cholesterol, midlife cholesterol, or changes in cholesterol and AD. There are several explanations for the inconsistent findings between studies. First, results differed according to study design. For example, Reitz et al., (2004) examined data from two cohorts (1992 – 1994, 1999 – 2002) of the Washington Heights-Inwood Columbia Aging Project to perform cross-sectional and prospective analyses on the relationship between cholesterol and AD. When data from both cohorts were combined and examined cross-sectionally, high HDL cholesterol was associated with lower odds for AD but no significant association between total cholesterol and AD was observed. When a prospective analysis using data from the 1992 cohort was performed, high total cholesterol during late life was associated with a reduced risk for AD and the finding for HDL cholesterol was not replicated. Reitz et al. (2004) did not specify if the 1992 and 1999 cohorts differed according to age, gender, education, statin use or other factors, and the inconsistent findings may be an artifact of differences between the 1992 and 1999 cohorts.
Differences in findings according to study design may also be due to the cross-sectional analysis including prevalent cases of AD, whereas the prospective design examines incident cases of AD. The disadvantage of utilizing a cross-sectional design is that some subjects with low cognitive performance not due to disease (e.g. low educational attainment) may have been incorrectly classified as having AD, which would potentially weaken the relationship between AD and cholesterol. The potential for misclassification is reduced in a prospective study design that includes incident cases of AD because all subjects entered into the study non-demented and a diagnosis of AD is made based on cognitive performance over a number of years.

Another potential explanation for the inconsistent findings is the wide range in the sample sizes examined by different studies. The sample sizes of the studies included in the review ranged from N=39 (Kalman et al., 1999) to N=848505 (Kimm et al., 2011), and it is likely that several studies were either under or over powered. Power is the likelihood that a statistical test will reject the null hypothesis given a specified level of significance (often $\alpha<0.05$), the strength of the relationship between independent and dependent variables (i.e. effect size), and sample size (J. Cohen, 1992). Studies that include a large number of participants are likely to detect a significant relationship between cholesterol and AD even when the effect size is small, whereas studies with small sample sizes will be less likely to detect a significant relationship unless the effect size is very large.

A third explanation for inconsistent findings is that some studies did not control for the effects of potentially important covariates in either the design stage or analysis stage of the study. Covariates are independent variables that may influence the outcome of interest and whose effect needs to be controlled for in the study. Common covariates included in studies that examine the relationship between cholesterol and AD include age, sex, and $APOE$ e4 allele status. A summary of the covariates included in the review is provided in Table 2.5. Surprisingly, several studies did not include what would seem to be potentially important covariates when performing multivariable analyses, and two studies (C. J. Chiang et al., 2007; Wieringa, Burlinson, Rafferty, 2007).
Gowland, & Burns, 1997) did not control for the effects of any covariates. Sixteen studies controlled for age and sex, and eight studies included age, sex and education as covariates when performing multivariable analyses. Six studies included history of statin use and seven studies included APOE e4 allele status as covariates in multivariable analyses, and only ten studies specified that they used fasting measures of cholesterol. Including additional variables such as age or sex is important to avoid confounding, which occurs when a third variable is related to both the independent variable and dependent variable, but is not in the causal pathway of the disease. Potentially confounding variables can most often be detected by conducting a thorough literature review and by comparing results of unadjusted and adjusted analyses. Not accounting for the effect of a confounding variable will falsely increase or decrease the strength of the association between independent and dependent variables (McNamee, 2003). For example, statins are effective treatments for lowering high cholesterol, but there is evidence that patients who have a history of taking a statin are less likely to develop AD later in life (Jick, Zornberg, Jick, Seshadri, & Drachman, 2000; Wolozin, Kellman, Ruosseau, Celesia, & Siegel, 2000). Therefore, if the effect of statin use is not accounted for in the study, then a relationship between low cholesterol and decreased risk for AD may actually be due to the confounding effect of statin use.

The effects of a confounding variable can be controlled for in the design phase or analysis phase of a study. Confounding can be controlled for in the design phase several ways. The first is randomization in which subjects are randomly assigned into a study group or control group. Randomization controls for confounding by making the treatment and control groups similar for known characteristics, such as age, gender, education, and unknown characteristics that may also be confounders. An investigator can ensure that the randomization was effective by comparing the characteristics of the treatment and control groups to make sure that there are no significant differences between the groups. Randomization is well suited for clinical trials where participants are randomly assigned to receive a placebo or the treatment, but is not possible in
observational studies. For example, it is not ethical to randomly assign a large group of people to consume a high fat diet so that they develop high cholesterol and then examine if they are at an increased risk for AD later in life. A second way to control for confounding is to restrict study recruitment according to a specific characteristic. For example, if an investigator is concerned that sex is a potential confounder then the sample population may only include men or women. While this approach is very straightforward, there are several limitations. Restriction makes it difficult to generalize the findings of the study to an entire population, may reduce the size of the final sample, and makes it impossible to examine the effect the factor that subjects were restricted against has on the outcome (e.g. cannot examine potential differences in the relationship between cholesterol and AD according to sex). The third way to control for confounding in the design phase of a study is called matching. Matching can be done at the population level or at the individual level. Individual level matching means that participants are chosen according to specific characteristics. For example, if a study matched subjects according to age then every 35 to 45 year old with high cholesterol that was enrolled in a study would be paired with a 35 to 45 year old with normal cholesterol. When matching is done at the population level, the goal is to make sure that the distribution of important characteristics, such as age and gender, are similar between cases and controls or exposed and unexposed individuals. This approach is effective when wanting to control for a complex characteristic such as socioeconomic status, but matching can be time consuming, greatly reduce sample size, and the effects of the characteristics that were matched for can no longer be evaluated. Also, the fact that subjects were matched in the design stage needs to be accounted for in the analysis stage of the study.

Confounding can be adjusted for in the analysis stage of a study by conducting either a stratified analysis or multivariable analysis. A stratified analysis means that the sample is divided according to a specific characteristic. For example, if sex is a potential confounding variable then subjects can be stratified so that only men are included in one analysis and only women are included in the other analysis. The results from these separate analyses can be compared to help
clarify if gender is confounding the relationship between the independent and dependent variables. Stratification is a straightforward method of controlling for confounding, but it is difficult to control for multiple confounding variables because the number of substrata increases rapidly. A multivariable analysis is appropriate when several variables need to be controlled for in a study, and allows for the effect of an independent variable on the dependent variable to be determined while controlling for the effects of potential confounders. A multivariable approach was utilized in the dissertation research to take into account the effects of gender, education, smoking, blood pressure and blood sugar, the use of cholesterol lowering medications, the use of estrogen replacement, and APOE e4 allele status when examining the relationship between cholesterol and AD.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Examples</th>
<th>Mechanism</th>
<th>Effects of treatment</th>
<th>Common side effects</th>
</tr>
</thead>
</table>
| Statins                     | Atorvastatin (Lipitor®)  
Rosuvastatin (Crestor®)  
Simvastatin (Zocor®)   | Inhibits HMG-CoA reductase to decrease synthesis of cholesterol by the liver.| Lowers LDL cholesterol and triglycerides. | Headache, dizziness, and flushing of the skin. Potentially more serious side effects include muscle inflammation (myositis) or muscle weakness. |
| Niacin                      | Nicolar Niaspan    | Decreases the amount of HDL cholesterol that is reabsorbed by the liver.    | Lowses LDL cholesterol and increases HDL cholesterol. | Flushing of the skin, headache, nausea, and diarrhea.    |
| Resins                      | Colestipol (Colestid®)  
Colesevelam (WelChol®) | Decreases the reabsorption of bile, which increases the conversion of cholesterol into bile salts. | Decreases LDL cholesterol and increases HDL cholesterol. | Constipation, diarrhea, and nausea.                      |
| Fibrates                    | Gemfibrozil (Lopid®)  
Fenofibrate (Tricor®) | Decreases the synthesis of triglycerides and increased synthesis of HDL by the liver. | Decrease triglycerides and increase HDL cholesterol. | Indigestion, abdominal pain, and headache.               |
<p>| Selective cholesterol absorption inhibitors | Ezetimibe (Zetia®) | Decreases cholesterol absorption by the small intestines. | Decreases LDL cholesterol. | Constipation, dizziness, diarrhea.                        |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Baseline Age/Year</th>
<th>Follow up Age/Year</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kivipelto et al., 2000</td>
<td>Finland</td>
<td>48 AD, 1352 cntrl</td>
<td>1972, 1977, 1982</td>
<td>Participants between 65-70 yrs./1997</td>
<td>&lt;6.5 mmol/L vs. ≥6.5 mmol/L OR 2.1 (1.2, 4.7) <em>P&lt;0.05</em></td>
</tr>
<tr>
<td>Mielke et al., 2010</td>
<td>Sweden (women only)</td>
<td>80 AD, 1382 cntrl</td>
<td>Midlife 38 – 60 yrs.</td>
<td>2000–2001</td>
<td>≥6.5 mmol/L HR 1.48 (0.73, 2.96) <em>P&gt;0.05</em> Q1 vs. Q2 HR 2.05 (0.70, 6.04) <em>P&gt;0.05</em> Q1 vs. Q3 HR 2.51 (0.87, 7.26) <em>P&gt;0.05</em> Q1 vs. Q4 HR 2.82 (0.94, 8.43) <em>P&gt;0.05</em></td>
</tr>
<tr>
<td>Solomon et al., 2009</td>
<td>United States</td>
<td>469 AD, 9248 cntrl</td>
<td>Midlife 40 – 45 yrs.</td>
<td>2005–2007</td>
<td>&lt;200 mg/dl vs. 200-239 mg/dl HR 1.2 (.97, 1.6) <em>P&gt;0.05</em> &lt;200 mg/dl vs. ≥240 mg/dl HR 1.57 (1.23, 2.01) <em>P&lt;0.05</em> Q1 vs. Q2 HR 1.25 (0.96, 1.63) <em>P&gt;0.05</em> Q1 vs. Q3 HR 1.31 (1.01, 1.71) <em>P&gt;0.05</em> Q1 vs. Q4 HR 1.58 (1.22, 2.06) <em>P&gt;0.05</em></td>
</tr>
<tr>
<td>Chiang et al., 2007</td>
<td>Taiwan</td>
<td>73 AD, 292 cntrl</td>
<td>Midlife ≥30 yrs./1982 – 1986</td>
<td>2000 – 2001</td>
<td>Chi-square (2df) 0.96, <em>P&gt;0.05</em></td>
</tr>
<tr>
<td>Notkola et al., 1998</td>
<td>Finland (men only)</td>
<td>27 AD, 397 cntrl, 20 other dementia</td>
<td>Midlife age 40 – 59</td>
<td>1989</td>
<td>&lt;6.5 mmol/L vs. ≥6.5 mmol/L OR 3.1 (1.2, 8.5) <em>P&lt;0.05</em></td>
</tr>
</tbody>
</table>

**Table 2.2: Midlife Cholesterol and Alzheimer’s Disease**

Abbreviations: AD (Alzheimer’s disease), VD (vascular dementia), NA (data not provided), cntrl (control), OR (odds ratio), RR (relative risk) HR (hazard ratio).
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Baseline Age/Year</th>
<th>Follow up Age/Year</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al., 2000</td>
<td>African American, ≥65 yrs</td>
<td>N=77, AD 46, cntrl 31</td>
<td>1990</td>
<td>NA</td>
<td>OR 1.018 (NA) P=0.027</td>
</tr>
<tr>
<td>Kalman et al., 1999</td>
<td>Hungary</td>
<td>N=39, AD 24, cntrl 15</td>
<td>AD 70.2, cntrl 64.8</td>
<td>NA</td>
<td>AD 160 mg/dl vs. cntrl 160 mg/dl</td>
</tr>
<tr>
<td>Lepara et al., 2009</td>
<td>Sarajevo, Bosnia and Herzegovina, ≥65 yrs</td>
<td>N=60, AD 30, cntrl 30</td>
<td>AD 79.9, cntrl 77.5</td>
<td>NA</td>
<td>AD 5.4 mmol/L vs. cntrl 5.9 mmol/L</td>
</tr>
<tr>
<td>Lesser et al., 2001</td>
<td>United States</td>
<td>N=106, AD 22, cntrl 84</td>
<td>1986 – 1994</td>
<td>Median 3.26 yrs (median age 89)</td>
<td>AD 210.0 mg/dl vs. cntrl 194.0 mg/dl</td>
</tr>
<tr>
<td>Li et al., 2005</td>
<td>United States, ≥65 yrs</td>
<td>N=2141, AD 152, cntrl 1989</td>
<td>74.9 years</td>
<td>Mean follow up 5.6 yrs.</td>
<td>HR 1.001 (1.0, 1.1) P&gt;0.05</td>
</tr>
<tr>
<td>Merched et al., 2000</td>
<td>France</td>
<td>N=157, AD 98, cntrl 59</td>
<td>77.6 case; 75.4 cntrl</td>
<td>NA</td>
<td>AD 5.44 mmol/L vs. cntrl 5.9 mmol/L</td>
</tr>
<tr>
<td>Reitz et al., 2004</td>
<td>United States, Medicare recipients ≥65 yrs</td>
<td>N=2820, AD 244, VD 119, stroke 231, cntrl 2226</td>
<td>AD 82.6, cntrl 76.4</td>
<td>NA</td>
<td>Q1 vs. Q2 OR 0.96 (0.61, 1.53) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q3 OR 0.72 (0.44, 1.16) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q4 OR 0.94 (0.58, 1.52) P&gt;0.05</td>
</tr>
<tr>
<td>Reitz et al., 2004</td>
<td>United States, Medicare recipients ≥65 yrs</td>
<td>N=1168, AD 119, VD 48, cntrl 856</td>
<td>1992 – 1994</td>
<td>AD 81.5, cntrl 77.8</td>
<td>Q1 vs. Q2 HR 0.58 (0.34, 0.79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q3 HR 0.82 (0.48, 1.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q4 HR 0.48 (0.26, 0.86)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AD (Alzheimer’s disease), VD (vascular dementia), NA (data not provided), cntrl (control), OR (odds ratio), RR (relative risk) HR (hazard ratio).
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Baseline Age/Year</th>
<th>Follow up Age/Year</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wieringa et al., 1997</td>
<td>United Kingdom</td>
<td>N=70, AD 37, cntrl 33</td>
<td>77.4 case; 77.9 cntrl / 1994</td>
<td>NA</td>
<td>AD 6.01 mmol/L vs. cntrl 6.1 mmol/L; P&gt;0.05</td>
</tr>
<tr>
<td>Yoshitake et al., 1995</td>
<td>Japan, ≥65 yrs</td>
<td>N=828, AD 42, 725 cntrl, 61 other dementia</td>
<td>1985 – 1992</td>
<td>1985 – 1992</td>
<td>RR 1.10 (0.80, 1.51); P&gt;0.05</td>
</tr>
<tr>
<td>Hayden et al., 2006</td>
<td>United States, &gt;65 years</td>
<td>N=3264, AD 104, cntrl 3123, 37 VD</td>
<td>1995-1998</td>
<td>81.5 case; 73.7 cntrl / 1998 – 1999</td>
<td>History of high cholesterol (No; ref) HR 0.47 (0.19, 0.98); P&lt;0.05</td>
</tr>
<tr>
<td>Dufouil et al., 2005</td>
<td>France, ≥65 yrs</td>
<td>N=8506, AD 112, cntrl 8394</td>
<td>AD 79.1, cntrl 74.1 / 1999 – 2001</td>
<td>NA</td>
<td>&lt;6.2 mmol/L vs. ≥6.2 mmol/L OR 1.18 (.62, 2.23); P&gt;0.05</td>
</tr>
<tr>
<td>Kimm et al., 2010</td>
<td>Korea, ≥40 yrs</td>
<td>N=848505, AD 1851, cntrl 846654</td>
<td>1992 – 1995</td>
<td>1993 – 2006</td>
<td>Normal vs. borderline high: Men 1.2 (1.0, 1.4); P=0.05 Normal vs. high: Men 1.2 (1.0, 1.5); P=0.05 Normal vs. borderline: Women 1.0 (0.9, 1.2); P=0.05 Normal vs. high: Women 1.1 (0.9, 1.3); P&gt;0.05</td>
</tr>
<tr>
<td>Kuusisto et al., 1997</td>
<td>Finland, 65-74 yrs</td>
<td>N=961, AD 46, cntrl 915</td>
<td>1986-1988</td>
<td>1990 – 1991</td>
<td>OR 0.69 (0.52, 0.92); P=0.011</td>
</tr>
<tr>
<td>Ghebranious et al., 2011</td>
<td>United States, ≥60 yrs. for cases, ≥80 yrs for cntrls</td>
<td>N=455, AD 153, cntrl 302</td>
<td>AD 78.2, cntrl 87.2</td>
<td>NA</td>
<td>AD 259.3 mg/dl vs. cntrl 259.0 mg/dl; P&gt;0.05</td>
</tr>
</tbody>
</table>

**Table 2.3 (Continued)**

Abbreviations: AD (Alzheimer’s disease), VD (vascular dementia), NA (data not provided), cntrl (control), OR (odds ratio), RR (relative risk) HR (hazard ratio)
### Total Cholesterol

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Baseline Age/Year</th>
<th>Follow up Age/Year</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mielke et al., 2005</td>
<td>Sweden, 70 yrs</td>
<td>N=382</td>
<td>AD 19, 337 cntrl, 23 VD, 3 other dementia</td>
<td>70 yrs / 1971 - 1972</td>
<td>88 yrs / 1989 – 1990</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siest et al., 2000</td>
<td>ApoEurope</td>
<td>N=918</td>
<td>AD 489, 429 cntrl</td>
<td>AD 74.5, 71.0 cntrl/1996 – 1998</td>
<td>NA</td>
</tr>
<tr>
<td>Tan et al., 2003</td>
<td>United States</td>
<td>N=1026</td>
<td>AD 77, cntrl 949</td>
<td>1988 - 1989</td>
<td>NA</td>
</tr>
</tbody>
</table>

### LDL Cholesterol

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Baseline Age/Year</th>
<th>Follow up Age/Year</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalman et al., 1999</td>
<td>Hungary</td>
<td>N=39</td>
<td>AD 24, cntrl 15</td>
<td>AD 70.2, cntrl 64.8</td>
<td>NA</td>
</tr>
<tr>
<td>Lepara et al., 2009</td>
<td>Sarajevo, Bosnia and Herzegovina, ≥65 yrs</td>
<td>N=60</td>
<td>AD 30, cntrl 30</td>
<td>AD 79.9, cntrl 77.5</td>
<td>NA</td>
</tr>
<tr>
<td>Lesser et al., 2001</td>
<td>United States</td>
<td>N=106</td>
<td>AD 22, cntrl 84</td>
<td>1986 – 1994 (median age 86)</td>
<td>Median 3.26 yrs (median age 89)</td>
</tr>
<tr>
<td>Wieringa et al., 1997</td>
<td>United Kingdom</td>
<td>N=70</td>
<td>AD 37, cntrl 33</td>
<td>77.4 case; 77.9 cntrl</td>
<td>NA</td>
</tr>
<tr>
<td>Yoshitake et al., 1995</td>
<td>Japan, ≥65 yrs</td>
<td>N=828</td>
<td>AD 42, 725 cntrl, 61 other dementia</td>
<td>1985 – 1992</td>
<td>1985 – 1992</td>
</tr>
<tr>
<td>Ghebranious et al., 2011</td>
<td>United States, ≥60 yrs. for cases, ≥80 yrs for cntrls</td>
<td>N=455</td>
<td>AD 153, cntrl 302</td>
<td>AD 78.2, cntrl 87.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AD (Alzheimer’s disease), VD (vascular dementia), NA (data not provided), cntrl (control), OR (odds ratio), RR (relative risk) HR (hazard ratio)
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Baseline Age/Year</th>
<th>Follow up Age/Year</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reitz et al., 2004</td>
<td>United States, Medicare recipients ≥65 yrs</td>
<td>N=2820</td>
<td>AD 82.6, cntrl 76.4</td>
<td>1992 – 1994</td>
<td>Q1 vs. Q2 OR 0.87 (0.54, 1.40) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q3 OR 0.84 (0.52, 1.36) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q4 OR 1.02 (0.63, 1.65) P&gt;0.05</td>
</tr>
<tr>
<td>Reitz et al., 2004</td>
<td>United States, Medicare recipients ≥65 yrs</td>
<td>N=1168</td>
<td>1992 – 1994</td>
<td>AD 81.5, cntrl 77.8</td>
<td>Q1 vs. Q2 HR 0.99 (0.59, 1.65) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q3 HR 0.78 (0.46, 1.34) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q4 HR 0.80 (0.46, 1.40) P&gt;0.05</td>
</tr>
<tr>
<td>Kalman et al., 1999</td>
<td>Hungary</td>
<td>N=39</td>
<td>AD 70.2, cntrl 64.8</td>
<td>NA</td>
<td>AD 49.3 mg/dl vs. cntrl 39.4 mg/dl P&lt;0.05</td>
</tr>
<tr>
<td>Lepara et al., 2009</td>
<td>Sarajevo, Bosnia and Herzegovina, ≥65 yrs</td>
<td>N=60</td>
<td>AD 79.9, cntrl 77.5</td>
<td>NA</td>
<td>AD 1.26 mmol/L vs. cntrl 1.17 mmol/L P&gt;0.05</td>
</tr>
<tr>
<td>Lesser et al., 2001</td>
<td>United States</td>
<td>N=102</td>
<td>1986 – 1994 (median age 86)</td>
<td>Median 3.26 yrs (median age 89)</td>
<td>AD 41.5 mg/dl, cntrl 38.5 mg/dl P&gt;0.05</td>
</tr>
<tr>
<td>Li et al., 2005</td>
<td>United States, ≥65 yrs</td>
<td>N=2141</td>
<td>74.9 years / 1994 – 1996</td>
<td>Mean follow up 5.6 yrs.</td>
<td>HR 1.00 (0.99, 1.01) P&gt;0.05</td>
</tr>
<tr>
<td>Merched et al., 2000</td>
<td>France</td>
<td>N=157</td>
<td>77.6 case; 75.4 cntrl</td>
<td>NA</td>
<td>AD 1.03 mmol/L vs. cntrl 1.45 mmol/L P&lt;0.0001</td>
</tr>
<tr>
<td>Tan et al., 2003</td>
<td>United States</td>
<td>N=1026</td>
<td>76.4 male; 76.1 female</td>
<td>NA</td>
<td>HR 1.1 (0.93, 1.31) P&gt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: AD (Alzheimer’s disease), VD (vascular dementia), NA (data not provided), cntrl (control), OR (odds ratio), RR (relative risk) HR (hazard ratio)
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Baseline Age/Year</th>
<th>Follow up Age/Year</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wieringa et al., 1997</td>
<td>United Kingdom</td>
<td>N=70 AD 37, cntrl 33</td>
<td>77.4 case; 77.9 cntrl</td>
<td>NA</td>
<td>AD 1.42 mmol/L vs. cntrl 1.39 mmol/L</td>
</tr>
<tr>
<td>Yoshitake et al., 1995</td>
<td>Japan</td>
<td>N=828 AD 42, cntrl 725, 61 other dementia</td>
<td>1985 – 1992</td>
<td>1985 – 1992</td>
<td>RR 1.06 (0.77, 1.47) P&gt;0.05</td>
</tr>
<tr>
<td>Reitz et al., 2004</td>
<td>United States, Medicare recipients ≥65 years</td>
<td>N=2820 AD 244, VD 119, stroke 231, cntrl 2226</td>
<td>AD 82.6, cntrl 76.4</td>
<td>NA</td>
<td>Q1 vs. Q2 OR 0.47 (0.28, 0.78) P&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q3 OR 0.58 (0.35, 0.97) P&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q4 OR 0.66 (0.41, 1.08) P&gt;0.05</td>
</tr>
<tr>
<td>Reitz et al., 2004</td>
<td>United States, Medicare recipients ≥65 years</td>
<td>N=1168 AD 119, vascular dementia 48, cntrl 856</td>
<td>1992 – 1994</td>
<td></td>
<td>Q1 vs. Q2 HR 0.79 (0.44, 1.42) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q3 HR 0.97 (0.54, 1.75) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 vs. Q4 HR 0.70 (0.37, 1.32) P&gt;0.05</td>
</tr>
<tr>
<td>Ghebranious et al., 2011</td>
<td>United States, ≥60 yrs. for cases, ≥80 yrs for cntrls</td>
<td>N=455 AD 153, cntrl 302</td>
<td>AD 78.2, cntrl 87.2</td>
<td>NA</td>
<td>AD 59.5 mg/dl vs. cntrl 62.9 mg/dl P&gt;0.05</td>
</tr>
<tr>
<td>Kuusisto et al., 1997</td>
<td>Finland, 65-74 yrs</td>
<td>N=961 AD 46, cntrl 915</td>
<td>1986-1988</td>
<td>1990 – 1991</td>
<td>OR (0.25, 1.45) P&gt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: AD (Alzheimer’s disease), VD (vascular dementia), NA (data not provided), cntrl (control), OR (odds ratio), RR (relative risk) HR (hazard ratio)
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Baseline Age/Year</th>
<th>Follow up Age/Year</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mielke et al., 2010</td>
<td>Sweden (women 38 – 60 yrs baseline)</td>
<td>AD 80, cntrl 1382</td>
<td>1968 - 1969</td>
<td>1974–1975, 1980–1981, 1992–1993, and 2000–2001</td>
<td>Stable vs. decline HR 1.66 (0.71, 3.89) P&gt;0.05 Stable vs. increase HR 1.03 (0.35, 3.04) P&gt;0.05</td>
</tr>
<tr>
<td>Stewart et al., 2007</td>
<td>Japanese-Americans (males only)</td>
<td>AD 56, cntrl 971</td>
<td>1965-1968</td>
<td>1970-1972, 1971-1974, 1980-1982, and 1991-1993</td>
<td>AD x time Coefficient 2.2 AD x time² Coefficient -0.33 AD x time³ Coefficient 0.0097</td>
</tr>
<tr>
<td>Tan et al., 2003</td>
<td>United States</td>
<td>AD 77, cntrl 949</td>
<td>1948 – 1953</td>
<td>Biannual exams from 1948 – 1990</td>
<td>Change in cholesterol over 10 yr. period H.R. 1.01 (0.92, 1.11)</td>
</tr>
<tr>
<td>Notkola et al., 1998</td>
<td>Finland (men only)</td>
<td>27 AD, 397 cntrl, 20 other dementia</td>
<td>Midlife age 40 – 59</td>
<td>1989</td>
<td>Greater decline in total cholesterol for AD cases compared to controls (P&lt;0.008)</td>
</tr>
</tbody>
</table>

Abbreviations: AD (Alzheimer’s disease), VD (vascular dementia), NA (data not provided), cntrl (control), OR (odds ratio), RR (relative risk) HR (hazard ratio)
<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Sex</th>
<th>Edu</th>
<th>Smoking</th>
<th>Statin</th>
<th>APOE</th>
<th>BMI</th>
<th>Diabetes</th>
<th>Hyper</th>
<th>Heart disease</th>
<th>Fasting cholest.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al., 2000</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalman et al., 1999</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lepara et al., 2009</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesser et al., 2001</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al., 2005</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Merched et al., 2000</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Reitz et al., 2004</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Siest et al., 2000</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Tan et al., 2003</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wieringa et al., 1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshitake et al., 1995</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hayden et al., 2006</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.5: Covariates

Abbreviations: BMI (body mass index), Edu (education), hyper (hypertension)
<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Sex</th>
<th>Edu</th>
<th>Smoking</th>
<th>Statin</th>
<th>APOE</th>
<th>BMI</th>
<th>Diabetes</th>
<th>Hyper</th>
<th>Heart disease</th>
<th>Fasting</th>
<th>cholest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuusisto et al., 1997</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghebranious et al., 2011</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mielke et al., 2005</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mielke et al., 2000</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kivipelto et al., 2000</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mielke et al., 2010</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solomon et al., 2009</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiang et al., 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notkola et al., 1998</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stewart et al., 2007</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dufouil et al., 2005</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kimm et al., 2010</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI (body mass index), Edu (education), hyper (hypertension)
Chapter Three: A Life Span Approach to the Epidemiology of Alzheimer’s Disease

Previous epidemiological research provides evidence for a significant relationship between cholesterol and AD, but the direction of this relationship appears to be dependent upon if cholesterol is measured during midlife or late life. The age dependent relationship between cholesterol and AD makes it important for investigators to provide strong justification for how and why specific age boundaries to define midlife or late life were used. Unfortunately, the age boundaries used to define midlife and late life in previous studies appear to be defined arbitrarily and justification for why specific age boundaries were chosen has been limited to citing previous studies that used similar boundaries. Based on the literature review presented in Chapter Two, the sample populations of previous studies that have examined the relationship between cholesterol and AD come from a variety of ethnic and cultural backgrounds and the historical time periods in which these populations were examined also vary between studies. These factors should be considered when conducting research on the relationship between distinct stages of the life span because the normative behaviors and characteristics associated with distinct life stages are shaped by social, cultural and historical influences that are dynamic. As a result, the normative behaviors and characteristics associated with distinct life stages may change, which leads to the socially imposed age boundaries used to define life stages to also change. Therefore, sufficient justification as to how and why specific age boundaries were chosen to define life stages when conducting research needs to be provided. The dissertation research used concepts of the life span research framework to construct age boundaries for midlife and late life that were based on changes in the relationship between cholesterol and chronological age. This approach was influenced by the large body of research in developmental psychology that has focused on defining life stages according to changes in mental, cognitive and personality characteristics with age. More importantly, this approach provides sufficient justification for how and why specific age boundaries for midlife and late life were chosen.
The purpose of this chapter is to describe how the concepts of a life span framework were engaged in this dissertation research. This chapter begins by providing necessary background information for the reader to appreciate why age boundaries for midlife and late life were constructed according to distinct changes in the relationship between cholesterol and chronological age. This includes an introduction to the life span research framework, a summary of the major concepts of life span research, and brief review of pertinent research from developmental psychology that influenced the dissertation research. Section one concludes by briefly describing how normative behaviors associated with distinct life stages are influenced by social, cultural and historical contexts that change over time. This is relevant to the dissertation research because behavioral changes initiated by social, cultural and historical events may contribute to changes in the socially constructed age boundaries associated with distinct life stages. Section two is a detailed description of the approach used to define age boundaries for midlife and late life according to trends in the relationship between total cholesterol and chronological age. This chapter concludes by summarizing the findings presented in section two and describing the contributions of a life span approach to research on the etiology, progression and prevention of AD. This section also introduces the life course perspective and briefly summarizes the differences between the life course and life span. The life course perspective is introduced in this chapter because the terms life course and life span are often used interchangeably, but there are important differences between these terms that are relevant to the dissertation research.

Review of the Life Span Research Framework

At the most basic level, the life span is the duration of time from birth to death. The life span of an individual organism is influence by biological and environmental characteristics and the life span of any given organism can range from only a few minutes or hours to many decades or even centuries. When studying the human life span, biologists and scientists in related fields focus their efforts on understanding the endogenous changes that occur over time and identifying
factors that influence the duration of the life span, whereas social scientists are concerned with understanding the behavioral, emotional and psychological changes that occur over time and the influence of exogenous factors on the life span. All areas of science have made significant contributions to our understanding of the human life span and there is growing appreciation for the importance of studying how the life span is influenced by interactions between endogenous and exogenous factors. As a research framework, the life span seeks to understand the physiological, behavioral, cognitive and psychosocial changes that occur over time and to identify factors that contribute to and influence the within person changes that occur as people age. Studies that utilize the life span framework may examine a prolonged period of the life span and often times study the relationship between two or more distinct life stages (childhood, young adulthood, middle age or old age).

The concept of life span has a long history that is believed to have originated over two hundred years ago when German psychologist J. N. Tetens wrote the first manuscript on human development utilizing a life span perspective (Muller-Brettel & Dixon, 1990), which subsequently ushered in the field of developmental psychology\(^{12}\) (Baltes, Reese, & Lipsitt, 1980). The theories of several prominent developmental psychologists that describe the stages of psychosocial (Erikson, 1980), cognitive (Piaget, 1977) and personality (Jung, 2001) development have contributed to the evolution of life span framework. A review of specific developmental theories is beyond the scope of this chapter, but it is necessary to understand how these theories have contributed to understanding the life span. Sigmund Freud is arguably the most influential developmental theorist and many theories were proposed in response to his theory of psychosexual development. Freud’s theory emphasized that an adult’s personality is heavily influenced by childhood experiences and that personality traits are for the most part established within the first five to six years of life. Many developmental theorists who studied under Freud

\(^{12}\) G. Stanley Hall has also been credited with founding developmental psychology in the United States (White, 1992).
also focused their attention on childhood and adolescence. However, Carl Jung, who was a
former student of Freud’s, recognized that humans continue to develop after childhood. Jung’s
theory of personality included four periods (childhood, youth, middle life and old age), but he
emphasized the importance of development during adulthood. One of the first theorists to
acknowledge that human development is a life long process and that no one stage is more
important than the others was Erik Erikson. Erikson’s stage theory of psychosocial development
was a direct response to the psychosexual development work conducted by Sigmund Freud.
Erikson agreed with Freud that early life experiences are important to human development, but
disagreed with the notions that childhood experiences are more important to development than
later life experiences, and that the majority of human development occurs within the first few
years of life. Erikson’s original theory of psychosocial development includes eight stages from
childhood through old age. His wife Joann Erikson added a ninth stage after he passed away to
account for the growing proportion of older adults who were living into their 80’s and 90’s and
displayed unique characteristics that differentiated them from younger age groups.

**Concepts of Developmental Psychology and the Life Span Framework**

Seven major concepts of developmental psychology are commonly incorporated into the
life span framework (Baltes, 1987). The first concept emphasizes that human development is a
life long process and that there is no distinct age period that takes precedence in regulating human
development. The second concept states that development does not always move in a positive
direction (i.e. growth) and that periods of growth may be followed by prolonged periods in which
a developmental domain remains constant or declines. Similarly, the third concept recognizes
that development is multidirectional. This means that during the same age period some domains
may exhibit trajectories of growth whereas other domains may exhibit trajectories of decline or
remain constant. The fourth concept states that early life events influence later life outcomes and
that an individual’s developmental trajectory is shaped by environmental conditions and
individual experiences. The fifth concept acknowledges that human development is influenced
by the social and cultural factors that may be unique to a specific generation. The sixth concept builds upon this notion by stating that historical context along with normative age related developmental changes and unique non-normative events all interact to influence an individual’s development over time. Therefore, to gain a complete understanding of human development requires taking into account the environment in which a person has lived and the unique events and experiences that shape a person’s development from birth until death. The final concept of the life span framework acknowledges that gaining a complete understanding of human development requires a multidisciplinary approach. The life span framework emerged from the field of developmental psychology and research on the psychological, cognitive and intellectual changes that occur with age, but a complete understanding of human development also requires knowledge of the biological, physical and behavioral changes that occur with age.

**Socially Constructed Stages of the Life Span**

Chronological age by itself has little meaning and age should not be accepted as a valid explanation for a behavior or health event. The perceived significance of chronological age is due to the correlation between chronological age and important biological, physical, cognitive, behavioral and social characteristics or events. This correlation allows for people to generate a preconceived notion of a person’s physical or cognitive abilities, social standing or likelihood to experience a particular health event based on their chronological age. However, changes to the social structure and environment in which people age may alter the timing (i.e. age) in which a person passes through socially constructed developmental landmarks (e.g. graduating college, marriage, starting a family). This may lead to a change in the behavior associated with a particular age period and change the social perceptions for specific life stages such as childhood, young adulthood, middle age and old age. As an example, most Americans in the 1990’s believed that men should be finished having children in their mid-forties and women in their late thirties (Settersten & Hagedst, 1996). These social expectations are beginning to change, especially among women, as more people are choosing to start a family later in life. This is
indicated by a steady decline in the birth rates for women between 20 and 29 years of age from 1990 to 2010, but the birth rates among women between 30 and 44 have steadily increased over the same period (Martin et al., 2012). The observed increase in fertility may be due to women choosing to have children at an older age in order to pursue advanced educational opportunities because of the emphasis that has been placed on education in Western societies due to an increasingly competitive job market. Over time this may lead to a change in the socially imposed age boundaries associated with young adulthood and middle age.

**Defining Age Boundaries for Midlife and Late Life According to Trends in Total Cholesterol**

Previous studies that have examined the relationship between cholesterol and AD define midlife and late life using predetermined age boundaries, and the justification for why specific boundaries were chosen is limited to citing previous studies that used similar boundaries. While this limited justification is generally accepted, such an approach to defining life stages does not take into account that the age periods associated with distinct life stages are influenced by the social and cultural characteristics of the environment in which people age. Therefore, instead of using predetermined age boundaries for midlife and late life, the dissertation research employed a more rigorous approach that define midlife and late life that was motived by the research of Erikson, Jung, and other theorists who constructed developmental stages based on observed changes to cognitive, psychosocial and emotional characteristics that occur with age. This approach allowed for age boundaries to define midlife and late life to emerge out of the observed trends between chronological age and total cholesterol.

The results from cross-sectional and longitudinal studies indicate that cholesterol tends to increase during young adulthood and middle age and decline during old age (Carroll et al., 2005; Ferrara et al., 1997; P. W. Wilson et al., 1994). While dietary changes (Johansson et al., 2012), weight loss and weight gain (Ferrara et al., 1997) and the use of cholesterol lowering medications (Carroll et al., 2005) all contribute to the apparent relationship between cholesterol and
chronological age, there is evidence that the rate of cholesterol synthesis by the liver also increases through middle age and then declines later in life (Miettinen, Gylling, Raitakari, Hallikainen, & Viikari, 2008; Tilvis et al., 2011). Visually examining the cross-sectional and longitudinal changes in total cholesterol with age will provide insight into the developmental trajectory of total cholesterol across the life span and suggests a novel approach to obtain age cutoffs to define midlife and late life. The following section provides a detailed description of how the life span framework was utilized to determine age cutoffs for midlife and late life based on the trajectories of total cholesterol among participants of the Framingham Heart Study (FHS) Original and Offspring Cohorts.

Methods

Age boundaries for midlife and late life were obtained by visually examining cross-sectional trends in the relationship between total cholesterol and chronological age during the first clinical examinations for the Original and Offspring Cohort. The Original and Offspring Cohorts were examined separately to account for potential cohort effects that may influence cholesterol. A total of 3,092 participants of the Original Cohort (60.9% of initial cohort) had a recorded measure for total cholesterol for the first clinical examination (exam dates 1948 – 1953) and 4,928 participants of the Offspring Cohort (98.2% of initial cohort) had a recorded measure of total cholesterol for the first clinical examination (exam dates 1971 – 1975). The age range during the first clinical examination for participants of the Original Cohort with a recorded measure of total cholesterol was 29 – 74 (mean 44.1 years). The mean age of the 1,987 participants of the Original Cohort who did not have a recorded measure of total cholesterol was 44.2 years (range 28 – 62), which was not significantly different compared to the participants who did have measure of total cholesterol. The age range during the first clinical examination for participants of the Offspring Cohort with a recorded measure of total cholesterol was 6 – 70 (mean 36.2 years).
Scatterplots describing the relationship between total cholesterol and age during the first clinical examination for the Original and Offspring Cohorts were created to determine if there were any outlying values in the data (Figures 3.1 and 3.2). The average measure of total cholesterol for the Original Cohort was 221.5 mg/dl (range 96 mg/dl – 503 mg/dl) and the majority of measures were between 191 mg/dl and 249 mg/dl. The Offspring Cohort had lower average total cholesterol (196.0 mg/dl, range 96 mg/dl – 450 mg/dl) and the majority of measures were between 169 mg/dl and 220 mg/dl. Subjects with recorded measures of total cholesterol that were 1.96 standard deviations above or below what would be expected based on their age and sex or had a history of using cholesterol lowering medications were removed from the sample populations. This was done so that the relationship between cholesterol and chronological age would not be influenced by unexpectedly high or low measures of cholesterol potentially due to genetic factors or diseases that disrupt cholesterol homeostasis. Once these subjects were removed, the trends in the cross-sectional relationship between total cholesterol and chronological age were visually examined to identify age boundaries for midlife and late life.

Results

Age Ranges for Midlife in the Original and Offspring Cohorts: Apparent differences in the trends for total cholesterol between the Original (Figure 3.3) and Offspring Cohorts were observed (Figure 3.4) and there were differences in the trends of total cholesterol according to sex in both cohorts (Figures 3.5 and 3.6). Based on Figure 3.3, total cholesterol increased steadily among subjects of the Original Cohort who were in their early thirties to mid fifties. However, total cholesterol increased steadily among women who were 30 to 55 years of age and then plateaued among women in their late fifties and early sixties (Figure 3.5). In general, there was little change in total cholesterol among men with increasing age. Total cholesterol increased slightly for men in their thirties and fifties before plateauing between fifty and sixty years of age.

---

13 Figure 3.1 indicates that there was one subject in the Original Cohort who was considerably older than the other subjects during the first clinical exam and was therefore removed from the analysis. There were no outlying values for age in the Offspring Cohort (Figure 3.2).
(Figure 3.5). Based on Figure 3.5, midlife was defined in the Original Cohort as between 30 and 55 years of age.

The relationship between age and total cholesterol appeared to be almost perfectly linear in the Offspring Cohort (Figure 3.4). When the Offspring Cohort was stratified according to sex, total cholesterol appeared to plateau in men by 50 years of age, whereas the trend for total cholesterol remained linear for women (Figure 3.6). The linear trend in total cholesterol for the Offspring Cohort may be due to the age distribution of subjects during the first clinical exam. While the age range during the first clinical exam for the Offspring Cohort was similar to the Original Cohort, only 2.5 percent of subjects in the Offspring Cohort were older than 55 years of age compared to 12.6 percent in the Original Cohort during their respective first clinical exams. Therefore, the above analysis was repeated for the Offspring Cohort utilizing data from the second clinical exam because 15.4 percent of the subjects were older than 55 years. A total of 43 subjects reported using cholesterol-lowering medications during the second clinical exam. There were 143 subjects in the 95th percentile and 45 subjects in the 5th percentile for total cholesterol (see Figure 3.7). Based on Figure 3.8, total cholesterol increased steadily until approximately 55 years of age when the trend plateaued and then began to decline. However, there were clear differences in the trends for total cholesterol when subjects were stratified according to sex (Figure 3.9). Women exhibited four distinct trends in total cholesterol. There was a decreasing trend for total cholesterol among women in their late teens to late twenties, which was followed by a steady increase among women in their early thirties to mid-forties. The trend in total cholesterol increased slightly among women in their late forties to early fifties, which may indicate the approaching onset of menopause. A total of 404 women reported that they had not menstruated during the previous year due to natural causes. The average age of these women was 54.5 years and their average total cholesterol was 226.5 mg/dl. The trend in total cholesterol plateaued among women in their late fifties and early sixties. There was an increase in total cholesterol among women in their mid to late sixties, but it is unlikely that this increase is of any
real meaning because there were relatively few subjects between the ages of sixty and seventy during the second clinical exam. There were no observable fluctuations in the trend for total cholesterol for men as was observed in women. In general there was a slight increasing trend in total cholesterol until the mid forties at which point the trend plateaued. Based on Figure 3.9, midlife was defined for the Offspring Cohort as between 30 and 45 years of age.

**Age Cutoffs for Late Life in the Original and Offspring Cohorts:** While distinct trends in total cholesterol that may be used to define midlife in both FHS cohorts were identified, the above analysis did not detect specific ages where the trend in total cholesterol began to decline that may indicate the transition to late life. A potential explanation is that the age in which cholesterol begins to decline may not actually occur within the age range of the subjects included in the cross sectional analyses and that subjects with older chronological age would need to be included in the sample before a decreasing trend in total cholesterol may be observed. A second explanation for the observed trends in cholesterol is a sampling bias due to the cross sectional design of the analysis. A decline in body mass, muscle mass and other health characteristics are representative of an overall decline in functioning that occurs as a person approaches death (Bales & Ritchie, 2002). Subjects with low cholesterol, especially among older age groups, may not have been recruited to participate in the FHS due to illness or death and may explain why a decreasing trend in total cholesterol consistent with the transition into late life was not detected in the cross-sectional analysis. Another limitation of utilizing a cross-sectional design is that apparent age related differences in the outcome of interest are often times confounded by the unique characteristics of a particular age group, also known as a cohort effect. The relationship between cholesterol and chronological age for the Original and Offspring Cohorts were plotted separately, but the wide age distribution among participants recruited into both Cohorts means that there is still the potential for cohort effects to be present.

The limitations of examining cross-sectional trends in cholesterol can be addressed by utilizing the repeated measures of cholesterol that have been collected from participants of the
FHS Original and Offspring Cohorts over the course of the study. The trajectories of total cholesterol for subjects in the Original and Offspring Cohorts who were within their respective age ranges for midlife during the first clinical exam were examined longitudinally to determine late life according to the age of onset for a prolonged decline in total cholesterol for men and women. Subjects who had a history of ever using cholesterol-lowering medications [Original Cohort n= 493 (9.7%); Offspring Cohort n= 926 (18.5%)] were excluded from the analysis and all measures of total cholesterol were within the 5th and 95th percentiles according to age and gender adjusted norms.

The trajectories of total cholesterol for the Original and Offspring Cohorts both had a parabolic shape in which there was a prolonged increasing trend in total cholesterol, followed by a plateau and then a decreasing trend. Despite the similarities in the overall trajectories of total cholesterol, there were apparent differences between the Original and Offspring cohorts and when the trajectories were stratified according to sex. The longitudinal trajectory of total cholesterol for men and women in the Original Cohort indicates that total cholesterol began to decline at approximately 65 years of age (Figure 3.10). The accelerated decline in total cholesterol for men was preceded by a slight decline in total cholesterol beginning at roughly 50 years of age, whereas the trajectory of total cholesterol for women continued to increase until 55 and remained constant until 65 years of age (Figure 3.11). Therefore, based on the ages in which changes in the trajectory of total cholesterol were observed in Figures 3.10 and 3.11 late life will be defined as 65 years of age or older in the Original Cohort.

The overall trajectory of total cholesterol for the Offspring Cohort followed a smooth trend and there were no abrupt changes in the trajectories of total cholesterol (Figure 3.12), but differences in the longitudinal trends of total cholesterol between men and women were visually apparent once the trajectories of total cholesterol were stratified according to sex (Figure 3.13). Total cholesterol began to decline at approximately 60 years of age for women, but similar to what was observed in the Original Cohort, the initial decline in total cholesterol for men occurred
earlier at approximately 50 years of age. Based on Figure 3.13, late life will be defined in the Offspring Cohort as 60 years of age and older.

**Summary**

Based on the cross-sectional and longitudinal trends between cholesterol and chronological age, midlife was defined as between 30 and 55 years of age for the Original Cohort and between 30 and 45 years of age for the Offspring Cohort. Late life was defined as 65 years of age in the Original Cohort and 60 years of age in the Offspring Cohort\(^\text{14}\). These definitions for midlife and late life are similar to those used in previous studies, but the approach employed in the dissertation research provides stronger justification for the proposed age cutoffs than citing previous research. A narrower age range was chosen for the Offspring Cohort because of the observed increase in total cholesterol among women that occurred at approximately 50 years of age. The slight increase in total cholesterol may be partly due to the onset of menopause. This trend was not observed among women in the Original Cohort and data regarding the onset of menopause was not collected during the first clinical exam for the Original Cohort, which prevented the potential influence of menopause on cholesterol from being examined. Subtle differences in the average age at which cholesterol began to decline between the Original and Offspring Cohort were also observed. Based on the longitudinal changes in cholesterol with advancing age, late life was defined as 65 years of age and older for the Original Cohort and 60 years of age and older for the Offspring Cohort. The younger age cutoff for late life used for the Offspring Cohort does not suggest these participants are approaching late life at a younger age compared to participants of the Original Cohort. Rather, the younger average age in which total cholesterol begins to decline may be due to an increased understanding of the importance of controlling high cholesterol. The most apparent differences between the Original and Offspring Cohort are not meant to imply that adults who are 60 or 65 years of age and older are a homogeneous group. It is generally accepted that there are specific stages within late life (old, old-old and oldest old) that have distinct physical, cognitive and psychosocial characteristics.
Cohorts in the longitudinal trajectories of total cholesterol is that participants of the Original Cohort had much higher total cholesterol by the time they were 60 years of age due to a rapid increase in total cholesterol from approximately 30 to 55 years of age, whereas participants of the Offspring Cohort exhibited a much more subtle increase in total cholesterol during the same period and therefore had much lower cholesterol by the time they were 60 years of age. These differences in total cholesterol may be due to differences in diet, exercise, smoking history and other factors that directly modify total cholesterol. By the time the Offspring Cohort was initiated in 1971, the discoveries from several studies that utilized data from the Original Cohort had made significant progress towards identifying risk factors for heart disease (Dawber, 1960; Kannel, 1967; Kannel, Dawber, Kagan, Revotskie, & Stokes, 1961). These discoveries contributed to the growing social awareness of the importance of controlling high cholesterol, high blood pressure, engaging in regular exercise and the dangers of smoking. The influence of the greater social awareness is reflected by the lower total cholesterol, on average, of the Offspring Cohort compared to the Original Cohort. The Offspring Cohort had lower average total cholesterol (196.0 mg/dl, range 96 mg/dl – 450 mg/dl) and the majority of measures were between 169 mg/dl and 220 mg/dl. The difference in average total cholesterol between the Offspring and Original Cohorts during their respective examinations may also be due to differences in the use of cholesterol lowering medications between the two cohorts. Data regarding the use of cholesterol lowering medications was not collected until the sixth clinical examination for the Original Cohort (years 1958 – 1963) because the benefits of niacin, also known as vitamin B3, for controlling high cholesterol were not reported until 1955 by Altschul et al. (1955). By the time the Offspring Cohort was initiated in 1971, several anti-cholesterol agents were available and the use of cholesterol lowering medications has been assessed during each clinical examination for the Offspring Cohort.
Contributions of the Life Span Framework to Alzheimer’s Disease Research

Alzheimer’s disease is characterized by the accumulation of neuritic plaques that are comprised of the amyloid beta (Aβ) protein and neurofibrillary tangles that form from the hyperphosphorylation of the protein tau in the brain (McKhann et al., 2011). The progressive decline in cognitive functioning associated with AD does not begin to occur until the accumulation of these neuritic plaques and neurofibrillary tangles surpasses a critical threshold. This threshold model of AD was proposed by Blessed, Tomlinson, and Roth (1968) based on their findings that older adults with dementia had significantly higher plaque count compared to subjects without dementia, but the correlation between plaque count and dementia symptoms was not significant among subjects with advanced dementia. This led to the hypothesis that sufficient damage to the brain has occurred once the number of plaques in the brain surpasses a critical threshold, and continued accumulation does not necessarily result in more severe dementia symptoms (Blessed et al., 1968). The poor correlation between brain pathology and degree of cognitive impairment (Bennet et al., 2006; Giannakopoulos et al., 2003; Haroutunian et al., 2008; Knopman et al., 2003) suggests that the relationship is influenced by a person’s ability to engage other cognitive processes to compensate for increasing neuropathology (Stern, 2002). This supports the hypothesis that a critical threshold of brain pathology varies from person to person, which adds an additional challenge to determining where in the disease process a critical threshold is located. An active model of reserve provides an explanation for why people with anatomically similar brains and similar pathology may express differing degrees of cognitive impairment. An active model of reserve is supported by evidence that older adults with higher educational attainment engage additional regions of the brain when performing cognitive tasks (Scarmeas et al., 2003; Springer, McIntosh, Winocur, & Grady, 2005), have higher cognitive function despite similar AD pathology (Bennett et al., 2003), and have greater brain pathology at time of AD diagnosis (Stern, Alexander, Prohovnik, & Mayeux, 1992) compared to older adults with less educational attainment. These findings have important implications when interpreted
using a life span framework because plausible pathways for the observed associations between psychosocial characteristics during childhood and the risk for dementia during old age become apparent. As an example, a child born into a family of high socioeconomic status will likely be provided with educational opportunities and a mentally stimulating environment from a young age. These early life advantages may contribute to additional advantages later in life, such as earning a college degree and working in a stimulating environment. Advantages accumulate over the life span and contribute to greater brain and cognitive reserves during old age. This decreases a person’s risk for AD by increasing the critical threshold that pathological changes to the brain must surpass before cognitive declines are observed.

The threshold model for AD has had significant implications for treatment and prevention because it has increased the urgency to determine when in the disease process a person who develops AD crosses the critical threshold. Available treatments for AD temporarily improve clinical symptoms and slow the progression of the disease (S. L. Rogers, Farlow, Doody, Mohs, & Friedhoff, 1998; Rosler et al., 1999), but there are currently no treatments that reverse or stop the declines in cognitive and physical functioning associated with AD. This is possibly due to treatments being administered too late in the disease process when irreversible damage to the brain has already occurred (Roh & Holtzman, 2012). This has led to a significant shift in the therapeutic approach to AD from administering disease-modifying treatments to patients who are in the mild to moderate stages of the disease to the preclinical stages of the disease before cognitive symptoms are observed. The challenge is determining how early in the disease process the critical threshold is crossed and sufficient and irreversible damage to the brain has occurred. Advances in brain imaging techniques and the discovery of biomarkers that reflect pathological changes to the brain have allowed for the presence of AD neuropathology to be detected many years before clinical symptoms associated with AD are observed (Jack et al., 2013; Jack et al., 2010). The period between the onset of AD neuropathology and clinically observable symptoms represents the preclinical stages of AD (Jack, Albert, et al., 2011). Adults with biomarker
evidence for accumulation of beta-amyloid (Aβ) protein in the brain, neurodegeneration, or both, but no detectable cognitive impairment are believed to be in the early stages of preclinical AD; adults with biomarker evidence for Aβ accumulation or neurodegeneration who exhibit subtle impairment on cognitive assessments are believed to be on the verge of progressing from preclinical AD into mild cognitive impairment (Sperling et al., 2011). Clinical trials to determine efficacy of disease-modifying treatments administered during preclinical AD will need to be large and will require prolonged follow up periods (Blennow, Hampel, & Zetterberg, 2014). Fortunately, these challenges have not discouraged investigation into this area of research and several programs are in place for clinical trials on disease-modifying agents and preclinical AD (Bateman et al., 2012; Garber, 2012; Reiman, Langbaum, & Tariot, 2010).

A life span approach also has implications for research focused on determining if there is a period within the life span that interventions may have the greatest lasting effects. In epidemiology, a critical period is a limited time frame in which an exposure has a greater protective or adverse effect for a disease compared to if the exposure is present outside of the critical period (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003). Midlife is a potential critical period for dementia due to the identification of factors related to vascular health associated with an increased risk for dementia, including hypertension (Kivipelto et al., 2000) high cholesterol (Kivipelto et al., 2002) and obesity (Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007). The relationship between middle age and cognitive functioning later in life is supported by evidence that pathological changes to the brain associated with AD begin many years or even decades prior to the onset of cognitive decline (Jack et al., 2013). There is evidence that hypertension and related conditions negatively impact the brain by decreasing blood flow to the brain (Beason-Held, Moghekar, Zonderman, Kraut, & Resnick, 2007). The decrease in blood flow deprives the brain of oxygen and may lead to brain infarcts or “mini” strokes. Over time the damage from these brain infarcts accumulates, making the brain more sensitive to AD neuropathology (Kalaria, 2010) and increasing the likelihood of developing AD (Vermeer et al.,
Furthermore, the inflammatory affects of poor vascular health on the brain may contribute to Aβ deposition (Lee et al., 2008). These plausible biological mechanisms suggest that interventions targeting vascular risk factors during midlife may substantially reduce the future prevalence of dementia (Barnes & Yaffe, 2011). The challenge, however, is several decades must pass before the effectiveness of interventions administered during middle age for cognitive functioning during old age can be determined. Furthermore, there may be a threshold effect in which a person must engage in regular exercise, consume a healthy diet or other positive health behaviors for a prolonged period of time for benefits to have a lasting effect into old age. This increases the importance of encouraging people to adopt positive health behaviors during adolescence and young adulthood so these behaviors become a part of their everyday routines and carry through middle age and into old age.

The vast majority of epidemiological studies have focused on midlife as a potential critical period for AD, but it is necessary to consider the importance of childhood and adolescence when examining AD. These life stages are potential critical periods because it is during childhood and adolescence that foundational experiences occur that often times shape health behaviors. These behaviors, when reinforced and carried through life as habits, may influence cognitive development through the life span. Childhood and adolescence have potentially significant implications to AD research when interpreted in the contexts of cumulative advantage and threshold models of AD, which points to the need for careful selection of controls during the design stage of a study that takes into account early life biopsychosocial characteristics.

**Differences between the Life Span and Life Course**

The life span framework acknowledges that the social and cultural environment in which people age changes over time and that these changes influence human development. An argument can be made that the fifth and sixth concepts of the life span framework add an additional layer of complexity that requires a life course perspective. The life course is the
temporal sequence of events, transitions, and trajectories that occur within socially constructed life domains (e.g. education, work, family) from birth until death, such as graduating from high school, entering the workforce, marriage or retirement (Elder, 2000; Elder, Johnson, & Crosnoe, 2003). Glen Elder and his colleagues have proposed five principals of the life course framework (Elder et al., 2003): (1) principal of life span development, (2) principle of agency, (3) principle of time and place, (4) principle of timing, and (5) the principle of linked lives. The principle of life span development is similar to the first concept of the life span framework and emphasizes that human development and aging is an ongoing process from birth until death. The remaining principles distinguish the life course framework from the life span framework. The second principle recognizes that an individual’s behavior and choices are influenced by the social constraints that are presented to them. The third principal of time and place acknowledges that an individual’s life course is influenced by historical events and geographic processes that shape the society and culture in which they live. The fourth principle of timing acknowledges that the influential effects of specific events depend on the timing (i.e. age and historic period) in which the event occurs. The fifth principle emphasizes that successive generations are connected through shared relationships that emerge, both predictably and vicariously, from membership in a vast array of social groups throughout life.

There are similarities between the life span and life course perspectives that need to be acknowledged. First, the life course and the life span recognize that human development and aging is a life long process that is ongoing from birth until death. Second, both constructs acknowledge the relationship between early life events and later life outcomes. Finally, both life course and life span emphasize the influence of characteristic social and cultural environments on human development and aging. These similarities often lead to confusion as when to use the term life span or life course, but there are important differences between these two terms. First, the life course perspective emphasizes that people live their lives interdependently (Alwin, 2012; Elder, 1994), meaning people are influenced by the choices, behaviors and actions of people around
them (Elder et al., 2003). The life span perspective does not acknowledge this interdependence in which people live their lives. Second, there is an important difference between the life span and life course in regards to the treatment of past time. Life span constrains the past to early life experiences, situations, and influences that occur once a person is born, whereas the life course recognizes that the pre-birth past influence of both current and anticipated future perceptions and behaviors. This needs to be acknowledged because lessons learned from the experiences of previous generations (e.g. parents, grandparents, societal/cultural events) can be passed down from generation to generation, which is not considered in the life span framework. Finally, the life course recognizes that the choices and decisions made in the present may be shaped by anticipation of what may happen in the future (Hosier, Downer, Watkins, & Zanjani, 2012b), which is also not considered in the life span framework. An example of how the anticipation of future events may influence present-day behavior is the use of cancer screening among women with a family history of breast cancer (Andersen, Smith, Meischke, Bowen, & Urban, 2003; Isaacs et al., 2002). Additional examples of this notion are readily available in scientific literature, but critical theoretical development of the future aspect of the life course is lacking.

The life course perspective emphasizes the trajectories of socially constructed domains, but health is an additional domain that plays a significant role in the life course. Incorporating health into the life course perspective makes this a useful approach for conducting AD research because genetic, physiological, behavioral and social factors all contribute to the etiology and progression of AD. A thorough discussion of the life course and the implications of a life course perspective for AD research are discussed in chapter six of this dissertation.
Figure 3.1: Scatter Plot of Total Cholesterol According to Chronological Age, Original Cohort

Figure 3.2: Scatter plot of total cholesterol according to chronological age, Offspring Cohort

Figure 3.3: Cross-Sectional Trend in Total Cholesterol, Original Cohort
Figure 3.4: Cross-Sectional Trend in Total Cholesterol, Offspring Cohort

Figure 3.5: Cross-Sectional Trends in Total Cholesterol Stratified by Sex, Original Cohort

Figure 3.6: Cross-Sectional Trends in Total Cholesterol Stratified by Sex, Offspring Cohort
Figure 3.7: Scatter Plot of Total Cholesterol According to Chronological Age, Offspring Cohort (Exam 2)

Figure 3.8: Cross-Sectional Trends in Total Cholesterol, Offspring Cohort (Exam 2)

Figure 3.9: Cross-Sectional Trends in Total Cholesterol Stratified by Sex, Offspring Cohort (Exam 2)
Figure 3.10: Longitudinal trends in total cholesterol, Original Cohort

Figure 3.11: Longitudinal Trends in Total Cholesterol Stratified by Sex, Original Cohort

Figure 3.12: Longitudinal Trend in Total Cholesterol, Offspring Cohort
Figure 3.13: Longitudinal Trends in Total Cholesterol Stratified by Sex, Offspring Cohort
Chapter Four: Research Design and Methodology

This dissertation presents a secondary analysis of cognitive, phenotypic and genetic data collected from subjects of the FHS Original Cohort and Offspring Cohort. A brief overview of the study design and methodology for each of the specific aims of the dissertation research is first provided followed by an overview of the FHS and detailed descriptions of the sample populations and statistical methods for each specific aim, which are provided in subsequent sections of this chapter.

Overview of Specific Aims

The research addressed three specific aims. Aim One utilized a cross-sectional study design and involved examining cognitive data collected from participants of the FHS Offspring Cohort between 1999 and 2005 using a neuropsychological battery to calculate a series of three composite scores of cognitive functioning: (1) a composite score that provided equal weight to each subtest included in the neuropsychological battery; (2) a composite score that provided equal weight to each cognitive domain assessed by the neuropsychological battery; and (3) an abbreviated summary score comprised of the subtests that assessed learning and memory. Receiver operating characteristic (ROC) analysis was conducted to determine which of the three summary scores was best able to differentiate between participants who were classified as having normal cognition, test-based impaired learning and memory (ILMTB), test-based multi-domain impaired (MDITB), or dementia based on the area under the curve (AUC), sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy for each of the summary scores. The summary score that was best able to differentiate between the cognitive groups was used as the measure of cognitive functioning in Aim Three. Aim Two utilized a longitudinal study design. Repeated measures of total cholesterol and HDL cholesterol collected from subjects of the FHS Original Cohort between 1948 and 2005 were used to model the longitudinal trajectories of total cholesterol, HDL cholesterol and total/HDL ratio from midlife to late life. Generalized additive mixed modeling allowed for the longitudinal trajectories of total cholesterol,
HDL cholesterol and total/HDL ratio according to AD status to be visually examined. Aim Three also utilized a longitudinal study design. For this aim, repeated measures of total cholesterol collected from participants of the FHS Offspring Cohort between 1971 and 2008 were used to predict subject-specific trajectories of total cholesterol using a growth-curve approach via mixed effects regression models. The subject-specific trajectories of cholesterol were plotted according to degree of cognitive functioning. This allowed for visual interpretations of the relationship between cognitive functioning and subject-specific trajectories of cholesterol to be made.

**The Framingham Heart Study**

The FHS is an ongoing prospective cohort study of residents from Framingham, Massachusetts created with the goal of generating knowledge on the onset and progression of cardiovascular disease and lung disease, as well as genetic and environmental risk factors for these diseases. The FHS includes a total of five cohorts: (1) Original, (2) Offspring, (3) Third Generation, (4) Omni 1, and (5) Omni 2.

The FHS Original Cohort was initiated in 1948 and included adults residing in Framingham, Massachusetts who did not have cardiovascular disease. A total of 5079 participants between the ages of 28 and 74 (mean age 44.2 years) completed a baseline clinical exam between 1948 and 1953. Thirty clinical examinations have been completed since 1948, and 141 participants (mean age 92, range 88-102) attended the thirtieth clinical exam, which concluded in 2010.

The Offspring Cohort was initiated in 1971 and includes children, and their spouses, who had one or both parents who were subjects of the Original Cohort (Feinleib, Kannel, Garrison, McNamara, & Castelli, 1975). A total of 5124 subjects between the ages of 5 and 70 (mean age 36) attended the first clinical exam between 1971 and 1975. Eight clinical exams have been completed since 1971 and 3021 (mean age 67, range 40 – 93) subjects attended the most recent examination, which concluded in 2008. Data collection for the ninth clinical examination began in 2011.
Beginning in 2002, 4095 individuals who had one or more parents who were subjects in
the FHS Offspring Cohort attended the first clinical examination for the Third Generation Cohort
(Splansky et al., 2007). Only two clinical exams have been completed since 2003.

The FHS also includes two Omni Cohorts, which were initiated to reflect the increasing
ethic diversity of Framingham Massachusetts. The Omni 1 cohort was initiated in 1994 and is
comprised of 506 residents of Framingham, Massachusetts and surrounding areas who responded
to being a member of a minority group (Quan et al., 1997). The third clinical exam was
completed in 2008 and was attended by 298 subjects. Data collection for the fourth examination
is ongoing. A second Omni cohort began in 2003 and included 410 subjects from Framingham
Massachusetts. The Omni 2 cohort includes subjects who are unrelated to subjects of the Omni 1
cohort, but many of the subjects in this cohort are related to subjects in the Omni 1 cohort. The
Omni Cohorts include subjects of African-American, Hispanic, Asian, Indian, and Native
American descent.

During each wave of data collection for the five cohorts, subjects received an extensive
physical examination, which included non-invasive tests (e.g. body composition, x-ray, and
pulmonary function), lab tests (e.g. lipid and hormone levels), and a health history questionnaire
to assess health behavior and the onset of any health conditions since the previous wave of data
collection. DNA collection from living members of the Original and Offspring Cohorts began in
the 1980’s and genotyping has been performed using Affymetrix 100K and 550K SNP chips
(Cuppes et al., 2007). Current information regarding the status, recruitment and data collection
for the five FHS cohorts can be found at http://www.framinghamheartstudy.org.

Aim One: Summary Score for the FHS Neuropsychological Battery

Sample Population

A total of 2557 members of the FHS Offspring Cohort received a neuropsychological
battery between 1999 and 2005. There were 1713 (67.0%) subjects from the Offspring Cohort
who attended a follow-up evaluation prior to 2007 in which they received the same
neuropsychological battery. There were 325 members of the FHS Original Cohort who also received a neuropsychological battery between 1999 and 2005. Members of the Original Cohort were excluded from all analyses in Aim One because of significant differences in cognitive functioning between the Original and Offspring Cohorts that remain after adjusting for education, age, and sex (Au et al., 2004). Subjects of the Offspring Cohort with missing data for one or more subtests of the neuropsychological battery during the baseline examination (n=54, 2.1%) were excluded from the final sample. This was done so the summary scores for each subject would reflect the same combination of overall measures of cognitive functioning. The final sample included 2503 subjects from the FHS Offspring Cohort.

The FHS Neuropsychological Battery

The cognitive assessments included in neuropsychological battery were the Boston Naming Test (Goodglass & Kaplan, 1983), Trail Making Tests A and B (TMT A, B) (Armitage, 1946), Finger Tapping Test (Shimoyama, Ninchoji, & Uemura, 1990), Hooper Visual Organization Test (Hooper, 1966), Wide Range Achievement Test-3 Reading (WRAT) (Wilkinson, 1993), and subtests from the Wechsler Memory Scale (Wechsler, 1945; logical memory immediate and delayed recall, paired-associate memory, visual reproduction immediate and delayed recall), and Wechsler Adult Intelligence Scale (Wechsler, 1955; similarities). A brief description of the cognitive abilities examined by each assessment is provided in the Table 4.1. A higher score on each subtest of the neuropsychological battery, with the exception of the TMT A and B, indicates better cognitive function. The TMT A and B are timed assessments that require a subject to connect a random alphabetic sequence (TMT A) and alphanumeric sequence (TMT B). The times to complete the TMT A and TMT B subtests were used to create an additional measure that represented cognitive flexibility by calculating TMT B minus TMT A (Arbuthnott & Frank, 2000; Corrigan & Hinkeldey, 1987).
Case Definitions for Dementia and Cognitive Impairment

Incident cases of dementia in the Offspring Cohort have been recorded as part of the Epidemiology of Dementia study since 1986 (Bachman et al., 1992; Bachman et al., 1993). Thirty-six subjects diagnosed with dementia received the FHS neuropsychological battery between 1999 and 2005, but seven cases (n=5 AD; n=2 other dementia) had missing data for one or more assessments.

Subjects included in the final sample were randomized to either a training set or validation set. The training set was used to estimate the effects of age, sex (coded as 0=male, 1=female), and education (≤ high school, some college, college degree) on cognitive performance among subjects with normal cognition (absent of dementia or a decline ≥1.5 standard deviations on one or more subtests). The effects of these characteristics on cognitive performance were determined using a univariate model (UV; Table 4.2) in which each variable was examined separately and a multivariable (MV) model that included age, sex, and education in the same model. The regression coefficients from the MV model were used to calculate predicted scores for each of the cognitive assessments based on a subject’s age, sex and educational attainment (Table 4.3). The cognitive assessments included in the FHS neuropsychological battery were used to classify subjects into the following cognitive groups: (1) normal cognition (NC); (2) test-based impaired learning and memory (ILM\textsubscript{TB}); and (3) test-based multidomain impaired (MDI\textsubscript{TB}). A classification of ILM\textsubscript{TB} was given to subjects with no dementia and who had impaired performance on one or more assessments of learning and memory, but non-impaired performance on all other assessments (Abner et al., 2012). A classification of MDI\textsubscript{TB} was given to participants with no dementia and who had impaired performance on one or more assessments in the neuropsychological battery, which could include learning and memory subtests. A classification of NC was given to participants who did not have an impaired performance on any assessments.

\textsuperscript{15} A more detailed description of the protocol used to diagnose dementia in the FHS is provided in the methods for Aim Two.
Impaired performance for each assessment was defined as ≥1.5 SD below age, sex, and education expected norms based on the estimates for age, sex, and education obtained from the test sample. This definition of impairment is consistent with the criteria provided by the National Institute on Aging- Alzheimer’s Association workgroup (Albert et al., 2011).

**Generating Summary Scores for the FHS Neuropsychological Battery**

*Composite Subtests Summary Score:* All of the assessments included in the FHS neuropsychological battery, with the exception of the Finger Tapping Test and WRAT, and the calculated measure of cognitive flexibility (TMT B minus TMT A) were included in this summary score. The Finger Tapping Test was excluded because this assessment is frequently used to measure motor functioning (Volkow et al., 1998). The WRAT was excluded because this assessment is a word identification test that measures literacy (Davis, Michielutte, Askov, Williams, & Weiss, 1998) and is often used as a proxy for educational quality (Manly, Jacobs, Touradji, Small, & Stern, 2002). The composite subtests summary score was calculated by first transforming the score of each assessment into a z-score by subtracting an individual subject’s assessment score minus the sample mean and dividing by the standard deviation. The z scores for TMT A and B and cognitive flexibility were multiplied by -1 to account for these being timed assessments. Once a z score was calculated for each assessment, the average of the z scores was calculated to obtain the summary score.

*Learning and Memory Summary Score:* The learning/memory summary score was obtained by calculating the average of the six z-scores for the subtests that assessed learning and memory. The average of the z-scores was used for the summary score as opposed to the sum of the scores so that each assessment provided equal weight to the summary score.

*Composite Domains Summary Score:* The specific cognitive domains assessed by the FHS neuropsychological battery were determined by conducting a factor analysis, followed by an orthogonal (varimax) rotation. A total of three factors were extracted (eigenvalue >1) and a fourth factor with an eigenvalue of 0.9 was also included (remaining eigenvalues <0.71). The
following subtests loaded onto the four factors based on a rotated factor pattern score above 0.5: visual/spatial memory [Visual Memory Immediate Recall (0.90), Visual Memory Delayed Recall (0.9), Hooper Visual Organization Test (0.5)]; verbal memory [Logical Memory Immediate Recall (0.93), Logical Memory Delayed Recall (0.90)]; new learning [Paired Associates Immediate Recall (0.88), Paired Associates Delayed Recall (0.9)]; and attention/concentration [TMT A (0.87), TMT B (0.77)]. Cognitive flexibility was added to the attention/concentration domain. Once these cognitive domains were identified, the next step was to sum the scores for the subtests to create a total score for each specific cognitive domain. These total scores were then transformed into z scores and the average of these z scores was calculated to obtain the composite domain summary score.

Statistical Analysis

Receiver operator characteristic (ROC) analysis was conducted to obtain ROC curves for each of the summary scores. The area under the curve (AUC) is interpreted as the probability that a randomly selected subject who is a case (dementia, ILM_{TB}, or MDI_{TB}) has a lower summary score than a randomly selected subject who was classified as having normal cognition. To control for the effects of age, sex and educational attainment, the residuals of the summary scores were obtained by calculating the difference between the observed summary score and predicted summary score given a subject’s age, sex and educational attainment. The ROC analysis was also used to determine the sensitivity (proportion of cases who were correctly identified), specificity (the proportion of controls who are correctly identified), positive predictive value (ppv; the probability that subjects who test positive for the disease are true cases), negative predictive value (npv; the probability that subjects who test negative are true controls), and diagnostic accuracy (proportion of cases and controls who are correctly identified) for the cut-point of the residuals for each summary score. The ROC curve analysis was conducted using data from the validation sample.
Aim Two: Differences in the Longitudinal Trajectories of Cholesterol from Midlife to Late Life According to Alzheimer’s Disease Status

Sample Population

A total of 5079 subjects of the FHS Original Cohort between the ages of 28 and 74 (mean age 44.2 years) completed a baseline clinical exam between 1948 and 1953. Thirty clinical examinations have been completed since 1948 and 141 participants (mean age 92, range 88-102) attended the thirtieth clinical exam, which concluded in 2010. A sub-cohort of subjects from the FHS Original Cohort who were said to be absent of dementia was established from 1976 to 1978 with the purpose of recording incident cases of dementia (Bachman et al., 1993). A total of 3210 subjects were said to be absent of dementia and these subjects have been evaluated during each biennial examination to assess dementia status (yes / no), date last known to be cognitively intact, and date of incident dementia, death or censoring. Because the purpose of this aim was to examine trajectories of cholesterol from midlife to late life, subjects who were younger than 30 years (n=21, <1%) or older than 55 years (n=174, 5.4%) during the first clinical exam were excluded from the final sample. An additional 124 subjects (3.9%) who were younger than 65 years of age when they were last known to be cognitively intact were also excluded. The age cutoffs for midlife (age 30 – 55) and late life (age ≥ 65) were based on distinct trends in the relationship between total cholesterol and chronological age among subjects of the Original Cohort (see Chapter Three for a detailed description of how the definitions for midlife and late life were obtained).

Diagnosis of Dementia in the FHS Original Cohort

The methods used in the FHS to diagnose dementia have been previously described (Bachman et al., 1992; Bachman et al., 1993). From 1976 to 1978 surviving members of the FHS Original Cohort were screened for dementia using the Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) to establish a dementia-free cohort of 3210 subjects. These 3210 subjects received the MMSE during each subsequent clinical examination. Subjects who scored
below the education-adjusted cut-off score on the MMSE (score ≤ 22 for ≤ 7 yrs. Education; score ≤ 24 for 8 to 11 yrs. Education; score ≤ 25 for high school graduate; and score ≤ 26 for any education beyond high school), declined three or more points since the previous examination, or were referred by themselves, a family member, family physician, or FHS physician were given a comprehensive neuropsychological battery. The neuropsychological battery included subtests that assessed the following cognitive domains: (1) verbal and visual learning, (2) attention, (3) language, (4) visuospatial construction, and (5) abstract thinking (Farmer et al., 1987). A subject was said to be cognitively impaired if they performed at a level one or more standard deviations below age-adjusted norms on three or more of the five cognitive domains assessed by the neuropsychological battery. An expert panel reviewed all available records for subjects who met the criteria for cognitive impairment to determine if the cognitive impairment was likely due to dementia. Subjects were considered as having dementia if they met the criteria for cognitive impairment for at least one year and exhibited progressive cognitive decline over a prolonged period. For cases of dementia, the panel also reviewed dementia severity (mild or moderate) and dementia subtype (Alzheimer’s disease [AD], AD with stroke, vascular dementia [VaD], AD with VaD [mixed dementia], or other). For the purposes of this study, only subjects diagnosed with AD were included in the final sample.

**Measures of Cholesterol**

Measures for total cholesterol and HDL cholesterol were collected from participants of the FHS Original Cohort using standard laboratory procedures (Abel, Levy, Brodie, & Kendall, 1952). Fasting measures for total cholesterol were collected during twenty clinical examinations (clinical exams 1-11, 13-15, 20, 22, 24-27) and measures of HDL cholesterol were collected during ten clinical examinations (clinical exams 9-11, 15, 20, 22, and 24-27). Total/HDL ratio was calculated by dividing the measure of total cholesterol by the measure of HDL cholesterol. The distributions for total/HDL ratios were highly right skewed so log transformations were used.
**Statistical Analysis**

The demographic characteristics of the final sample were described according to AD status (non-demented or AD). T-tests were used to compare group means for continuous variables and chi-square tests were used to compare group differences for categorical variables. The trajectories of total cholesterol, HDL cholesterol, and log-total/HDL ratio according to AD status were modeled using generalized additive mixed models (GAMM; Lin & Zhang, 1999) implemented using the gamm4 package (S. Wood & Scheipl, 2013) in R (http://www.r-project.org). GAMM are semi-parametric models that utilize a data driven approach to model a non-linear relationship between the dependent and independent variables as opposed to including quadratic, cubic or higher level polynomial terms. The general form of the GAMM used for this study is:

$$g(u_{ij}) = X_i^T \beta + s_{AD}(x_{ij})AD_i + s_{1-AD}(x_{ij})(1 - AD_i) + b_i + \epsilon_{ij} \quad (4.1)$$

where $u_{ij} = E(Y_{ij})$ is the expected value of cholesterol for the $i$th subject during the $j$th observation given the covariates included in the model (see **Covariates**), and $b_i$ is a subject-specific random effect that allows for the baseline value of cholesterol to vary for each subject; $g($ is the link function that specifies the relationship between the expected value of cholesterol and the covariates included in the model. The link function for the model was the identity function because total, HDL, and log-total/HDL cholesterol ratio were continuous variables. $X_i$ is a k-length vector comprising the k time-invariant covariates of subject $i$ and $\beta$ is a k-length vector of the fixed effects for the corresponding k covariates; $x_{ij}$ is the age of the $i$th subject during the $j$th observation; $s_{AD}$ and $s_{1-AD}$ are the smoothing terms that were generated for subjects with AD and subjects without dementia, respectively. $AD_i$ is an indicator variable denoting AD status in the $i$th subject. Since every subject is either AD or non-demented, the term $1-AD_i$ specifies subjects who do not have AD and prevents over parameterization of the model. The inclusion of two different smooth terms allowed for the trajectories of cholesterol to vary according to AD status.
status. The smoothing function models the potentially non-linear trajectory of cholesterol with advancing age. A thin plate regression spline function was applied to age for both AD and nondemented subjects. An advantage of the thin plate regression spline function over other smoothing functions is that the number and placement of knots that control the flexibility of the model do not need to be specified (S. Wood, 2003). The more knots included in the model, the more precisely the model will fit the data, but this is at the risk of over fitting the data and producing a curve that is not sufficiently smooth. Concerns of over fitting are addressed by adding a second derivative function on the penalty to the least squares fitting approach (S. Wood, 2003) providing a tradeoff between model fit and model smoothness (S. Wood, 2006). The term $\epsilon_{ij}$ is the within-subject error term, which is the difference between the observed measure of cholesterol and the expected measure of cholesterol based on the model. Both $b_i$ and $\epsilon_{ij}$ are assumed to be randomly distributed with mean zero and variances of $\sigma_b^2$ and $\sigma_e^2$, respectively. An additional assumption is that $b_i$ and $\epsilon_{ij}$ are independent of one another.

The estimated trajectories of total cholesterol, HDL cholesterol, and log-total/HDL ratio based on the models were plotted along with point-wise 95% confidence intervals that were constructed by calculating the upper and lower bounds for each predicted measure of cholesterol. This allowed for the trajectories of total cholesterol, HDL cholesterol and log-total/HDL ratio according to AD status to be visually examined. The degree to which the trajectories of cholesterol departed from linearity is reflected by the effective degrees of freedom (EDF) of the smooth term (James, Witten, Hastie, & Tibshirani, 2013). A smooth term with $x$ EDF can be interpreted as an $x$ degree polynomial term. An EDF of 1 indicates that the trajectory is linear and increasing values of EDF indicate greater degrees of non-linearity.

**Covariates**

Data for several potential confounding variables were collected during each clinical examination using standard laboratory procedures and a medical history interview. Educational
attainment was initially recorded according to the following categories: (1) none, (2) fourth grade or less, (3) fifth, sixth or seventh grade, (4) completed grade school, (5) some high school, (6) graduated high school, (7) some college, (8) college graduate or (9) post graduate. For the purposes of this study, educational attainment was dichotomized according to receiving a high school degree (≤ high school degree or > high school degree). Smoking status was assessed during each clinical examination and subjects were dichotomized as having ever reported smoking (yes/no). The use of cholesterol lowering medications (statins, fibrates, resins, or niacin) was assessed during clinical examinations 7-27. Subjects were dichotomized as having reported ever using a cholesterol lowering medication during a clinical examination (yes/no).

Data for systolic and diastolic blood pressure was collected during each clinical examination and blood glucose was measured during clinical exams 1-11, 13-15, 20, 22, 24-27. Blood pressure and blood glucose were included in the models as the average of these measures across all of the clinical examinations attended by the subject. APOE e4 allele status was dichotomized according to the presence of one or more APOE e4 alleles (e4+ or e4-).

A subsequent analysis was conducted that included the use of supplemental estrogen as a covariate. Estrogen replacement therapy is an effective approach for maintaining a healthy lipid profile for women who are approaching or experiencing menopause (Vehkavaara et al., 2001). There is evidence that women who take supplemental estrogen are at a decreased risk for AD (Kawas et al., 1997; Paganini-Hill & Henderson, 1994), but some studies have reported no benefits of estrogen use (Brenner et al., 1994) or even an increased risk for cognitive impairment among estrogen users (Shumaker et al., 2004; Shumaker et al., 2003). Based on the results from previous studies, additional models were used to visually inspect for differences in the trajectories of total cholesterol, HDL cholesterol and log-total/HDL cholesterol ratio according to AD status after controlling for the effects of a history of using supplemental estrogen. The use of supplemental estrogen (oral, patch, or cream) was assessed during clinical exams 17-27 and was included in the models as having reported using supplemental estrogen (yes/no).
Aim Three: Subject-Specific Trajectories of Total Cholesterol According to Cognitive Functioning

Sample population

The FHS Offspring Cohort began in 1971 and includes the children of the Original Cohort and their spouses. Details regarding the design and methods of data collection of the FHS Offspring Cohort have been described previously (Feinleib et al., 1975). Eight clinical examinations were completed between 1971 and 2008. A total of 5124 subjects between the ages of 5 and 70 (mean age 36) attended the first clinical exam and 3021 (mean age 67, range 40 – 93) subjects attended the eighth clinical examination.

Beginning in 1999, subjects who were actively participating in the FHS Offspring Cohort were recruited to participate in a secondary study in which they received a comprehensive neuropsychological battery (Massaro et al., 2004). A total of 2557 subjects of the Offspring Cohort received a neuropsychological battery between 1999 and 2005. Because the purpose of this study was to examine trajectories of cholesterol from midlife to late life, subjects who were not between 30 and 45 years of age during the first clinical examination and were not 60 years of age or older upon receiving the neuropsychological battery were not included in the final sample. The age cutoffs for midlife (age 30 – 45) and late life (age ≥ 60) were based on distinct trends in the relationship between total cholesterol and chronological age among subjects of the Offspring Cohort (see Chapter Three for a detailed description of how the definitions for midlife and late life were obtained). These definitions are different than those used in Aim Two because the ages in which visually apparent changes in total cholesterol varied between the Offspring and Original Cohorts. A total of 967 subjects (37.8%) were between 30 and 45 years of age during the first clinical exam and 60 years of age or older upon receiving a baseline neuropsychological battery. Subjects who had received a diagnosis of dementia (n=13) and did not complete all of the assessments included in the neuropsychological battery (n=16) were removed from the sample.
Finally, subjects who did not have data for apolipoprotein E (APOE) genotype (n=206) were removed from the sample. The final sample included 761 subjects.

**Measure of Cognitive Functioning**

A description of the FHS neuropsychological battery was provided in the methods for specific aim one. A summary score of the FHS neuropsychological battery was obtained by standardizing a subject’s raw score for each cognitive assessment according to the sample mean and standard deviation, followed by calculating the average of these standardized scores. The findings from aim one of the dissertation research provided evidence that this method produces a summary score that is able to accurately differentiate between subjects classified as having normal cognition, cognitive impairment, and dementia (see Chapter Five Aim One for complete results). Subjects were grouped into quartiles based on their summary score for the FHS neuropsychological battery. This was necessary to visually examine potential differences in subject-specific trajectories of total cholesterol according to cognitive functioning. Subjects in the first quartile represent those who had a summary score in the bottom 25 percent of the sample population and subjects in the fourth quartile were those who had a summary score in the top 25 percent of the sample population. Subjects in the second and third quartiles were treated as the reference category for the purposes of identifying potential differences in the trajectories of total cholesterol among subjects with low or high cognitive functioning.

**Measures of Cholesterol**

Fasting measures for total cholesterol have been collected from subjects during all eight clinical examinations. It should be noted that fasting cholesterol measures, especially when used for epidemiological studies, are subject to biases emerging from different effects that control individual adherence to prescriptive fasting prior to blood draws.

**Statistical Analysis**

The demographic characteristics of the final sample were described according to the quartiles of cognitive functioning. Analysis of variance was used to compare group means for
continuous variables and chi-square tests were used to compare group differences for categorical variables.

Mixed effects modeling (Laird & Ware, 1982) was used to visually examine the subject-specific trajectories of total cholesterol split according to the cognitive quartiles. This approach was used because it provides valid estimates when data are highly unbalanced due to differences in the number and timing at which subjects are observed (Cnaan, Laird, & Slasor, 1997). The general form of the mixed effects model is given by:

\[ Y_{ij} = X_i^T \beta + b_{1i} + b_{2i} \text{age}_{ij} + b_{3i} \text{age}_{ij}^2 + \epsilon_{ij} \]  

(4.2)

where \( Y_{ij} \) is the measure of cholesterol for subject \( i \) during the \( j \)th observation. \( X_i \) is a \( k \)-length vector of values for the time-invariant covariates for subject \( i \) and \( \beta \) is the \( k \)-length vector of fixed effects for the corresponding covariates; \( \text{age}_{ij} \) is the age of subject \( i \) during the \( j \)th observation; \( b_{1i} \) is the random intercept for subject \( i \) and \( b_{2i} \) is the random slope term for subject \( i \). A quadratic term for age was also included as a fixed effect and random effect to account for a non-linear relationship between cholesterol and age. The generalized additive mixed models that were used in Aim Two could not be utilized in this specific aim because a smoothing function cannot be included as a random effect, which is necessary for a smooth function to be applied to each subject’s trajectory of total cholesterol. The random effects \( b_{1i}, b_{2i} \) and \( b_{3i} \) are all assumed to be randomly distributed with mean zero and variances of \( \sigma^2_{b1}, \sigma^2_{b2} \) and \( \sigma^2_{b3} \), respectively. The random intercept represents how much an individual’s baseline measure of cholesterol deviates from the population average, whereas the random trajectory represents how an individual’s change in cholesterol with age deviates from the population average. Finally, \( \epsilon_{ij} \) is the within-subject measurement error, which allows for a measure of cholesterol during any observation period to vary randomly above or below a subject’s mean trajectory of cholesterol. The error terms are assumed to be independent and normally distributed with a mean 0 and variance \( \sigma^2_e \).
An additional assumption is that the random effects \((b_1, b_2, \text{ and } b_3)\) and \(\epsilon_{ij}\) are independent of one another.

Two-way interaction terms for age by cognition quartile and age-squared by cognition quartile were included in all models to determine if subjects in the first and fourth cognitive quartiles had different trajectories of cholesterol compared to subjects in the middle two quartiles. Two-way interactions between age and sex, and age-squared and sex were included to account for differences in the trajectories of cholesterol between men and women. Random effects for age and age-squared were included in the model to allow for the trajectory of cholesterol to vary for each subject. A random intercept term was also included to account for each subject having a different baseline measure of cholesterol. Estimates for subject-specific trajectories of cholesterol were obtained by combining the values for the random and fixed effects. As an example, if \(\hat{\beta}_1\) is the fixed effect for the intercept and \(\hat{\beta}_2\) and \(\hat{\beta}_3\) are the fixed effects for the trajectory of cholesterol (i.e. the population average cholesterol trajectory), and \(\hat{b}_{1i}\) is the random intercept and \(\hat{b}_{2i}\) and \(\hat{b}_{3i}\) are the random trajectories then the subject-specific intercept is \(\hat{\beta}_1 + \hat{b}_{1i}\) and the subject-specific trajectory is \(\hat{\beta}_2 + \hat{\beta}_3 + \hat{b}_{2i} + \hat{b}_{3i}\).

The random effects for each subject are predicted by the best linear unbiased predictor (BLUP) via maximum likelihood to estimate the covariance between the repeated measures of cholesterol (Fitzmaurice, Laird, & Ware, 2011). The BLUP shrinks each subject’s predicted trajectory towards the population average trajectory based on the degree of within-subject variability (i.e. the random fluctuations of the repeated measures of cholesterol from a single subject) compared to the between-subject variability (i.e. the variation in the measures of cholesterol from different subjects). The trajectory of cholesterol for a subject whose repeated measures of cholesterol have high within-subject variability relative to the between-subject variability will be shrunk closer to the population average trajectory compared to a subject whose repeated measures of cholesterol have relatively low within-subject variability. The degree to
which a subject’s trajectory is pulled towards the population average trajectory is also influenced by the number of times a subject has been observed. The fewer observations for a subject the closer their trajectory is shrunk to the population average.

Covariates

Data for several potential confounding variables were collected during each clinical examination using standard laboratory procedures and a medical history interview. Measures of total cholesterol were collected during all eight clinical examinations. Educational attainment was assessed during the neuropsychological battery and was recorded as: (1) less than high school, (2) high school degree, (3) some college and (4) college degree or higher. Smoking status was assessed during each clinical examination and subjects were dichotomized as having ever reported smoking (yes/no). The use of cholesterol lowering medications (statins, fibrates, resins, or niacin) was assessed during all eight clinical examinations. Subjects were dichotomized as having ever used a cholesterol lowering medication (yes/no). Data for systolic and diastolic blood pressure was collected during each clinical examination and measures for blood glucose were recorded for the first through seventh clinical examinations. Blood pressure and blood glucose were included in the analysis as the average of these measures across all of the clinical examinations attended by the subject. Data for apolipoprotein E (APOE) genotype was recorded for 761 subjects. There were 587 subjects who did not carry an APOE e4 allele, 158 who were heterozygous for the e4 allele and 16 who were homozygous for the e4 allele. APOE e4 allele status was dichotomized according to the presence of one or more APOE e4 alleles (e4+ or e4) due to the low number of APOE e4 homozygotes in the final sample.
### Table 4.1: Cognitive Assessments in the FHS Neuropsychological Battery

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Score</th>
<th>Cognitive ability</th>
<th>*Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Naming Test</td>
<td>0-36</td>
<td>Naming and language</td>
<td>27.4 (2.5)</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>0-300 (sec)</td>
<td>Simple attention</td>
<td>0.55 (0.26)</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>0-300 (sec)</td>
<td>Complex attention</td>
<td>1.4 (0.77)</td>
</tr>
<tr>
<td>HVOT</td>
<td>0-30</td>
<td>Visuoperceptual skills, executive function</td>
<td>25.0 (3.2)</td>
</tr>
<tr>
<td>WRAT</td>
<td>0-57</td>
<td>Premorbid intelligence</td>
<td>48.7 (5.1)</td>
</tr>
<tr>
<td>Logical memory immediate recall</td>
<td>0-24</td>
<td>Verbal memory</td>
<td>11.5 (3.5)</td>
</tr>
<tr>
<td>Logical memory delayed recall</td>
<td>0-24</td>
<td>Verbal memory</td>
<td>10.5 (3.7)</td>
</tr>
<tr>
<td>Paired-associates, immediate recall</td>
<td>0-21</td>
<td>New learning</td>
<td>13.9 (3.4)</td>
</tr>
<tr>
<td>Paired-associate delayed recall</td>
<td>0-21</td>
<td>New learning</td>
<td>8.2 (1.5)</td>
</tr>
<tr>
<td>Visual reproductions immediate recall</td>
<td>0-14</td>
<td>Visual memory</td>
<td>9.0 (3.2)</td>
</tr>
<tr>
<td>Visual reproduction delayed recall</td>
<td>0-14</td>
<td>Visual memory</td>
<td>8.2 (3.4)</td>
</tr>
<tr>
<td>Similarities</td>
<td>0-26</td>
<td>Abstract reasoning</td>
<td>16.8 (3.6)</td>
</tr>
</tbody>
</table>

The Trail Making Test (TMT) A and B are timed assessments with a maximum of five minutes (300 seconds) being allowed to complete the assessment. A longer time to complete each of the assessments indicates lower cognitive performance.

HVOT - Hooper visual organization test
WRAT - Wide range achievement test

The mean score for TMT B – TMT A was 0.85 (SD=0.66)

*Mean and SD for final sample (N=2503)
<table>
<thead>
<tr>
<th>Subtest</th>
<th>Univariate Model</th>
<th>Univariate Model</th>
<th>Univariate Model</th>
<th>Univariate Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td>Sex</td>
<td>Some College</td>
<td>College</td>
</tr>
<tr>
<td>LMI</td>
<td>-0.056</td>
<td>0.77</td>
<td>1.03</td>
<td>2.10</td>
</tr>
<tr>
<td></td>
<td>(-0.080, -0.31)</td>
<td>(0.31, 1.23)</td>
<td>(0.44, 1.62)</td>
<td>(1.58, 2.62)</td>
</tr>
<tr>
<td>LMD</td>
<td>-0.066</td>
<td>0.95</td>
<td>1.25</td>
<td>2.16</td>
</tr>
<tr>
<td></td>
<td>(-0.091, -0.40)</td>
<td>(0.47, 1.43)</td>
<td>(0.64, 1.87)</td>
<td>(1.62, 2.71)</td>
</tr>
<tr>
<td>PASI</td>
<td>-0.084</td>
<td>1.29</td>
<td>0.68</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>(-0.11, -0.059)</td>
<td>(0.83, 1.75)</td>
<td>(0.077, 1.29)</td>
<td>(0.70, 1.77)</td>
</tr>
<tr>
<td>PASD</td>
<td>-0.035</td>
<td>0.50</td>
<td>0.17</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>(-0.046, -0.024)</td>
<td>(0.31, 0.70)</td>
<td>(-0.89, 0.43)</td>
<td>(0.18, 0.64)</td>
</tr>
<tr>
<td>VRI</td>
<td>-0.11</td>
<td>-0.33</td>
<td>1.19</td>
<td>1.89</td>
</tr>
<tr>
<td></td>
<td>(-0.13, -0.088)</td>
<td>(-0.76, 0.11)</td>
<td>(0.63, 1.74)</td>
<td>(1.40, 2.38)</td>
</tr>
<tr>
<td>VRD</td>
<td>-0.11</td>
<td>-0.27</td>
<td>1.28</td>
<td>2.09</td>
</tr>
<tr>
<td></td>
<td>(-0.13, -0.085)</td>
<td>(-0.74, 0.19)</td>
<td>(0.69, 1.87)</td>
<td>(1.57, 2.61)</td>
</tr>
<tr>
<td>TMT A</td>
<td>0.0059</td>
<td>-0.029</td>
<td>-0.050</td>
<td>-0.057</td>
</tr>
<tr>
<td></td>
<td>(0.0044, 0.0074)</td>
<td>(-0.057, -8.0e^-4)</td>
<td>(-0.087, -0.013)</td>
<td>(-0.090, -0.024)</td>
</tr>
<tr>
<td>TMT B</td>
<td>0.024</td>
<td>0.022</td>
<td>-0.16</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>(0.020, 0.028)</td>
<td>(-0.62, 0.11)</td>
<td>(-0.27, -0.051)</td>
<td>(-0.41, -0.22)</td>
</tr>
<tr>
<td>TMT (B-A)</td>
<td>0.018</td>
<td>0.051</td>
<td>-0.011</td>
<td>-0.26</td>
</tr>
<tr>
<td></td>
<td>(0.014, 0.021)</td>
<td>(-0.020, 0.12)</td>
<td>(-0.20, -0.018)</td>
<td>(-0.34, -0.18)</td>
</tr>
<tr>
<td>HVOT</td>
<td>-0.12</td>
<td>0.20</td>
<td>0.59</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>(-0.14, -0.099)</td>
<td>(-0.22, 0.63)</td>
<td>(0.033, 1.14)</td>
<td>(0.53, 1.51)</td>
</tr>
<tr>
<td>Similarities</td>
<td>-0.089</td>
<td>-0.43</td>
<td>1.60</td>
<td>3.09</td>
</tr>
<tr>
<td></td>
<td>(-0.11, -0.064)</td>
<td>(-0.90, 0.034)</td>
<td>(1.04, 2.17)</td>
<td>(2.59, 3.59)</td>
</tr>
<tr>
<td>BNT</td>
<td>-0.064</td>
<td>-0.49</td>
<td>1.13</td>
<td>1.96</td>
</tr>
<tr>
<td></td>
<td>(-0.081, -0.047)</td>
<td>(-0.82, -0.17)</td>
<td>(0.74, 1.53)</td>
<td>(1.61, 2.31)</td>
</tr>
</tbody>
</table>

*Based on subjects included in the test set that were absent of dementia or decline ≥1.5 SD on one or more subtests.

**Bold P<0.01** Underlined P<0.05 but not P<0.01

Referent category for sex is male. Referent category for education is high school degree or less. LMI = Logical Memory, Immediate Recall; LMD = Logical Memory, Delayed Recall; PASI = Paired Associates, Immediate Recall; PASD = Paired Associates, Delayed Recall; VRI = Visual Reproductions, Immediate Recall; VRD = Visual Reproduction, Delayed Recall; TMT A (B) = Trail Making Test A (B); HVOT = Hooper Visual Organization Test; BNT = Boston Naming Test

TMT A, B and B-A are timed assessments; higher score indicates lower performance.
Table 4.3 Effects of Age, Sex and Education on Assessments in the FHS Neuropsychological Battery (Multivariable Model).

<table>
<thead>
<tr>
<th>Subtest</th>
<th>Multivariable Model</th>
<th>Age</th>
<th>Sex</th>
<th>Some College</th>
<th>College</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMI</td>
<td>-0.041 (-0.065, -0.017)</td>
<td>1.18 (0.73, 1.62)</td>
<td>0.90 (0.31, 1.48)</td>
<td>2.21 (1.69, 2.74)</td>
<td></td>
</tr>
<tr>
<td>LMD</td>
<td>-0.050 (-0.75, -0.25)</td>
<td>1.36 (0.89, 1.82)</td>
<td>1.09 (0.49, 1.70)</td>
<td>2.29 (1.74, 2.83)</td>
<td></td>
</tr>
<tr>
<td>PASI</td>
<td>-0.076 (-0.10, -0.052)</td>
<td>1.55 (1.10, 2.00)</td>
<td>0.44 (-0.15, 1.02)</td>
<td>1.30 (0.78, 1.83)</td>
<td></td>
</tr>
<tr>
<td>PASD</td>
<td>-0.033 (-0.043, -0.023)</td>
<td>0.60 (0.40, 0.79)</td>
<td>0.062 (-0.19, 0.31)</td>
<td>0.42 (0.20, 0.65)</td>
<td></td>
</tr>
<tr>
<td>VRI</td>
<td>-0.099 (-0.12, -0.077)</td>
<td>-0.052 (-0.46, 0.36)</td>
<td>0.85 (0.31, 1.38)</td>
<td>1.53 (1.05, 2.01)</td>
<td></td>
</tr>
<tr>
<td>VRD</td>
<td>-0.10 (-0.12, -0.072)</td>
<td>0.04 (-0.40, 0.48)</td>
<td>0.95 (0.38, 1.53)</td>
<td>1.75 (1.23, 2.27)</td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>0.0056 (4.0e⁻³, 7.0e⁻³)</td>
<td>-0.038 (-0.065, -9.8e⁻³)</td>
<td>-0.031 (-0.067, 4.8e⁻³)</td>
<td>-0.045 (-0.078, -0.013)</td>
<td></td>
</tr>
<tr>
<td>TMT B</td>
<td>0.022 (0.018, 0.026)</td>
<td>-0.028 (-0.11, 0.051)</td>
<td>-0.24 (-0.19, 0.019)</td>
<td>-0.24 (-0.33, -0.15)</td>
<td></td>
</tr>
<tr>
<td>TMT (B-A)</td>
<td>0.017 (0.013, 0.020)</td>
<td>0.0096 (-0.058, 0.077)</td>
<td>-0.053 (-0.14, 0.035)</td>
<td>-0.20 (-0.27, -0.12)</td>
<td></td>
</tr>
<tr>
<td>HVOT</td>
<td>-0.12 (-0.14, -0.095)</td>
<td>0.36 (-0.04, 0.76)</td>
<td>0.19 (-0.33, 0.71)</td>
<td>0.68 (0.21, 1.15)</td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>-0.068 (-0.091, -0.045)</td>
<td>0.074 (-0.36, 0.50)</td>
<td>1.37 (0.81, 1.92)</td>
<td>2.86 (2.36, 3.37)</td>
<td></td>
</tr>
<tr>
<td>BNT</td>
<td>-0.050 (-0.066, -0.034)</td>
<td>-0.20 (-0.50, 0.10)</td>
<td>0.96 (0.57, 1.34)</td>
<td>1.73 (1.38, 2.09)</td>
<td></td>
</tr>
</tbody>
</table>

*Based on subjects included in the test set that were absent of dementia or decline ≥1.5 SD on one or more subtests.

**Bold** P<0.01 **Underlined** P<0.05 but not P<0.01

Referent category for sex is male. Referent category for education is high school degree or less.

LMI = Logical Memory, Immediate Recall; LMD = Logical Memory, Delayed Recall; PASI = Paired Associates, Immediate Recall; PASD = Paired Associates, Delayed Recall; VRI = Visual Reproductions, Immediate Recall; VRD = Visual Reproduction, Delayed Recall; TMT A (B) = Trail Making Test A (B); HVOT = Hooper Visual Organization Test; BNT = Boston Naming Test

TMT A, B and B-A are timed assessments; higher score indicates lower performance.

Copyright © Brian Gregory Downer, 2014
Chapter Five: Results

Specific Aim One

Sample Characteristics

The demographic characteristics of the subjects included in the validation sample according to cognitive status are provided in Table 5.1. Among subjects who completed a neuropsychological battery, 619 (49.5%) were classified as having normal cognition (NC), 214 (17.1%) were classified as test-based impaired learning and memory (ILMTB), 399 (31.9%) were classified as multidomain impaired (MDITB). There were 19 (1.5%) subjects who had received a diagnoses of dementia. There were significant differences for age (P<0.01) and educational attainment (P=0.02) between all four of the cognitive groups. There were no differences in the proportion of males and females in any of the cognitive groups.

Effects of Age, Sex, and Education on Cognitive Function

Significant differences in the assessment scores of the FHS neuropsychological battery according to age, sex, and educational attainment were detected in the univariate (UV) and multivariable (MV) models. Cognitive performance on all of the assessments significantly decreased with age in the UV model (P<0.01). The effect of age remained after controlling for the effects of education and sex. Subjects with a college degree had significantly higher performance (P<0.01) on all assessments compared to subjects with <high school degree even after accounting for the effects of age and sex. Women performed better than men on Logical Memory (Immediate and Delayed Recall) and Paired Associates (Immediate and Delayed recall), whereas men performed better than women on TMT A and Boston Naming Test. However, the effect of sex on the Boston Naming Test was no longer significant once education was included in the model. No significant differences according to sex in the UV or MV models were observed for Visual Recognition (Immediate and Delayed recall); TMT B; Hooper Visual Organization Test; Similarities, or cognitive flexibility (TMT B – TMT A).
**Ability of Summary Scores to Differentiate between Cognitive Groups**

*NC and Dementia:* Older adults diagnosed with dementia were considered to be cases in this analysis. All three summary scores were very accurate when differentiating between subjects classified as NC and subjects diagnosed with dementia. The areas under the curve (AUC\(^16\); the probability that a randomly selected dementia case has a lower score than a randomly selected NC control) among the three summary scores were all greater than 96 percent (*Table 5.2*; *Figure 5.1*). The composite subtest summary score had significantly higher specificity and overall test accuracy compared to the composite domains summary score, but not compared to the learning/memory summary score. These results provide evidence for the use of the composite subtests summary score for differentiating between NC and dementia subjects.

*NC and ILM\(_{TB}\):* Subjects with ILM\(_{TB}\) were considered to be cases in this analysis. There were no significant differences in AUCs among the three summary scores (*Table 5.3*; *Figure 5.2*). The learning/memory summary score had the greatest sensitivity (84.6 [79.0-89.1]), specificity (78.8 [75.4-82.0]), npv (93.7 [91.2-95.6]), ppv (58.0 [52.3-63.6]), and overall test accuracy (80.3 [77.4-83.0]). However, these differences were not statistically significant compared to the other summary scores. Based on these results, there are no apparent differences between the three summary scores in their ability to differentiate between ILM\(_{TB}\) and NC.

*NC and MDI\(_{TB}\):* Subjects with MDI\(_{TB}\) were considered to be cases in this analysis. The composite subtests summary score had significantly greater AUC (90.5 [88.6-92.4]) and higher overall test accuracy (83.3 [80.9-85.5], compared to the composite domains and learning/memory summary scores (*Table 5.4*; *Figure 5.3*). In addition, the composite domains summary score had a significantly greater AUC (85.8 [83.4-88.1]) compared to the

\(^{16}\) A receiver operator characteristic (ROC) curve is a plot of the sensitivity and specificity for different cut-points of each summary score and shows the tradeoff between sensitivity and specificity (i.e. as sensitivity increases, specificity decreases). Sensitivity and specificity is for the optimal cut-off score for each summary score.
learning/memory summary score (80.0 [77.2-82.7]). The composite subtest summary score had significantly higher specificity, ppv, and overall test accuracy compared to the composite domains and learning/memory summary scores, in addition to a higher npv compared to the learning/memory summary score. Based on this evidence, a summary score that assesses only learning and memory should be avoided when differentiating between normal and MDI_{TB} subjects in the FHS.

**Dementia and ILM_{TB}**: Older adults diagnosed with dementia were considered to be cases in this analysis. The composite subtests summary score had the greatest AUC (89.3 [77.7-100]), but the wide confidence interval due to the small number of subjects diagnosed with dementia prevented any differences in AUC according to cognitive status from being observed. The composite subtests summary score also had the highest specificity (93.0 [88.7-96.0]), ppv (51.6 [33.1-69.8]) and overall test accuracy (92.2 [88.1-95.4]) among the three summary scores (Table 5.5; Figure 5.4). However, there were no significant differences between the three summary score for any of these measures. Based on these results, there is insufficient evidence for a summary score that performs substantially better when differentiating between ILM_{TB} and dementia.

**Dementia and MDI_{TB}**: Older adults diagnosed with dementia were considered to be cases in this analysis. There were no significant differences between the AUCs for any of the three summary scores (Table 5.6; Figure 5.5). The learning/memory summary score had higher specificity (92.2 [89.2-94.7]), ppv (29.5 [16.8-45.2]) and overall test accuracy (91.1 [88.0-93.7]), but these values were not significantly higher compared to the other summary scores. As was observed when comparing ILM_{TB} and dementia, there is insufficient evidence for a best summary score when differentiating between MDI_{TB} and dementia.

**ILM_{TB} and MDI_{TB}**: Subjects with MDI_{TB} were considered to be cases in this analysis. The composite subtest summary score had significantly greater AUC (65.7 [61.4-69.9]) compared to composite domains summary score, but not the learning/memory summary score (Table 5.7;
Figure 5.6). The composite subtests summary score had the highest sensitivity (58.6 [53.6-63.5]) among the three summary scores, which was significantly higher compared to the composite domains summary score (43.9 [38.9-48.9]). The composite domains summary score had a significantly higher specificity, but significantly lower sensitivity compared to the learning/memory summary score. There was no difference in specificity between the composite subtest and composite domains summary scores. Based on this evidence, the composite subtest score is best able to differentiate between ILM_{TB} and MDI_{TB} due to the significantly higher AUC and sensitivity compared to the composite domains summary score. However, the composite domains score should be utilized if there is a greater priority on correctly identifying ILM_{TB}.

Specific Aim Two

Sample Population

The descriptive characteristics of subjects of the FHS Original Cohort included in the final sample according to AD status are provided in Table 5.8. The final sample included a total of 2449 subjects, of which 2102 who did not have dementia and 347 who had received a diagnosis of AD. The final sample was comprised predominately of females (n=1428, 58.3%) and the majority of subjects had a high school degree or less (n=1632, 68.5%). There was no association between AD and educational attainment, but females were more likely than males to be diagnosed with AD (P<0.01). There were 386 (15.8%) subjects who reported taking a cholesterol-lowering medication during one or more clinical examinations. There was no difference in the proportion of subjects who reported using cholesterol-lowering medications according to AD status. Subjects diagnosed with AD had slightly, albeit significantly, lower average blood glucose (P<0.01), systolic blood pressure (P=0.01) and diastolic blood pressure (P<0.01) compared to subjects without dementia. Subjects without dementia were more likely to have a history of smoking compared to subjects diagnosed with AD (P<0.01). The apparent protective effect of smoking against AD may be due to smokers dying before they would have been diagnosed with AD (Kryscio et al., 2013).
Data for *APOE* genotype was available for 568 subjects (23.2%) included in the final sample. There were 125 subjects who carried one or more *APOE* e4 alleles (e4+) and 443 subjects who did not carry any *APOE* e4 alleles (e4-). As expected, subjects who were *APOE* e4+ were more likely to be diagnosed with AD compared to subjects who were *APOE* e4- (P<0.01).

**Trajectories of Cholesterol According to Alzheimer’s Disease Status**

The unadjusted and adjusted trajectories of total cholesterol, HDL cholesterol, and log-total/HDL ratio according to AD status are presented in **Figures 5.7-5.9**. Solid lines represent the mean measures of cholesterol according to AD status and the shaded regions represent the point-wise 95% confidence interval for each measure of cholesterol. The degree of non-linearity for the trajectories as reflected by the estimated EDF of the smoothing term, and the model fit by adjusted R², which is interpreted as the proportion of total variance explained by the model with an adjustment for model complexity, are presented in **Table 5.9**. According to visual inspection, there were no differences in the unadjusted mean trajectories of total cholesterol, HDL cholesterol, and log-total/HDL ratio as indicated by the considerable overlap of the 95% confidence intervals (**Figure 5.7 [unadjusted] – Figure 5.9 [unadjusted]**). Inclusion of covariates to the models noticeably reduced the variability in estimated cholesterol trajectories as indicated by the 95% confidence intervals for each trajectory; however, trajectories of cholesterol in **Figures 5.7-5.9** did not substantially change as covariates were added to the models as indicated by the consistent EDF values of the smooth terms and little change in the adjusted R² for each model (**Table 5.9**). This may be due to covariates being included solely as fixed effects and not being incorporated into the smoothing term of the model.

Trajectories of total cholesterol for non-demented subjects and subjects diagnosed with AD both followed non-linear trends (**Table 5.9**). There were little to no differences in the trajectories of total cholesterol between AD and non-demented subjects once the effects of sex, educational attainment, smoking history, blood pressure, blood glucose, and history of using
cholesterol-lowering medications were controlled for in the models (Figure 5.7, model 1 – model 4). When APOE e4 allele status was included as a covariate (Figure 5.7, model 5), non-demented and AD subjects exhibited a similar increasing trend in total cholesterol from 30 to 55 years of age, but AD subjects had consistently higher total cholesterol after 55 years of age compared to non-demented subjects. Subjects diagnosed with AD maintained a consistent level of HDL that remained linear even as covariates were added to the models as indicated by the EDFs of 1 in Table 5.9. HDL cholesterol also remained fairly constant from 50 to 75 years of age for non-demented subjects, but the overall trend was non-linear due to an increase in HDL cholesterol after 75 years of age. A declining trajectory for log-total/HDL ratio was observed for all subjects. There were little to no differences in the log-total/HDL ratios according to AD status from 50 to 70 years of age, but subjects without dementia did exhibit a greater decline in total/HDL ratio after 70 years of age.

Trajectories of Cholesterol According to APOE e4 Allele Status

The trajectories of total cholesterol, HDL cholesterol, and log-total/HDL ratio according to APOE e4 allele status were examined because of the established relationship between APOE and AD, the apoE protein’s role in cholesterol metabolism, and the known differences in the concentrations of cholesterol according to APOE genotype. Only the estimated trajectories of total cholesterol, HDL cholesterol, and log-total/HDL ratio for the unadjusted and fully adjusted models are provided in Figure 5.10 because there were no substantial changes in the EDF for the smoothing terms as covariates were added to the models (Table 5.10). Subjects who did not posses an APOE e4 allele (e4-) had consistently lower total cholesterol from midlife to late life compared to subjects with one or more e4 alleles (Figure 5.10). In general, subjects who were APOE e4- had slightly higher HDL cholesterol and lower log-total/HDL ratio from midlife to late life compared to subjects who possessed one or more APOE e4 alleles (e4+). All subjects exhibited a non-linear decline in log-total/HDL ratio due to an increase in HDL cholesterol with advancing age.
Trajectories of Cholesterol According to Alzheimer’s Disease and APOE e4 Allele Status

Models stratified according to AD and APOE e4 allele status were used to determine if the trajectories of total cholesterol, HDL cholesterol, and log-total/HDL ratio according to AD status differed between subjects who were APOE e4+ and those who were APOE e4- (Figure 5.11; Table 5.11). The trajectories of cholesterol stratified according to AD status and APOE e4 allele status did not change substantially as covariates were added to the models, and only the unadjusted and fully adjusted models that controlled for sex, education, smoking, average blood pressure, average blood glucose, and use of cholesterol lowering medications were used to examine the potential interactive effect of AD and APOE e4 allele status on trajectories of cholesterol.

Subjects diagnosed with AD and who were APOE e4+ maintained higher total cholesterol from midlife to late life compared to AD e4-, non-demented e4+, and non-demented e4- subjects (Figure 5.11, total cholesterol). This finding suggests that consistently higher total cholesterol among subjects diagnosed with AD is due to these subjects being more likely to be APOE e4+. A non-linear increase in HDL cholesterol with age was observed for non-demented e4- subjects, whereas subjects who were non-demented and APOE e4+ maintained consistent measures of HDL cholesterol with age (Figure 5.11, HDL cholesterol). The increase in HDL cholesterol was most pronounced among subjects diagnosed with AD and who were APOE e4+, but subjects diagnosed with AD and were APOE e4- exhibited a slight decrease in HDL cholesterol with age. Finally, AD e4+ subjects exhibited a linear decline in log-total/HDL ratio, whereas non-linear declines in log-total/HDL ratio were observed for all other groups.

Trajectories of Cholesterol According to Alzheimer’s Disease Status and Sex

Models stratified according to AD status and sex were used to determine if the trajectories of total cholesterol, HDL cholesterol, and log-total/HDL ratio for men and women differed according to AD status (Figure 5.12; Table 5.12). Based on the unadjusted and adjusted models for total cholesterol (Figure 5.12), women had lower total cholesterol compared to men
until approximately 50 years of age. Total cholesterol increased for both men and women during midlife, but there was visual evidence for a greater increase in cholesterol among women during this period. Total cholesterol appeared to decline at a similar trajectory for men and women following 60 years of age, although women maintained higher total cholesterol compared to men. Despite the clear differences in total cholesterol between men and women in the unadjusted and adjusted models, there were no dramatic differences in the trajectories of total cholesterol between men and women according to AD status. However, there was visual evidence for differences in the trajectories of total cholesterol according to AD status and sex once APOE was included as a covariate (Figure 5.12, total cholesterol fully adjusted) and these differences were most apparent among men. Total cholesterol increased for men regardless of AD status, but men without dementia exhibited a decline in total cholesterol at a younger age compared to men with AD. Compared to men without dementia, men diagnosed with AD had lower cholesterol during midlife, but maintained higher cholesterol following 60 years of age. A similar trend was observed among women, but the apparent differences in total cholesterol according to AD status were much less pronounced than in men. Women diagnosed with AD maintained slightly higher total cholesterol after 60 years of age compared to women who did not have dementia, but the overall trajectories of total cholesterol were similar for the two groups. The visually apparent differences in the trajectories of total cholesterol between the adjusted and fully adjusted models need to be interpreted with some caution because only 23 percent of the final sample (n=568 subjects) had data for APOE genotype.

There were obvious differences in the trajectories of HDL cholesterol according to sex, with women maintaining higher HDL cholesterol compared to men in the unadjusted, adjusted and fully adjusted models. The trajectories of HDL cholesterol for men and women without dementia in the unadjusted and adjusted models exhibited a cubic trend, whereas the trajectories for subjects with AD were more linear. When APOE e4 allele status was included as a covariate, there was an increasing trend in HDL cholesterol among women diagnosed with AD, whereas
men diagnosed with AD exhibited an accelerated decline at approximately 70 years of age. The visually observed differences between the adjusted and fully adjusted models may be partially due to the reduced sample size for the fully adjusted model.

Despite maintaining considerably higher total cholesterol compared to men, women had a lower log-total/HDL cholesterol ratio compared to men due to the higher measures of HDL cholesterol. Based on the adjusted model, there was a decreasing trend for the ratio of total to HDL cholesterol among men and women but there were no substantial differences according to AD status. The addition of APOE to the model did not have an apparent effect on trajectories of total cholesterol for women. Men without dementia exhibited an accelerated decline in log-total/HDL cholesterol ratio at approximately 75 years of age due to an increase in HDL cholesterol, whereas the decline in log-total/HDL cholesterol ratio for men with AD followed a linear trend.

Adjusting for the Effects of Supplemental Estrogen Use: A total of 133 subjects (3.6%) reported having used supplemental estrogen. Eight men reported using supplemental estrogen, but these subjects were excluded from the analysis to avoid confounding results. There were no discernable differences in the trajectories of total cholesterol, HDL cholesterol or log-total/HDL ratio according to AD status when supplemental estrogen use was included in the models (Figure 5.13) compared to the trajectories of total, HDL cholesterol and log-total/HDL ratio for women in Figure 5.12.

Specific Aim Three

Sample Characteristics

A summary of the descriptive characteristics for the final sample according to cognitive quartile is provided in Table 5.13. Subjects in the lowest quartile of cognitive functioning were significantly older during the first clinical exam (representing midlife) and upon receiving a neuropsychological battery (representing late life) compared to subjects in the highest quartile of cognitive functioning. Also, subjects in the lowest cognitive quartile had significantly lower
educational attainment compared to the other groups. Finally, the lowest cognitive quartile had slightly higher average blood glucose levels compared to the other quartiles. There were no differences in history of smoking, blood pressure, use of cholesterol lowering medications or APOE e4 allele status.

Relationship between Subject-Specific Trajectories of Total Cholesterol and Cognition

The subject-specific trajectories for total cholesterol were plotted according to cognitive quartile and visually examined (Figure 5.14). There was considerable variability in the subject-specific trajectories of total cholesterol within each of the cognitive quartiles. Upon close visual examination, subjects in the lowest cognitive quartile appeared to exhibit a slightly greater decline in total cholesterol compared to the other quartiles.

A subsequent analysis was performed to determine if significant differences in the population-average trajectories of total cholesterol according to cognitive quartile could be detected. Subjects in the fourth cognitive quartile had significantly lower total cholesterol compared to the second and third quartiles ($\hat{\beta}=-6.4 \text{ mg/dl}, \text{ SE}=2.3 \text{ mg/dl}, P=0.02$). This difference remained significant after controlling for the effects of sex, educational attainment, smoking, cholesterol medication use, blood glucose, blood pressure, and APOE e4 allele status (Figure 5.15; Table 14). There were no significant differences in the quadratic trend in total cholesterol according to cognitive quartile.

Conclusion

In general, the findings from the specific aims were surprising given what has been reported in previous studies. Subjects in the FHS Offspring Cohort diagnosed with dementia had higher than expected cognitive performance on the neuropsychological battery, and the utility of the three summary scores to differentiate between normal and dementia subjects was lower than expected. This may be due to a sampling bias in which subjects with severe physical or cognitive impairments due to dementia would not be healthy enough to receive a neuropsychological battery. The findings from Aim Two and Three were surprising because there was not sufficient
evidence to suggest that there are differences in midlife cholesterol according to AD status, but older adults with high cognitive functioning had significantly lower cholesterol during midlife compared to subjects with low cognition. The inconsistent findings of Aims Two and Three may be due to the peculiar characteristics of FHS participants and cohort differences between the Original and Offspring Cohorts. A thorough summary of the findings from the dissertation research, and an interpretation of these findings within the context of prior research, is provided in Chapter Six.
Table 5.1: Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal (n=619)</th>
<th>ILM (n=214)</th>
<th>MDI (n=399)</th>
<th>Dementia (n=19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>60.7 (9.2)</td>
<td>59.7 (8.7)</td>
<td>63.5 (9.8)</td>
<td>73.6 (5.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ High school</td>
<td>193 (31.1)</td>
<td>68 (31.8)</td>
<td>164 (41.1)</td>
<td>8 (42.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Some college</td>
<td>159 (25.7)</td>
<td>84 (39.2)</td>
<td>103 (25.8)</td>
<td>6 (31.6)</td>
<td></td>
</tr>
<tr>
<td>College degree</td>
<td>267 (43.1)</td>
<td>62 (29.0)</td>
<td>132 (33.1)</td>
<td>5 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>282 (45.6)</td>
<td>97 (45.3)</td>
<td>197 (49.4)</td>
<td>7 (36.8)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Results based on subjects included in the validation set.
SD = standard deviation, n = number of subjects

Table 5.2: Differentiating between Normal and Dementia

<table>
<thead>
<tr>
<th>Normal and dementia</th>
<th>Composite, subtest</th>
<th>Composite, domains</th>
<th>Learning/memory subtests</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95% CI)</td>
<td>97.2 (93.6-100.0)</td>
<td>97.1 (93.7-100.0)</td>
<td>96.9 (94.0-99.7)</td>
</tr>
<tr>
<td>Cut-off</td>
<td>-0.18</td>
<td>-0.13</td>
<td>-0.19</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>89.5 (66.9-98.7)</td>
<td>89.5 (66.9-98.9)</td>
<td>84.2 (60.4-96.6)</td>
</tr>
<tr>
<td>Specificity</td>
<td>96.8 (95.1-98.0)</td>
<td>92.7 (90.4-94.6)</td>
<td>93.5 (91.3-95.3)</td>
</tr>
<tr>
<td>PPV</td>
<td>45.9 (29.5-63.1)</td>
<td>27.4 (16.9-40.2)</td>
<td>28.6 (17.3-42.2)</td>
</tr>
<tr>
<td>NPV</td>
<td>99.7 (98.8-100.0)</td>
<td>99.7 (98.8-100.0)</td>
<td>99.5 (98.5-99.9)</td>
</tr>
<tr>
<td>Test accuracy</td>
<td>96.6 (94.8-97.8)</td>
<td>92.6 (90.3-94.5)</td>
<td>93.3 (91.0-95.1)</td>
</tr>
</tbody>
</table>

The optimal cut-off score for each summary score is the point on the receiver operating characteristic curve that is closest to (0, 1).

Table 5.3: Differentiating between Normal and ILM_{TB}

<table>
<thead>
<tr>
<th>Normal and ILM_{TB}</th>
<th>Composite, subtest</th>
<th>Composite, domains</th>
<th>Learning/memory subtests</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95% CI)</td>
<td>86.6 (83.9-89.4)</td>
<td>87.4 (84.8-90.1)</td>
<td>89.5 (87.2-91.9)</td>
</tr>
<tr>
<td>Cut-off</td>
<td>0.13</td>
<td>0.14</td>
<td>0.11</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>83.2 (77.5-87.9)</td>
<td>79.9 (73.9-85.1)</td>
<td>84.6 (79.0-89.1)</td>
</tr>
<tr>
<td>Specificity</td>
<td>75.1 (71.5-78.5)</td>
<td>78.7 (75.2-81.4)</td>
<td>78.8 (75.4-82.0)</td>
</tr>
<tr>
<td>PPV</td>
<td>53.6 (48.1-59.1)</td>
<td>56.4 (50.6-62.1)</td>
<td>58.0 (52.3-63.6)</td>
</tr>
<tr>
<td>NPV</td>
<td>92.8 (90.2-94.9)</td>
<td>91.9 (89.2-94.1)</td>
<td>93.7 (91.2-95.6)</td>
</tr>
<tr>
<td>Test accuracy</td>
<td>77.2 (74.2-80.0)</td>
<td>79.0 (76.1-81.7)</td>
<td>80.3 (77.4-83.0)</td>
</tr>
</tbody>
</table>
### Table 5.4: Differentiating between Normal and MDITB

<table>
<thead>
<tr>
<th>Normal and MDITB</th>
<th>Composite, subtest</th>
<th>Composite, domains</th>
<th>Learning/memory subtests</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95% CI)</td>
<td>90.5 (88.6-92.4)</td>
<td>85.8 (83.4-88.1)</td>
<td>80.0 (77.2-82.7)</td>
</tr>
<tr>
<td>Cut-off</td>
<td>0.02</td>
<td>0.14</td>
<td>0.19</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>79.2 (74.9-83.1)</td>
<td>75.7 (71.2-79.8)</td>
<td>70.9 (66.2-75.3)</td>
</tr>
<tr>
<td>Specificity</td>
<td>85.9 (83.0-88.6)</td>
<td>78.7 (75.2-81.8)</td>
<td>72.9 (69.2-76.3)</td>
</tr>
<tr>
<td>PPV</td>
<td>78.4 (74.1-82.3)</td>
<td>69.6 (65.0-73.9)</td>
<td>62.7 (58.1-67.2)</td>
</tr>
<tr>
<td>NPV</td>
<td>86.5 (83.5-89.1)</td>
<td>83.4 (80.1-86.3)</td>
<td>79.5 (76.0-82.8)</td>
</tr>
<tr>
<td>Test accuracy</td>
<td>83.3 (80.9-85.5)</td>
<td>77.5 (74.8-80.0)</td>
<td>72.1 (69.2-74.8)</td>
</tr>
</tbody>
</table>

### Table 5.5: Differentiating between Dementia and ILMTB

<table>
<thead>
<tr>
<th>Dementia and ILMTB</th>
<th>Composite, subtest</th>
<th>Composite, domains</th>
<th>Learning/memory subtests</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95% CI)</td>
<td>89.3 (77.7-100.0)</td>
<td>88.1 (76.0-100.0)</td>
<td>80.7 (67.1-94.3)</td>
</tr>
<tr>
<td>Cut-off</td>
<td>-0.49</td>
<td>-0.62</td>
<td>-0.90</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>84.2 (60.4-96.6)</td>
<td>84.2 (60.4-96.6)</td>
<td>68.4 (43.4-87.4)</td>
</tr>
<tr>
<td>Specificity</td>
<td>93.0 (88.7-96.0)</td>
<td>90.7 (85.9-94.2)</td>
<td>92.5 (88.1-95.7)</td>
</tr>
<tr>
<td>PPV</td>
<td>51.6 (33.1-69.8)</td>
<td>44.4 (27.9-61.9)</td>
<td>44.8 (26.4-64.3)</td>
</tr>
<tr>
<td>NPV</td>
<td>98.5 (95.7-99.7)</td>
<td>98.5 (95.6-99.7)</td>
<td>97.1 (93.7-98.9)</td>
</tr>
<tr>
<td>Test accuracy</td>
<td>92.2 (88.1-95.4)</td>
<td>90.1 (85.6-94.2)</td>
<td>90.6 (86.1-94.0)</td>
</tr>
</tbody>
</table>

### Table 5.6: Differentiating between Dementia and MDITB

<table>
<thead>
<tr>
<th>Dementia and MDITB</th>
<th>Composite, subtest</th>
<th>Composite, domains</th>
<th>Learning/memory subtests</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95% CI)</td>
<td>84.2 (71.3-97.1)</td>
<td>85.9 (74.2-97.5)</td>
<td>84.4 (74.0-94.7)</td>
</tr>
<tr>
<td>AUC (95% CI)</td>
<td>-0.81</td>
<td>-1.1</td>
<td>-0.89</td>
</tr>
<tr>
<td>Cut-off</td>
<td>78.9 (54.4-93.9)</td>
<td>78.9 (54.4-93.9)</td>
<td>68.4 (43.4-87.4)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87.5 (83.8-90.6)</td>
<td>89.2 (85.8-92.1)</td>
<td>92.2 (89.2-94.7)</td>
</tr>
<tr>
<td>Specificity</td>
<td>23.1 (13.5-35.2)</td>
<td>25.9 (15.3-39.0)</td>
<td>29.5 (16.8-45.2)</td>
</tr>
<tr>
<td>PPV</td>
<td>98.9 (97.1-99.7)</td>
<td>98.9 (97.2-99.7)</td>
<td>98.4 (96.5-99.4)</td>
</tr>
<tr>
<td>NPV</td>
<td>87.1 (83.5-90.1)</td>
<td>88.8 (85.3-91.6)</td>
<td>91.1 (88.0-93.7)</td>
</tr>
</tbody>
</table>

### Table 5.7: Differentiating between ILMTB and MDITB

<table>
<thead>
<tr>
<th>ILMTB and MDITB</th>
<th>Composite, subtest</th>
<th>Composite, domains</th>
<th>Learning/memory subtests</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95% CI)</td>
<td>65.7 (61.4-69.9)</td>
<td>56.1 (51.6-60.6)</td>
<td>59.7 (55.3-64.2)</td>
</tr>
<tr>
<td>Cut-off</td>
<td>-0.19</td>
<td>-0.40</td>
<td>-0.21</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>58.6 (53.6-63.5)</td>
<td>43.9 (38.9-48.9)</td>
<td>57.6 (52.6-62.5)</td>
</tr>
<tr>
<td>Specificity</td>
<td>65.0 (58.2-71.3)</td>
<td>74.3 (67.9-80.0)</td>
<td>57.9 (51.0-64.6)</td>
</tr>
<tr>
<td>PPV</td>
<td>75.7 (70.6-80.4)</td>
<td>76.1 (70.0-81.4)</td>
<td>71.9 (66.6-76.7)</td>
</tr>
<tr>
<td>NPV</td>
<td>45.7 (40.0-51.5)</td>
<td>41.5 (36.5-46.6)</td>
<td>42.3 (36.6-48.2)</td>
</tr>
<tr>
<td>Test accuracy</td>
<td>60.8 (56.9-64.7)</td>
<td>54.5 (50.4-58.5)</td>
<td>57.7 (53.7-61.7)</td>
</tr>
</tbody>
</table>
Table 5.8: Demographic Characteristics according to Alzheimer’s Disease Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Dementia (n=2102)</th>
<th>AD (n=347)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Age, midlife (SD)</td>
<td>40.2 (6.7)</td>
<td>42.2 (6.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>**Age, late life (SD)</td>
<td>81.9 (7.6)</td>
<td>78.6 (6.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female</td>
<td>1196 (56.9)</td>
<td>232 (66.9)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>906 (43.1)</td>
<td>115 (33.1)</td>
<td></td>
</tr>
<tr>
<td>§Educational attainment, n (%)</td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>&lt; High school</td>
<td>1410 (68.9)</td>
<td>222 (65.7)</td>
<td></td>
</tr>
<tr>
<td>&gt; High school</td>
<td>636 (31.1)</td>
<td>116 (34.3)</td>
<td></td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>663 (31.5)</td>
<td>160 (46.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1439 (68.5)</td>
<td>187 (53.9)</td>
<td></td>
</tr>
<tr>
<td>Use of cholesterol lowering medications, n (%)</td>
<td></td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>No</td>
<td>1770 (84.2)</td>
<td>293 (84.4)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>332 (15.8)</td>
<td>54 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Avg. blood glucose, mg/dl (SD)</td>
<td>108.2 (19.0)</td>
<td>105.2 (15.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Avg. systolic blood pressure, mmHg (SD)</td>
<td>136.5 (15.0)</td>
<td>134.4 (13.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Avg. diastolic blood pressure, mmHg (SD)</td>
<td>80.1 (8.0)</td>
<td>78.0 (6.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>§§APOE e4 allele status, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>APOE e4-</td>
<td>378 (80.9)</td>
<td>65 (64.4)</td>
<td></td>
</tr>
<tr>
<td>APOE e4+</td>
<td>89 (19.1)</td>
<td>36 (35.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Age during the first clinical examination represents midlife
**Age in which a person was last observed to be cognitively intact represents late life
§A total of 2384 had data for educational attainment
 §§A total of 568 had data for APOE e4 allele status
SD = standard deviation and n = number of subjects
T-tests were used to compare group means for continuous variables (age, blood glucose, and blood sugar) and chi-square tests were used to compare group differences for categorical variables (sex, education, cholesterol medication use, and APOE e4 allele status).
Percentages for categorical variables are based on column total. Value may exceed 100 due to rounding.
Table 5.9: EDF and Adjusted $R^2$ for Trajectories of Total, HDL and Total/HDL Ratio according to Alzheimer’s Disease Status

<table>
<thead>
<tr>
<th>Model</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Log-total/HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDF</td>
<td>Adj. $R^2$</td>
<td>EDF</td>
</tr>
<tr>
<td>1. Unadjusted (n=2449)</td>
<td>0.09</td>
<td>0.002</td>
<td>0.06</td>
</tr>
<tr>
<td>Non-demented</td>
<td>7.6</td>
<td>5.4</td>
<td>5.7</td>
</tr>
<tr>
<td>AD</td>
<td>6.4</td>
<td>1.7</td>
<td>4.2</td>
</tr>
<tr>
<td>2. Model 1 + gender and education (n=2384)</td>
<td>0.11</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>Non-demented</td>
<td>7.6</td>
<td>5.4</td>
<td>5.7</td>
</tr>
<tr>
<td>AD</td>
<td>6.5</td>
<td>1.9</td>
<td>4.1</td>
</tr>
<tr>
<td>3. Model 2 + smoking (n=2384)</td>
<td>0.11</td>
<td>0.11</td>
<td>0.10</td>
</tr>
<tr>
<td>Non-demented</td>
<td>7.6</td>
<td>5.4</td>
<td>5.7</td>
</tr>
<tr>
<td>AD</td>
<td>6.5</td>
<td>1.9</td>
<td>4.1</td>
</tr>
<tr>
<td>4. Model 3 + blood pressure and blood glucose (n=2384)</td>
<td>0.13</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-demented</td>
<td>7.6</td>
<td>5.4</td>
<td>5.7</td>
</tr>
<tr>
<td>AD</td>
<td>6.5</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>5. Model 4 + cholesterol medications (n=2384)</td>
<td>0.17</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-demented</td>
<td>7.6</td>
<td>5.4</td>
<td>5.7</td>
</tr>
<tr>
<td>AD</td>
<td>6.5</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>6. Model 6 + APOE e4 allele status (n=557)</td>
<td>0.19</td>
<td>0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-demented</td>
<td>7.0</td>
<td>3.7</td>
<td>4.3</td>
</tr>
<tr>
<td>AD</td>
<td>5.5</td>
<td>2.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

There were 65 subjects who had missing data for educational attainment. Data for APOE was recorded for 568 subjects, but 11 of these subjects had missing data for educational attainment. There were no missing data for smoking, blood pressure, blood glucose or use of cholesterol lowering medications.
Table 5.10: EDF and Adjusted R\textsuperscript{2} for Trajectories of Total, HDL and Total/HDL Ratio according to \textit{APOE} e4 Allele Status

<table>
<thead>
<tr>
<th>Model</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Log-total/HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDF</td>
<td>Adj. R\textsuperscript{2}</td>
<td>EDF</td>
</tr>
<tr>
<td>1. Unadjusted (n=568)</td>
<td>0.11</td>
<td>0.003</td>
<td>4.4</td>
</tr>
<tr>
<td>e4-</td>
<td>7.2</td>
<td>3.6</td>
<td>2.2</td>
</tr>
<tr>
<td>e4+</td>
<td>5.4</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>2. Model 1 + gender and education (n=557)</td>
<td>0.12</td>
<td>0.13</td>
<td>0.09</td>
</tr>
<tr>
<td>e4-</td>
<td>7.2</td>
<td>3.3</td>
<td>4.2</td>
</tr>
<tr>
<td>e4+</td>
<td>5.5</td>
<td>1.9</td>
<td>3.1</td>
</tr>
<tr>
<td>3. Model 2 + smoking history (n=557)</td>
<td>0.12</td>
<td>0.13</td>
<td>0.09</td>
</tr>
<tr>
<td>e4-</td>
<td>7.2</td>
<td>3.3</td>
<td>4.3</td>
</tr>
<tr>
<td>e4+</td>
<td>5.5</td>
<td>1.9</td>
<td>3.1</td>
</tr>
<tr>
<td>4. Model 3 + blood pressure and blood glucose (n=557)</td>
<td>0.14</td>
<td>0.14</td>
<td>0.11</td>
</tr>
<tr>
<td>e4-</td>
<td>7.2</td>
<td>3.3</td>
<td>4.2</td>
</tr>
<tr>
<td>e4+</td>
<td>5.5</td>
<td>1.9</td>
<td>3.1</td>
</tr>
<tr>
<td>5. Model 4 + use of cholesterol lowering medications (n=557)</td>
<td>0.18</td>
<td>0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>e4-</td>
<td>7.2</td>
<td>3.3</td>
<td>4.2</td>
</tr>
<tr>
<td>e4+</td>
<td>5.5</td>
<td>1.9</td>
<td>3.1</td>
</tr>
</tbody>
</table>

There were 11 subjects who had missing data for educational attainment. There were no missing observations for smoking history, blood pressure, blood glucose or use of cholesterol lowering medications.

Table 5.11: EDF and Adjusted R\textsuperscript{2} for Trajectories of Total, HDL and Total/HDL Ratio Stratified by AD and \textit{APOE} e4 Allele Status

<table>
<thead>
<tr>
<th>Model</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Log-total/HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDF</td>
<td>Adj. R\textsuperscript{2}</td>
<td>EDF</td>
</tr>
<tr>
<td>Unadjusted (n=568)</td>
<td>0.12</td>
<td>0.01</td>
<td>4.4</td>
</tr>
<tr>
<td>Non-demented e4-</td>
<td>7.2</td>
<td>3.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Non-demented e4+</td>
<td>5.4</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>AD e4-</td>
<td>4.9</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>AD e4+</td>
<td>4.3</td>
<td>3.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Adjusted (n=557)</td>
<td>0.19</td>
<td>0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-demented e4-</td>
<td>7.1</td>
<td>3.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Non-demented e4+</td>
<td>5.4</td>
<td>2.2</td>
<td>3.0</td>
</tr>
<tr>
<td>AD e4-</td>
<td>4.9</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>AD e4+</td>
<td>4.3</td>
<td>2.9</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Adjusted model included sex, educational attainment (\leq high school, > high school), smoking history, diastolic and systolic blood pressure, blood glucose and history of cholesterol lowering medications. Of the 568 subjects with \textit{APOE} data, 11 had missing data for educational attainment.
Table 5.12: EDF and Adjusted R² for Trajectories of Total, HDL and Total/HDL Ratio Stratified by AD and Sex

<table>
<thead>
<tr>
<th>Model</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Log-total/HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDF</td>
<td>Adj. R²</td>
<td>EDF</td>
</tr>
<tr>
<td>Unadjusted (n=2449)</td>
<td>0.14</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>Non-demented female</td>
<td>7.7</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Non-demented male</td>
<td>7.9</td>
<td>4.7</td>
<td>6.3</td>
</tr>
<tr>
<td>AD female</td>
<td>6.5</td>
<td>1.8</td>
<td>3.1</td>
</tr>
<tr>
<td>AD male</td>
<td>5.6</td>
<td>1.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Adjusted (n=2384)</td>
<td>0.19</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-demented female</td>
<td>7.7</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Non-demented male</td>
<td>7.9</td>
<td>4.5</td>
<td>6.3</td>
</tr>
<tr>
<td>AD female</td>
<td>6.6</td>
<td>2.1</td>
<td>3.0</td>
</tr>
<tr>
<td>AD male</td>
<td>5.6</td>
<td>1.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Fully adjusted (n=557)</td>
<td>0.22</td>
<td>0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-demented female</td>
<td>7.1</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Non-demented male</td>
<td>6.1</td>
<td>2.9</td>
<td>4.3</td>
</tr>
<tr>
<td>AD female</td>
<td>5.5</td>
<td>1.9</td>
<td>4.3</td>
</tr>
<tr>
<td>AD male</td>
<td>3.9</td>
<td>1.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Adjusted model included educational attainment (< high school, > high school), smoking history, diastolic and systolic blood pressure, blood glucose and history of cholesterol lowering medications.

Fully adjusted model includes the covariates from the adjusted model plus APOE e4 allele status. There were 65 subjects who had missing data for educational attainment. Data for APOE was recorded for 568 subjects, but 11 of these subjects had missing data for educational attainment.
Table 5.13: Demographic Characteristics of Final Sample According to Cognitive Quartile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1</th>
<th>Quartile 2-3</th>
<th>Quartile 4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Age, midlife (SD)</td>
<td>40.1 (3.3)</td>
<td>39.1 (3.7)</td>
<td>38.1 (3.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>**Age, late life (SD)</td>
<td>67.1 (3.3)</td>
<td>66.3 (3.7)</td>
<td>65.2 (3.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Female</td>
<td>88 (44.4)</td>
<td>192 (50.9)</td>
<td>102 (54.8)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>110 (55.6)</td>
<td>185 (49.1)</td>
<td>84 (45.2)</td>
<td></td>
</tr>
<tr>
<td>Educational attainment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt; High school</td>
<td>26 (13.1)</td>
<td>11 (2.9)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>High school degree</td>
<td>88 (44.4)</td>
<td>137 (36.3)</td>
<td>36 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>52 (26.3)</td>
<td>111 (29.4)</td>
<td>46 (24.7)</td>
<td></td>
</tr>
<tr>
<td>College degree</td>
<td>32 (16.2)</td>
<td>118 (31.3)</td>
<td>103 (55.4)</td>
<td></td>
</tr>
<tr>
<td>Ever smoked, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>No</td>
<td>56 (28.3)</td>
<td>125 (33.2)</td>
<td>55 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>142 (71.7)</td>
<td>252 (66.8)</td>
<td>131 (70.4)</td>
<td></td>
</tr>
<tr>
<td>Use of cholesterol lowering medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>No</td>
<td>95 (48.0)</td>
<td>172 (45.6)</td>
<td>89 (47.8)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>103 (52.0)</td>
<td>205 (54.4)</td>
<td>97 (52.2)</td>
<td></td>
</tr>
<tr>
<td>Avg. blood glucose, mg/dl (SD)</td>
<td>102.2 (20.3)</td>
<td>100.7 (17.9)</td>
<td>97.8 (15.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Avg. systolic blood pressure, mmHg (SD)</td>
<td>127.6 (11.9)</td>
<td>127.5 (12.0)</td>
<td>125.1 (12.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Avg. diastolic blood pressure, mmHg (SD)</td>
<td>77.5 (6.6)</td>
<td>77.2 (6.3)</td>
<td>76.6 (6.3)</td>
<td>0.33</td>
</tr>
<tr>
<td>APOE e4 allele status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>APOE e4-</td>
<td>163 (82.3)</td>
<td>281 (74.5)</td>
<td>143 (76.9)</td>
<td></td>
</tr>
<tr>
<td>APOE e4+</td>
<td>35 (17.7)</td>
<td>96 (25.5)</td>
<td>43 (23.1)</td>
<td></td>
</tr>
</tbody>
</table>

*A* Age during first clinical examination represents midlife
**A* Age upon receiving neuropsychological battery represents late life
SD = standard deviation, n = number of subjects

Analysis of variance was used to compare group means for continuous variables (age, blood glucose, and blood pressure) and chi-square tests were used to compare group differences for categorical variables (sex, education, cholesterol medication use, and APOE e4 allele status). Percentages for categorical variables are based on column total. Value may exceed 100 due to rounding.
Table 5.14: Association between Cholesterol Trajectory and Cognitive Quartile

<table>
<thead>
<tr>
<th></th>
<th>Estimate (SE)</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.14 (0.09)</td>
<td>1.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Age^2</td>
<td>-0.09 (0.006)</td>
<td>-15.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 2-3 (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>-1.5 (2.6)</td>
<td>-0.56</td>
<td>0.58</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>-5.7 (2.7)</td>
<td>-2.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Age*quartile 1</td>
<td>-0.14 (0.13)</td>
<td>-1.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Age^2*quartile 1</td>
<td>-0.001 (0.009)</td>
<td>-0.16</td>
<td>0.87</td>
</tr>
<tr>
<td>Age*quartile 4</td>
<td>-0.06 (0.14)</td>
<td>-0.47</td>
<td>0.64</td>
</tr>
<tr>
<td>Age^2*quartile 4</td>
<td>0.01 (0.009)</td>
<td>1.2</td>
<td>0.23</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-12.1 (2.3)</td>
<td>-5.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>5.0 (4.3)</td>
<td>1.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Some college</td>
<td>0.08 (2.2)</td>
<td>0.04</td>
<td>0.97</td>
</tr>
<tr>
<td>College degree</td>
<td>-2.9 (2.2)</td>
<td>-1.3</td>
<td>0.19</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.1 (1.9)</td>
<td>0.57</td>
<td>0.57</td>
</tr>
<tr>
<td>Cholesterol medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8.7 (1.8)</td>
<td>4.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>-0.09 (0.05)</td>
<td>-1.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.11 (0.11)</td>
<td>1.0</td>
<td>0.30</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.18 (0.20)</td>
<td>0.92</td>
<td>0.36</td>
</tr>
<tr>
<td>APOE e4 allele</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e4- (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e4+</td>
<td>0.05 (2.1)</td>
<td>0.03</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Results based on mixed effects regression model controlling for the effects of sex, education, smoking, cholesterol medication use, blood glucose, blood pressure and APOE e4 allele status
Figure 5.1: ROC Curves, Normal Cognition and Dementia.

Figure 5.2: ROC Curves, Normal Cognition and ILM_{TB}

Figure 5.3: ROC Curves, Normal Cognition and MDI_{TB}
Figure 5.4: ROC Curves, Dementia and ILM_{TB}

Figure 5.5: ROC Curves, Dementia and MDI_{TB}

Figure 5.6: ROC Curves, ILM_{TB} and MDI_{TB}
Figure 5.7: Trajectories of Total Cholesterol Stratified by Alzheimer’s Disease Status

Model 1: adjusted for sex and educational attainment (≤ high school, > high school) n=2384
Model 2: model 1 plus smoking (ever smoker yes, no) n=2384
Model 3: model 2 plus average blood pressure and average blood glucose n=2384
Model 4: model 3 plus use of cholesterol lowering medications (ever user yes, no) n=2384
Model 5: model 4 plus APOE e4 allele status (e4+, e4-) n=557

Figure 5.8: Trajectories of HDL Cholesterol Stratified by Alzheimer’s Disease Status

Model 1: adjusted for sex and educational attainment (≤ high school, > high school) n=2384
Model 2: model 1 plus smoking (ever smoker yes, no) n=2384
Model 3: model 2 plus average blood pressure and average blood glucose n=2384
Model 4: model 3 plus use of cholesterol lowering medications (ever user yes, no) n=2384
Model 5: model 4 plus APOE e4 allele status (e4+, e4-) n=557
Figure 5.9: Trajectories of Total/HDL Ratio Stratified by Alzheimer’s Disease Status

Model 1: adjusted for sex and educational attainment (≤ high school, > high school) n=2384
Model 2: model 1 plus smoking (ever smoker yes, no) n=2384
Model 3: model 2 plus average blood pressure and average blood glucose n=2384
Model 4: model 3 plus use of cholesterol lowering medications (ever user yes, no) n=2384
Model 5: model 4 plus APOE e4 allele status (e4+, e4-) n=557

Figure 5.10: Trajectories of Total, HDL and Total/HDL Ratio Stratified by APOE e4 Allele Status

Adjusted trajectories control for the effects of sex, educational attainment, smoking, average blood pressure, average blood glucose, and use of cholesterol lowering medications. Unadjusted model includes 568 subjects. Eleven subjects who had missing data for educational attainment were excluded from the adjusted models (n=557).
Figure 5.11: Trajectories of Total, HDL, and Total/HDL Ratio Stratified by Alzheimer’s Disease and APOE e4 Allele Status

Adjusted trajectories control for the effects of sex, educational attainment, smoking, average blood pressure, average blood glucose and use of cholesterol lowering medications. Adjusted models include 557 subjects.
The adjusted models controlled for the effects of educational attainment, smoking, average blood pressure, average blood glucose and use of cholesterol lowering medications. The fully adjusted models included $APOE$ e4 allele status plus all of the covariates in the adjusted model. The sample sizes for the unadjusted, adjusted and fully adjusted models were 2449, 2384 and 557 subjects, respectively. There were 65 subjects who had missing data for educational attainment. Data for $APOE$ was recorded for 568 subjects, but 11 of these subjects had missing data for educational attainment.
Figure 5.13: Trajectories of Total, HDL and Total/HDL Ratio Among Women Adjusted for Supplemental Estrogen use Stratified by Alzheimer’s Disease Status

The adjusted models controlled for the effects of sex, educational attainment, smoking, average blood pressure, average blood glucose, use of cholesterol lowering medications and use of supplemental estrogen. The fully adjusted models included \( APOE \) e4 allele status plus all of the covariates in the adjusted model. There were 1390 subjects included in the adjusted models. There were 337 subjects included in the fully adjusted models.

Figure 5.14: Subject-Specific Trajectories of Total Cholesterol Stratified by Cognitive Quartile

Subject-specific trajectories of total cholesterol were obtained by combining the fixed and random effects for the model that included sex, educational attainment, smoking, cholesterol medications, blood glucose, blood pressure, and \( APOE \) e4 allele status as covariates.
Figure 5.15: Total Cholesterol Trajectories Stratified by Cognitive Quartile

Trajectories of total cholesterol adjusted for the effects of sex, educational attainment, smoking, cholesterol medications, blood glucose, blood pressure, and APOE e4 allele status.
Chapter Six: Discussion and Conclusion

A number of factors have been implicated in pathological changes in cognition later in life, and in pathological changes that eventually lead to AD. Diet represents one dominant set of factors, and cholesterol is one particular factor within this domain that has attracted recent attention in scholarship. This dissertation has sought to add to this scholarship.

The research reported in this dissertation, based on longitudinal data taken from the FHS, employed a life span approach to promote understanding of the relationship between cholesterol levels and cognitive function. A first task (and Specific Aim One) of the research was to determine the best way to empirically express cognitive functioning, given that FHS includes multiple measures of cognitive function. The resulting metric was later applied (in Specific Aim Three) to an analysis of the relationship between life span cholesterol trajectories and cognitive function among older adults who had not received a diagnosis of dementia. An intermediate task (Specific Aim Two) sought to identify relationships between life span cholesterol trajectories (specifically total, HDL, and total/HDL ratio) and AD, recognizing that this pathological condition was not addressed in the last Specific Aim.

This final chapter of the dissertation offers a critical summary of the findings from Specific Aims one through three, which will be presented in turn. A central theme that emerges from critical evaluation, not only of the findings but also of the foundational literature, is the potential of life course concepts for informing ongoing epidemiological research involving cognitive function. The life course concepts will be covered, and will be followed by specific directions for research that may effectively situate this dissertation’s research within a life course framework and, consequently, identify areas of ongoing research.

Discussion of Research Findings

Defining Midlife and Late Life Based on Total Cholesterol

This segment of the research employed a rigorous approach to define age boundaries for midlife and late life by visually examining age-related changes in total cholesterol and identifying
age periods in which there was a prolonged increase in total cholesterol (representing midlife) and the ages in which there was a prolonged decline in total cholesterol (representing late life). Based on examination of both the cross-sectional and longitudinal trends, midlife was defined as between 30 and 55 years of age for the Original Cohort, and between 30 and 45 years of age for the Offspring Cohort. Late life was defined as 65 and older for the Original Cohort, and 60 years and older for the Offspring Cohort. Findings illuminated potentially significant cohort differences in changes to total cholesterol across the life span. Subsequent research should focus on identifying factors that may have contributed to these cohort differences and if these factors also contribute to potential cultural differences in life span trajectories of cholesterol and other measures of vascular health.

This portion of the research also presents a clear challenge to widely accepted notions of what constitutes old age, middle age, and other life stages. Aging research has seemingly taken for granted the importance of sufficiently justifying why certain age boundaries for various life stages are chosen and the implications that arbitrarily selecting age boundaries may have on findings. A critical evaluation of how age boundaries for midlife, late life, and other life stages should be obtained is warranted. It is commonly recognized, for example, that age 65 represents a dominant stage boundary largely as a consequence of policy measures in the U.S. dating back to 1935 (REF). These policies, though based on cursory observation of physiological change and health status at the time, were essentially derived from consideration of the balance between chronological age and economic productivity and need, even though productivity and need are not simply a matter of physiological capacity. Once established, a break-point of 65 years (‘retirement age’) gathered a certain temporal momentum and has endured as an emerging requirement of replication of results within the ‘Scientific Method’ that gained increasing credibility through the 20th Century (REF?). Yet a life course view would suggest that complex societal changes, ranging from medical advances to political economic priorities and communication/media technologies might well be expected to alter health status at advanced ages.
along with the potential productivity levels associated with age. In short, the link between chronological age and both physiological capacity and economic productivity is likely much different today than it was in 1935.

**Specific Aim One**

Aim One sought to calculate a series of three summary scores for the FHS neuropsychological battery and utilize receiver operating characteristic analysis to determine which summary score was best able to differentiate between subjects classified as having normal cognitive function, test-based impaired learning and memory (ILM\textsubscript{TB}), test-based multidomain impairment (MDI\textsubscript{TB}), and dementia. The relatively high values for the area under the curve (AUC), sensitivity, and specificity indicate that all three summary scores were able to accurately differentiate between the four cognitive groups, but significant differences between the three summary scores were detected when classifying normal versus dementia, normal versus MDI\textsubscript{TB}, and ILM\textsubscript{TB} versus MDI\textsubscript{TB}. When compared to the composite subtests summary score, the composite domains summary score was not as accurate when differentiating between normal versus dementia, and ILM\textsubscript{TB} versus MDI\textsubscript{TB}, whereas the learning/memory score was less accurate when differentiating between normal versus MDI\textsubscript{TB}. Based on these findings, the composite subtests summary score was determined to have the highest utility when differentiating between the four cognitive groups and was used as the measure of cognitive functioning for Aim Three.

Many population-based cohort studies assess cognitive functioning using a neuropsychological battery comprised of a collection of cognitive assessments that are included for reasons linked to the specific goals of the study. But there are considerable differences between studies in the number and type of cognitive assessments included in the neuropsychological battery, which makes it challenging to compare the results of the subtests summary score obtained in Specific Aim One from the FHS neuropsychological battery to summary scores obtained from other studies. A total score for the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuropsychological battery has been reported to
accurately differentiate between older adults with normal cognition, mild cognitive impairment (MCI) and AD (Chandler et al., 2005). Compared to the results reported by Chandler et al. (2005), the composite subtests summary score from Specific Aim One had a similar AUC, sensitivity, and specificity when differentiating between normal, cognitively impaired and dementia subjects. This suggests that a summary score that is the sum of the subtests included in the neuropsychological battery has similar utility compared to the composite subtest method used in Specific Aim One.

A total score was not calculated in Specific Aim One because this method does not take into account the differential weighting of each assessment within the summary score due to the variation in the minimum and maximum possible scores for each assessment. As a result, a subject’s total score may not accurately represent their overall level of cognitive functioning because the total score may be highly influenced by performance on only one or two subtests. Furthermore, a total score approach does not account for the different scales in which some cognitive assessments are scored. The FHS neuropsychological battery includes the Trail Making Test (TMT) A and B, which are timed assessments measured in either minutes or seconds (subjects are typically allowed a maximum of five minutes, 300 seconds, to complete each assessment). The relative weight of the TMT A and TMT B scores in a total summary score would vary substantially depending on if the time to complete the assessments was measured in seconds or minutes. A potential resolution would be to not include the TMT A and B assessments in a total summary score, but these assessments are sensitive to the presence of dementia (Rasmussen, Zonderman, Kawas, & Resnick, 1998) and mild cognitive impairment (Ashendorf et al., 2008) and not including these assessments would potentially decrease the utility of the summary score.

**Limitations:** There are important limitations of Specific Aim One that should be acknowledged. First is the low number of participants who had received the neuropsychological battery and were diagnosed with dementia. A total of 1251 subjects in the validation sample
completed a neuropsychological battery, but only 19 of these subjects had received a diagnosis of dementia. The low prevalence of dementia is due to the relatively young age of the Offspring Cohort. This limited the ability to detect statistically significant differences between the three summary scores when classifying between dementia and the other cognitive groups. The low power was reflected by the wide confidence intervals for area under the curve (AUC), sensitivity, specificity, negative predictive value (npv), positive predictive value (ppv) and total accuracy in the analyses that included participants with dementia. The low prevalence of dementia must also be taken into consideration when interpreting the ppv and npv for the summary scores because these metrics are influenced by disease prevalence (Altman & Bland, 1994). The ppv of a diagnostic measure increases as the prevalence of the disease increases, whereas the npv decreases as the prevalence of the disease increases. This means that in a population were the prevalence of a disease is low, a relatively high number of people will be incorrectly classified as having the disease compared to the number of people who test positive and truly have the disease.

A second limitation is that calculating specificity, sensitivity, ppv, npv and overall accuracy of the three summary scores required comparing the classification results from the summary scores to those obtained from a predetermined gold standard. The gold standard for classifying participants as MDITB and ILMTB was consistent with the diagnostic criteria for MCI established by the National Institute on Aging and Alzheimer’s Association (NIA-AA) workgroup (Albert et al., 2011). The NIA-AA workgroup defines MCI as cognitive performance that is $\geq 1.5$ standard deviations below what a person would be expected to perform based on their age and level of education. The NIA-AA workgroup emphasizes that persons diagnosed with MCI are able to maintain their ability to independently perform activities of daily living (ADLs), such as paying bills, cooking a meal, or shopping. While the FHS includes measures for ADLs, this criterion was not included in the classification of MDITB and ILMTB because these measures were not collected concurrently with the neuropsychological battery. Not including the ability to independently perform activities of daily living in the diagnostic criteria utilized in Aim One
raises the possibility that some participants classified as ILM_{TB} or MDI_{TB} may have dementia if their level of cognitive impairment limited their ability to independently perform ADLs.

Finally, the results from the ROC analysis may over-estimate the ability of the summary scores to differentiate between the cognitive subgroups because the cognitive assessments used to classify participants as normal, MDI_{TB} and ILM_{TB} were also used to create the three summary scores. However, biases that may have arisen as a result of utilizing this approach were minimized because the summary scores were not used to classify subjects as normal, MDI_{TB}, and ILM_{TB}.

**Future Research:** The findings from this Specific Aim have identified important research questions and limitations that need to be addressed by future research. First, this analysis should be replicated using data from a study that has specifically recruited subjects with dementia. The increased number of dementia cases would bias the ppv and npv of the summary scores, but would increase the likelihood of detecting significant differences in the classification accuracy of the three summary scores. This would also potentially allow analyses for specific subtypes of dementia, such as AD and vascular dementia, to be conducted. Next, the gold standard criteria used to classify participants as normal, ILM_{TB}, and MDI_{TB} in this research can be refined by including measures of ADLs, repeated measures of cognitive functioning to assess cognitive decline, and measures for brain pathology. Including these measures may improve the ability to accurately classify participants as normal, ILM_{TB} and MDI_{TB} according to the gold standard. Finally, the mini-mental status exam (MMSE; Folstein, Folstein & McHugh, 1975) was not included as part of the neuropsychological battery. The MMSE is commonly used in clinical settings to assess cognitive functioning and it would be beneficial to determine if the summary scores are better able to differentiate between specific cognitive groups compared to the MMSE.

**Conclusion:** All three summary scores were able to accurately differentiate between the normal, ILM_{TB}, MDI_{TB} and dementia subgroups, but the findings indicate that the composite subtests summary score has the highest utility among the three summary scores. Based on the
results of this Specific Aim, the composite subtests summary score was deemed appropriate as
the measure of cognitive functioning in aim three. Furthermore, the study design and methods
utilized in aim one can be replicated and used by other investigators to create summary scores for
the neuropsychological batteries employed in other studies.

Specific Aim Two

Specific Aim Two utilized a longitudinal study design to examine the relationship
between trajectories of total cholesterol, high-density lipoprotein (HDL) cholesterol and
total/HDL cholesterol ratio from midlife to late life and AD using generalized additive mixed
models (GAMMs). The purpose of this Specific Aim was to determine if there were differences
in the longitudinal trajectories of cholesterol between older adults diagnosed with AD and those
who do not have dementia.

In general, Specific Aim Two findings do not provide strong evidence that there are
substantial differences in the trajectories of total cholesterol, HDL cholesterol or total/HDL ratio
from midlife to late life between older adults diagnosed with AD and older adults without
dementia. Total cholesterol increased until approximately 60 years of age, which was followed
by a steady decline with advancing age for older adults with AD, as well as for older adults
without dementia. HDL cholesterol increased with age for older adults diagnosed with AD and
those without dementia. The increase in HDL followed a linear trend for subjects with AD,
whereas the increase in HDL cholesterol followed a cubic trend for subjects without dementia.
Finally, both subjects with AD and subjects without dementia exhibited a steady decline in
total/HDL cholesterol ratio, which accelerated at approximately 70 years of age.

There were slight differences in the trajectories of total, HDL and total/HDL cholesterol
ratio according to AD status when the effects of sex, educational attainment, smoking history,
blood pressure, blood glucose and history of using cholesterol-lowering medications were
controlled for in the adjusted models\textsuperscript{17}. These differences became more apparent when apolipoprotein E (\textit{APOE}) e4 allele status was added to the adjusted models\textsuperscript{18}. The overall trajectories of cholesterol did not dramatically change once \textit{APOE} e4 allele status was added as a covariate, but older adults diagnosed with AD had higher measures of total cholesterol and HDL cholesterol compared to older adults without dementia. Older adults without dementia had slightly higher total/HDL cholesterol ratio, but these subjects exhibited an accelerated decline in total/HDL cholesterol ratio following 70 years of age, whereas older adults with AD maintained a constant decline.

There were substantial differences in the trajectories of total cholesterol, HDL cholesterol, and total/HDL cholesterol ratio when stratified according to sex and AD status. Women had lower total cholesterol during midlife compared to men, but women exhibited a dramatic increase in total cholesterol up until approximately 60 years of age. Men and women exhibited a similar rate of decline in total cholesterol following 60 years of age. The measures of HDL cholesterol remained relatively constant with age for men and women; however, women had much higher measures of HDL cholesterol compared to men. Finally, the ratio of total cholesterol to HDL cholesterol declined with age for both men and women, with an accelerated rate of decline occurring at approximately 70 years of age. While there were visually apparent differences in total cholesterol, HDL cholesterol and total/HDL cholesterol ratio between men and women, there were little to no differences according to AD status for men or women according to the adjusted models. When \textit{APOE} e4 allele status was included as a covariate (fully adjusted model), men who developed AD had lower cholesterol from 30 to 50 years of age and maintained higher total cholesterol following 55 years of age compared to men who did not develop dementia. Women who developed AD maintained slightly higher total cholesterol

\textsuperscript{17} The adjusted model included sex, educational attainment, smoking history, blood pressure, blood glucose and history of using cholesterol-lowering medications

\textsuperscript{18} The fully adjusted models included \textit{APOE} e4 allele status plus all of the covariates in the adjusted model.
following 55 years of age compared to women who did not develop AD. In the fully adjusted model, men who developed AD had higher HDL cholesterol compared to men who did not develop AD, but AD subjects exhibited a decline in HDL cholesterol at 70 years of age whereas non-demented subjects exhibited a slight increase in HDL cholesterol. These differences in HDL cholesterol among men contributed to an accelerated decline in the total/HDL cholesterol ratio among men without dementia whereas men with AD exhibited a steady decline in total/HDL cholesterol ratio. There were no substantial differences in the trajectories of HDL cholesterol or total/HDL cholesterol ratio according to AD status among women.

When the trajectories of total cholesterol were stratified according to AD status and $APOE\text{ e4}$ allele status, subjects who were diagnosed with AD and carried one or more $APOE\text{ e4}$ alleles had consistently higher cholesterol from midlife to late life compared to non-demented subjects who did not carry an $APOE\text{ e4}$ allele. When the trajectories of HDL cholesterol were stratified according to AD and $APOE\text{ e4}$ allele status, subjects diagnosed with AD and who were e4+ exhibited an increase in HDL cholesterol, whereas HDL cholesterol declined for AD e4- subjects. The trajectories of total/HDL cholesterol ratio, according to AD and $APOE\text{ e4}$ status, followed a similar decreasing trend. The greatest differences in total/HDL cholesterol ratio were observed during midlife, but these differences became less apparent with advancing age.

There is limited research on the relationship between longitudinal trajectories of cholesterol and AD. A study conducted by Stewart et al. (2007) examined the longitudinal trajectories of total cholesterol according to dementia status utilizing data from the Honolulu-Asia Aging study. In this study, men who developed AD exhibited an accelerated decline in total cholesterol compared to men who did not develop dementia, whereas the opposite relationship was observed among men in the FHS Original Cohort. Men who did not develop AD in the FHS Original Cohort exhibited a greater rate of decline in total cholesterol beginning at 45 to 50 years of age compared to men who eventually developed AD. Furthermore, men who did not develop AD had higher cholesterol during midlife and lower cholesterol during late life compared to men
who did develop AD. These findings conflict with findings from previous studies that have reported high total cholesterol during midlife (Notkola et al., 1998; Solomon, Kivipelto, et al., 2009) and low total cholesterol during late life (Reitz et al., 2004; Siest et al., 2000) to be associated with AD. The findings from Specific Aim Two are consistent with a study conducted by Lesser et al. (2001) in which older adults with AD had, on average, higher total cholesterol and HDL cholesterol compared to older adults without dementia. Furthermore, a study conducted by Solomon et al. (2007) observed that subjects who developed dementia had a significantly greater decline in total cholesterol from midlife to late life, but had higher concentrations of total cholesterol during midlife and late life compared to older adults without dementia.

One hypothesis for an age-dependent relationship between peripheral cholesterol and AD is that high peripheral cholesterol contributes to an increase in AD neuropathology, which may lead to a decline in cholesterol due to a disruption in neurological mechanisms that regulate peripheral cholesterol homeostasis (Mielke et al., 2005). The findings from this Specific Aim do not support such a hypothesis19. Rather, the longitudinal trajectories of total cholesterol according to AD status suggest that men in particular with high cholesterol during midlife, who are able to reduce their cholesterol later in life, may be less likely to develop AD compared to men who do not reduce their cholesterol with advancing age. The use of cholesterol lowering medications was controlled for in the analysis and there were no differences in the use of cholesterol lowering medications among men according to AD status. Other factors that may lower total cholesterol, such as consuming a low fat diet and regular physical activity, may contribute to the apparent decline in cholesterol during midlife among men who do not develop AD.

Limitations: Certain limitations in this Specific Aim Two need to be acknowledged. First, potentially important covariates such as smoking, measures for blood pressure and blood

---

19 A significant limitation of the hypothesis proposed by Mielke (2005) is the blood brain barrier effectively limits the exchange of cholesterol between the periphery and the brain.
glucose, and use of cholesterol lowering medications, were not able to be included in the models as time-dependent covariates. A time-dependent covariate means that the value or status of the variable changes over time, whereas the value or status of a time-independent covariate remains fixed for the duration of the study, e.g. sex. Dichotomizing subjects as ever smokers and ever medication users, or calculating the averages for blood pressure and blood glucose may, for example, oversimplify the potential relationship between these variables and the trajectories of cholesterol. This is a possible explanation for why adjusted R² values in the models did not substantially change as these covariates were added to the models. An alternative approach that was used in the dissertation research was to calculate the total number of clinical examinations that a person reported being a smoker or taking cholesterol lowering medications. This was done to account for the duration in which a person was a smoker or took cholesterol-lowering medications. A limitation of this approach, however, was it did not account for differences between subjects in the number of times a subject was observed over the course of the study. To clarify, a subject who attended twelve clinical examinations and reported smoking during six examinations is likely to be much different compared to a subject who attended seven examinations and reported smoking during six examinations. The difference in the number of clinical examinations attended by the two subjects is potentially meaningful because of the higher proportion of clinical exams in which the second subject reported smoking. Additional research can address this limitation by including the ratio of clinical exams in which a subject reported smoking or using cholesterol-lowering medications as covariates. A second limitation of treating smoking and medication use as time-independent covariates is the age in which a person started or stopped these behaviors and the duration of these behaviors are not accounted for in the analysis. This can be addressed by including the age in which a person first reported smoking or using cholesterol-lowering medications as covariates in the models.

Another limitation is that data regarding the use of symptomatic treatments for AD, such as Donepezil and Memantine, do not appear to have been collected from subjects of the FHS
Original Cohort. The use of symptomatic treatments for AD may be an important confounding variable because there is evidence that acetylcholinesterase inhibitors (AChEI) influence cholesterol levels. In a cross-sectional study of 105 AD patients conducted by Adunsky, Chesnin, Ravona, Harats, and Davidson (2004), patients who had been prescribed donepezil (n=35) had significantly higher total cholesterol, VLDL, LDL, and triglycerides, but not HDL cholesterol, compared to AD patients who had not been prescribed donepezil. Furthermore, efficacy of atorvastatin, a frequently prescribed cholesterol medication commonly known as Lipitor, for the treatment of mild to moderate AD has been shown to be higher among patients with total cholesterol levels above 220 mg/dl compared to patients with total cholesterol < 200 mg/dl (Sparks et al., 2006). These findings provide evidence that the higher cholesterol among older adults who developed AD relative to subjects without dementia may be due to a healthy volunteer bias among AD subjects. Older adults diagnosed with AD who remained in the FHS may have been able to do so because of their use of AChEI and other symptomatic treatments for AD, which may have altered their lipid profile.

Conclusion: The findings from Specific Aim Two do not provide sufficient evidence that the longitudinal trajectories of total cholesterol, HDL cholesterol and total/HDL cholesterol ratio differ between older adults with AD and those without dementia. Immediate attention should be placed on conducting research that uses more refined techniques for controlling for the effects of smoking and medication use. These techniques should focus on accounting for the timing and duration of smoking and medication use. Additional research should also focus on quantifying the differences in cholesterol according to AD status that were identified in this dissertation research using other longitudinal methods such as group based modeling. Finally, future research should focus on generating evidence that provides insight into potential biological mechanisms that support cholesterol being an important risk factor for AD and the potential confounding effects of symptomatic treatments for AD. An area of research worth investigating is examining if cholesterol outside of the brain is correlated with measures of biomarkers that reflect
pathological changes in the brain consistent with AD. A significant relationship between cholesterol and AD biomarkers would provide evidence that there are potential biological mechanisms that explain how abnormal concentrations of cholesterol during the life span modify the risk for AD. Plausible biological mechanisms for a relationship between cholesterol and AD would justify additional research in this area.

**Specific Aim Three**

There is considerable heterogeneity in cognitive functioning among older adults who do not have dementia and subtle cognitive impairment may be an early warning sign of dementia. This, along with evidence for a significant relationship between total cholesterol and cognitive functioning among older adults without dementia (Elias, Elias, D'Agostino, Sullivan, & Wolf, 2005; Henderson, Guthrie, & Dennerstein, 2003; Solomon, Kareholt, et al., 2009), were the motivating factors for investigating if there is a visually apparent relationship between a person’s unique trajectory of total cholesterol and cognitive functioning during old age.

Specific Aim Three utilized a longitudinal study design to examine the relationship between subject-specific trajectories of total cholesterol from midlife to late life and cognitive functioning among older adults without dementia. There was not strong visual evidence for a relationship between the subject-specific trajectories of total cholesterol from midlife to late life and a subject’s level of cognitive functioning during old age. When the averages of the subject-specific trajectories for each of the cognitive quartiles were examined, subjects in the fourth quartile had significantly lower total cholesterol compared to the second and third quartiles at 55 years of age. However, the estimated difference in total cholesterol between the two groups was only 5.7 mg/dl and this difference, while statistically significant, is unlikely to have significant clinical meaning. Subjects in the first cognitive quartile also had lower total cholesterol at 55 years of age compared to the second and third quartiles, but this difference was not statistically significant. Interaction terms between the linear term and cognition, and the quadratic term and cognition were included in the mixed effects models to determine if the trajectories of total

---

138
cholesterol from midlife to late life differed according to cognitive quartile. Neither of the interaction terms were statistically significant indicating that there was not a significant difference in the mean trajectories of total cholesterol from midlife to late life according to cognitive quartile.

The results from this Specific Aim align with a study reporting that high total cholesterol during midlife (age 47 - 51) was associated with lower episodic memory and psychomotor speed twenty-one years later (Solomon, Kareholt, et al., 2009). However, another study that utilized data from the FHS Original Cohort reported that non-demented older adults, between the ages of 55 and 88 during the 14th or 15th clinical examination, whose average total cholesterol from the 4th through 12th clinical examinations was < 200 mg/dl had lower cognitive functioning compared to subjects whose average measures of total cholesterol were between 200 to 239 mg/dl or ≥ 240 mg/dl (Elias et al., 2005). Also, Henderson et al. (2003) reported a positive correlation among healthy women 52 to 63 years of age between memory function and an increase in total cholesterol eight years before memory function was assessed. Finally, a study of adults 65 years of age and older did not report a significant relationship between total cholesterol and memory or language (Reitz, Luchsinger, Tang, Manly, & Mayeux, 2005).

There are several explanations for the apparent differences in the findings of aim three of the dissertation research compared to the findings reported by Elias et al. (2005). First, there are important differences in overall approaches of the two studies. Based on how the repeated measures of total cholesterol were utilized in the analysis, Elias et al. (2005) were able to determine if the average measure of total cholesterol during a prolonged period is associated with cognitive functioning later in life. This approach did not allow for potentially important changes in the trajectory of total cholesterol to be detected, which was the purpose of the Third Specific Aim. Second, the wide age range of subjects included in the final sample by Elias et al. (2005) may have influenced the relationship between total cholesterol and cognition. The age range of subjects during the 4th through 12th clinical examinations was between 30 and 35 years, with the
youngest subject during the 4th clinical examination being 34 years of age and the oldest being 69 years of age. The findings presented in Chapter Three of this dissertation indicate a strong relationship between total cholesterol and chronological age in the FHS Original Cohort, with total cholesterol increasing during midlife and declining later in life. Subjects who were in their thirties during the fourth clinical examination likely exhibited an increase in total cholesterol during the subsequent nine clinical examinations, whereas total cholesterol likely decreased over the same period for subjects in the 50’s and 60’s during the fourth clinical examination. While age was included as a covariate by Elias et al. (2005), this may not have fully accounted for the potential confounding effects of age on the relationship between cholesterol and cognition. A third explanation is the unique characteristics of the Offspring and Original Cohorts that may contribute to the differences in total cholesterol across the life span. These characteristics have been highlighted in Chapter Three of this dissertation.

**Limitations:** There are limitations of the research for Specific Aim Three that need to be acknowledged. First, potentially important covariates, such as smoking, use of cholesterol lowering medications, blood pressure and blood glucose were included in the models as time-independent covariates. Not taking into account the time-dependent nature of these covariates may not adequately adjust for the effects that these variables have on the relationship between cholesterol and AD. This is especially relevant for smoking and medication use because the age and duration of these behaviors influence vascular health (Celermajer et al., 1993; Dempsey & Moore, 1992; Herrington et al., 2002; Young-Xu et al., 2003). A second limitation is that characterizing non-linear trajectories using mixed effects models requires specifying a functional form by including quadratic, cubic or higher order polynomial terms in the model. Imposing a predetermined structure on the data may be too restrictive and this was the motivating factor for utilizing GAMM in Specific Aim Two. Despite this limitation, mixed effects models were still utilized for Specific Aim Three because the methods that allow for smoothing terms to be applied to subject-specific trajectories fall outside the feasible limits of the immediate dissertation.
research. Finally, dividing subjects into quartiles according to their cognitive summary score does not take into account that some older adults maintain normal functioning in certain cognitive domains but may have impairment in other cognitive domains. This prevented potential relationships between the subject-specific trajectories of total cholesterol and specific cognitive domains from being detected. Identifying subjects who are ILM<sub>T</sub>B, MDI<sub>T</sub>B and normal cognition and then examining the subject-specific trajectories of total cholesterol according to these cognitive groups can address this limitation.

**Conclusion:** To summarize, the findings from this Specific Aim do not provide strong evidence of a significant relationship between an individual’s unique trajectory for total cholesterol from midlife to late life and their level of cognitive functioning during old age. Subjects who were in the highest quartile for cognitive functioning had significantly lower total cholesterol compared to subjects in the middle two cognitive quartiles. Additional research is needed to clarify the relationship between the longitudinal trajectories of total cholesterol and cognitive functioning later in life. This research should focus on incorporating the duration of smoking and cholesterol medication use, as well as the age in which these behaviors started, into the analysis as these characteristics may play an important role in the relationship between cholesterol and cognitive function.

**The Life Course as a Conceptual Lens**

The life span perspective is well suited for conducting research that is focused on understanding the developmental characteristics of humans as they age, identifying factors that may modify physiological, intellectual or other developmental characteristics with advancing age, or the relationship between different developmental stages. This dissertation employed a life span perspective by examining trajectories of cholesterol from midlife to late life to determine if these trajectories were related to AD and cognitive functioning later in life. A life span approach also supports an age-continuous view to reveal subtle but potentially important time points of change that are often obscured by a life stage emphasis. This approach offers avenues to advance
current understanding of the relationship between cholesterol and cognition, but does not prove an adequate conceptual framework for examining the true complexity of the interacting factors that influence cholesterol levels through the life span and their association with cognitive functioning during old age. A life course view may resolve this shortcoming of the life span approach.

Simply put, the life course is a person’s life, or life span, in full context (J. F. Watkins, 1999). This context refers to the notion that aging is more than the passage of time measured chronologically by the accumulation of years. Rather, aging is reflected by ongoing changes that occur within personal (e.g. physical, cognitive and psychological) and social (e.g. family, work and education) domains from birth until death (Settersten, 2006). Many of the significant events and transitions that occur within these personal and social domains (e.g. acquiring verbal language, puberty, graduating high school, leaving the family home, entering the workforce) are highly correlated with chronological age. This has made chronological age a useful index for predicting a person’s physical, cognitive or psychological characteristics, as well as their social standing and the roles a person is expected to fill within society (Settersten & Mayer, 1997).

Furthermore, this use of chronological age has resulted in normative behaviors and characteristics associated with distinct life stages that are socially constructed. This leads to the expectation that people move through the life course in a sequential fashion that follows a predictable order and questions or concerns are often raised when a person deviates from these social norms (e.g. developmental delays during childhood, teenage pregnancy, older adult in a college classroom). The variability in the timing and order in which events, experiences and transitions within personal and social domains occur are due to the influence that family, education, health, and social and cultural factors (e.g. cohort effects) and the complex interactions between these factors have on a person’s life course. These factors provide the context of the life span and introduce the socio-cultural influences that shape the life course. Additional layers of complexity are added
to this context when the influences of time (past, present, future), space (the environment in which events occur), and the actions of those around us are taken into account.

The scholarly pursuit of identifying factors that modify the timing and ordering of the life course and the potential implications that mistimed events and transitions have on later life outcomes has made the life course an extensively studied area of research. However, the concepts of the life course are valuable tools for developing research questions, designing studies and even influencing data collection (Elder et al., 2003; Settersten, 2006). Engaging the life course as a conceptual research framework is the focus of the rest of this chapter. The remainder of this chapter is organized as follows. First, the core concepts of the life course are presented along examples from relevant areas of research. Next, the application of life course concepts in epidemiology is introduced. These sections are meant to provide sufficient background knowledge on life course concepts so that the influence these concepts have for conceptualizing future research in AD can be better appreciated. This chapter concludes by describing how life course concepts can be applied to future research that will, hopefully, advance the current scientific understanding of AD.

Concepts of the Life Course

Every person has their own unique life course that is shaped by (1) endogenous (internal) and exogenous (external) factors, (2) early life choices, events and experiences, as well as the choices, events and experiences we anticipate happening in the future, (3) the timing in which events, experiences, and transitions occur and (4) the interdependence in which people live their lives with those around them.

*Endogenous and Exogenous Factors that Shape the Life Course:* Endogenous factors that shape a person’s life course include the genes they inherit from their parents, their physical and mental traits, as well as their intelligence, and emotional and personality characteristics. Endogenous factors shape a person’s life course by influencing the choices and decisions a person makes in response to their environment. Exogenous factors that shape a person’s life course may
be grouped into distinct life domains\textsuperscript{20}. These domains include: (1) Family, which includes personal relationships outside of our immediate and extended family; (2) Place and home, which refers to the places/homes that we have lived, as well as personal notions of home; (3) Education, which includes formal learning experiences (e.g. high school, college) and informal learning experiences (e.g. learning a skill from a family member); (4) Employment, which includes formal work experiences (e.g. paying jobs) and informal work experiences (e.g. helping a friend for no pay); (5) Recreation and leisure, which are the hobbies and activities we engage in for enjoyment; (6) Spirituality, which includes traditional religious activities as well as personal beliefs; (7) Historical context, which is the current cultural and social environment that is shaped by significant events (e.g. war, economic climate, or political events); and (8) Health, which includes personal and family health characteristics, significant health events and health behaviors.

\textit{Components of Time and Space:} The notion that the life course is influenced by events and experiences that occurred earlier in life is one of the key constructs of the life course perspective. In some cases the influence of an event or experience on the life course is immediately apparent, such as getting married or having a child. Other times the significance of a past event is not recognized until many years later once a person has been able to reflect back on their experiences. The majority of life course scholars emphasize the influence an actual event or experience has on a person’s life course, but the memories associated with that event or experience often times have far greater implications than the event itself. This is especially relevant for life course research that is interested in outcomes among older adults. Normative declines in memory can make it challenging to recall the specific details of a past experience or the details may become altered or exaggerated as a result of a person rehearsing the story in their mind.

\textsuperscript{20} The formal conceptualization of life domains is largely unpublished. Focus has been given to the domains of education, family, work, and historical context and the influence of these domains on the life course (Elder, 1994, 1998; Elder, Shanahan, & Clipp, 1994), but less attention has been given to leisure (Settersten, 2006), health (Moser & Watkins, 2008; Settersten, 2006) and the interdependence of the life domains (Hosier, Downer, Watkins, & Zanjani, 2012a).
The influence of previous events and experiences on the life course provides a link between the past and the present, but the present is also linked with the future. Many of the choices and decisions we make in the present are made with the mindset of what we anticipate may happen in the future. This may include a person deciding to start saving for college once their child is born in the anticipation that their child will want to attend college or a person choosing to complete an advanced directive in case they are unable to express the type of medical care they want to receive. The future time frame of the life course is often times neglected by researchers, but recognizing the influence that anticipated events have on the present has significant implications for research that is focused on identifying motivating factors for present health behaviors. These implications are elaborated upon in subsequent sections of this chapter.

The concept of space is important for the context of the life course because it emphasizes the socio-cultural factors that influence a person’s life. Space refers to the environment in which events and experiences take place. There are several different levels, or zones, of space that range from “personal” space all the way to the social and cultural environments in which people live their lives. Social and cultural factors play an important role in shaping the life course because these factors can change over time as significant events alter social and cultural norms. These changes in social and cultural norms often times manifest as cohort effects.

**Influence of Timing on the Life Course:** Chronological age by itself has little meaning and age alone is typically not accepted as a valid explanation for a behavior or health event. The perceived significance of chronological age is due to the correlation between chronological age and important biological, physical, cognitive, behavioral and social characteristics or events. Significant educational, career, or family events often times mark the transition from one distinct life stage to another. For example, leaving a parent’s home, graduating from college and entering the workforce is a series of life events within the domains of family, education and work that signify the transition from young adulthood into adulthood. The correlation between chronological age and events within socially constructed domains has allowed for the life course
to be recognized as a collection of distinct and sequential life stages (e.g. childhood, adolescence, young adulthood, middle age, and old age). The structuring of the life course serves an important purpose because it guides members of a society on what role they are expected to play in society, as well as plan for significant life events, such as marriage or retirement, which tend to occur within a specific age range.

The principle of timing proposes that the effect a significant life event has on a person's life course depends on the timing in which the event occurs (Elder et al., 2003). Because many social constructs, such as education and work, are structured according to chronological age, a person’s life course can be altered if they experience a significant life event at an age that is not within the normative age range imposed by their cultural or society. For example, early entry into parenthood often times has dramatic consequences and teenage mothers and fathers complete fewer years of education (Pirog-Good, 1993), are more likely to require government assistance (Bissell, 2000), and have lower income during adulthood (Moore et al., 1993) compared to those who delay parenthood.

The effect of timing on the life course is exemplified by the study The Children of the Great Depression (Elder, 1974). In this study, Elder utilized data from the Oakland Growth Study and Berkeley Guidance Study to examine the effects that economic deprivation early in life, as a consequence of the Great Depression, had on educational attainment, career success and family during adulthood and if these effects differed based on the age in which children experienced the Great Depression. The children of the Oakland Growth Study were born during the early 1920’s and were able to progress through childhood during the stable economic climate prior to the Great Depression, whereas children of the Berkeley Guidance Study were born during the late 1920’s and experienced early childhood during the worst period of the Great Depression (Elder, 1998). In general, children of the Oakland Growth Study had better outcomes for educational attainment, work, and family during adulthood compared to the children of the Berkeley Guidance Study. Elder attributed these differences between the Oakland Growth Study and Berkeley Guidance
Study to the different life experiences of the two cohorts during the Great Depression. The hardships and disadvantages experienced by the participants the Berkeley Guidance Study during childhood influenced their life course trajectories in education, career and family through adolescence and young adulthood, and caused the trajectories of these domains to be much different than those for children born several years earlier.

*Interdependence of Lives:* The notion that a person’s life course is shaped by the choices, behaviors and actions of others is an important characteristic of the life course perspective (Elder et al., 2003). The influence of the interdependent nature in which people live their lives on the life course is exemplified by examining how children’s health behaviors are often modeled after the behavior of their parents. In a study examining parental smoking history and adolescent smoking behavior, adolescents who had one parent who was a current smoker were 2.3 times as likely to have ever tried smoking and adolescents with two parents who were current smokers were four times as likely to have ever tried smoking compared to adolescents whose parents were never smokers (den Exter Blokland, Engels, Hale, Meeus, & Willemsen, 2004).

The social implications of the principle of linked lives are apparent by research on the relationship between social networks and smoking behavior (Christakis & Fowler, 2008). Utilizing data from the FHS, Christakis and Fowler (2008) observed that people whose spouse quit smoking decreased that person’s chances of smoking by 67 percent, if a sibling quit smoking then that person’s chances of smoking decreased by 25 percent and if a co-worker quit smoking then that person’s chances of smoking decreased by 34 percent. Relationships between social networks and social connectedness for self-reported levels of happiness (Fowler & Christakis, 2008) and obesity (Christakis & Fowler, 2007) have also been observed in the FHS.

In order to fully appreciate the complexity of the life course, it is necessary to examine the interplay between all of the factors that shape the life course. An example is to identify the factors that may influence a person’s career choice as an adult. The type of career a person chooses to pursue is likely to have been influenced by their intellectual capacity, previous
educational experiences and family expectations. A person who excelled in school from an early age due to their natural ability to learn or because their parents had the means to provided them with resources that fostered educational development will likely have different career aspirations compared to a child who struggled early on in school due to delays in intellectual development or because their family did not place significant importance on education. A person’s career choices may be further modified based on the current social and economic environment in which they live. For example, college students who graduate during an economic recession may choose to attend graduate school to pursue an advanced degree or to receive training in a profession that may show promising opportunities for gainful employment.

**The Life Course as a Research Perspective**

As a research perspective, Elder et al. (2003) describes the life course as a conceptual framework for creating research questions, developing concepts and designing studies. Following Elder’s landmark study The Children of the Great Depression (Elder, 1974), there has been a steady increase in the amount of research that has utilized a life course perspective due to the growing appreciation for the complex interplay between the domains of people’s lives and the influence that social and cultural characteristics have on these relationships. The majority of research has focused on the influence that interactions within socially constructed domains, such as family, education and work have on the life course and only recently has the influence of health on the life course begun to receive attention by the life course research community. In one of the first studies to utilize a life course perspective to study health, Elder et al. (1994) examined the effects that late military deployment to World War II (i.e. deployment after age 33) had on the health outcomes of men later in life. In general, men who were older than 33 years of age upon military deployment were at greater risk for poor physical health after returning from war compared to men who were deployed at a younger age potentially as a consequence of more severe disruptions to work, family and other domains of social support.


_Life Course Epidemiology:_ The majority of life course research has been conducted in the fields of psychology, sociology, demography and related disciplines, but the life course perspective has begun to be utilized by other disciplines. Epidemiology is one such discipline that has adopted a life course perspective to study the potential long-term effects that biological, behavioral and psychosocial exposures during gestation, childhood, adolescence, young adulthood and across generations have on health outcomes during adulthood (Kuh & Ben-Shlomo, 2004). The purpose of life course epidemiology is to examine the cumulative effects that prolonged exposures to specific risk factors have on disease risk later in life (Ben-Shlomo & Kuh, 2002), the temporal relationship between risk factors (Kuh et al., 2003) and to identify critical periods during the life span where interventions can have the greatest impact for modifying disease risk (Launer, 2005). Based on the description of life course epidemiology, it is clear that the motivation for applying a life course perspective to epidemiological research is the relationship between early life events and health outcomes later in life. This aspect of the life course is not different than the life span framework and if life course epidemiology were only interested in examining the relationship between early life exposures and later life outcomes then it would be more appropriate to use the term life span epidemiology. However, the use of the term life course is justified for two reasons. First is the emphasis by life course epidemiology that generations are linked by common genetic and social factors and that these commonalities may influence health. Second, life course epidemiology recognizes the dynamic nature of socio-cultural factors and that secular changes in specific risk factors influence the overall health of a population.

**Life Course as a Conceptual Lens for Alzheimer’s Disease Research**

There is strong empirical evidence that the biological cascade of events that may ultimately lead to AD is initiated many years or even decades before cognitive decline is observed. This, along with the identification of several midlife risk factors for poor cognition and AD later in life, have contributed to the growing interest in a life course approach to study AD
(Launer, 2005; Whalley, Dick, & McNeill, 2006). However, AD research has been focused on examining biopsychosocial characteristics during midlife and there has been limited research that has examined characteristics earlier in the life span. Midlife is a critical period for preventing AD because the pathological changes to the brain associated with AD are unlikely to have occurred, but it is necessary to consider the factors that influence health outcomes during midlife when utilizing a life course perspective to study AD.

Many of the midlife risk factors that have been associated with AD can be linked with living in a disadvantaged environment. Children who grow up in poverty are more likely to engage in poor health behaviors (van de Mheen, Stronks, Looman, & Mackenbach, 1998), be diagnosed with a chronic disease (Kittleson et al., 2006; van de Mheen et al., 1998), and have lower educational attainment (Lawlor et al., 2005) as adults compared to children who grew up in families of moderate or high socioeconomic status. When examined using a life course perspective, several pathways that link childhood socioeconomic status (SES) with adult health can be identified (S. Cohen, Janicki-Deverts, Chen, & Matthews, 2010). An example is the influence that SES has on the physical environment and how this may modify psychological and physical development. A child born into a family of low SES may live in an overcrowded home that is in a neighborhood with poor air and water quality and limited access to education. These disadvantages may cause a child to have developmental delays in language and reading due to limited educational opportunities, consume a poor diet because of limited access to healthy foods, and not engage in physical activity because their neighborhood is too dangerous to play outside. Collectively, these disadvantages increase the risk for poor health as an adult and ultimately increase the risk for poor cognitive functioning during old age if the person maintains their current behavior. Compare this to a child who grows up in a family of moderate or high SES who may live in a stable home in a neighborhood with good air and water quality and access to quality educational opportunities. These advantages early in life would allow for a child to excel in school from an early age and engage in positive health behaviors by modeling the behaviors of
their parents. Collectively, these advantages decrease the risk for poor health as an adult and may ultimately decrease the likelihood of having poor cognitive functioning later in life if the person maintains their current behaviors.

The challenge of identifying potential AD risk factors prior to midlife is there are not longitudinal studies that have sufficiently examined the physical, behavioral and social characteristics of participants beginning in childhood through old age. An alternative approach would be to have participants recall what their physical environment was like as a child and how their environment influenced their psychological and physical development. This approach is not realistic because of the difficulty of accurately recalling childhood experiences, especially among older adults who may be cognitively impaired. The FHS provides a unique opportunity to conduct life course research on AD because of the multi-generational design of the study. As previously described, the life course principle of linked lives states that people live their lives interdependently. Therefore, examining the social and behavioral characteristics of participants of the Original Cohort can provide broad insight into what the physical environment may have been like for participants of the FHS Offspring Cohort during childhood. The influences that parental socioeconomic status, health behaviors and health characteristics have on the health characteristics of subsequent generations can then be examined by linking data between the Original and Offspring Cohorts. Since a large proportion of the Offspring Cohort was over 60 years of age upon receiving a neuropsychological battery, the influence that parental characteristics have on the cognitive functioning among children who have progressed to old age can be examined. The findings from this research have the potential to provide empirical evidence that cognitive functioning during old age is influenced by parental characteristics.

The majority of life course research has focused on the relationship between early life experiences and circumstances and later life outcomes, but it is important to not discount the influence that the anticipation of future events has on behavior and decision-making in the present. There is ongoing research that is examining how perceptions of future risk for AD
influences present behaviors. The Risk Evaluation and Education for Alzheimer’s disease (REVEAL) Study is an ongoing study in which healthy adults are informed of their APOE genotype and are provided with a numerical risk assessment for AD based on their gender, age, family history and APOE genotype (Roberts et al., 2005). The findings from the REVEAL Study indicate that adults who learn they carry one or more copies of the APOE e4 allele are more likely to start engaging in health behaviors that may reduce their risk for AD later in life, such as changes to diet, exercise and medication or vitamin use, compared to adults who learned that they did not carry an APOE e4 allele. This research exemplifies how anticipated future events can influence present behavior.

**Engaging a Life Course Approach to the Dissertation Research**

The principles of the life course perspective can be utilized to create novel research questions based on the findings generated by the dissertation research. One of the most important principles of the life course perspective is that the timing in which an event or experience occurs may have a significant impact on a person’s life course. Aims two and three of the dissertation research modeled the trajectories of cholesterol according to chronological age, but an alternative approach would be to model the trajectories of cholesterol in relation to the age in which AD was diagnosed and determine if the trajectories of cholesterol differ before and after a diagnosis of AD has been given. In this approach, the age in which a person was diagnosed with AD is subtracted from their age during each observation period. The age in which a person was diagnosed with AD would be zero and the time (in years) prior to AD diagnosis would be negative and the time after diagnosis would be positive. This approach takes into account the variability in age at which subjects are diagnosed with AD by setting the time of diagnosis to zero. This method may provide insight to whether a distinct change in the trajectory of cholesterol occurs a certain number of years before a subject is diagnosed with AD. A limitation of this approach is that subjects who do not develop AD would be excluded from the analysis and therefore the trajectories of cholesterol for AD subjects could not be compared to a control group.
AD risk may also be modified according to the age at which a person is able to begin controlling high cholesterol. The findings from aim two indicate that men who do not develop AD have higher total cholesterol during midlife, but exhibit a decline in total cholesterol at a younger age compared to men who go on to develop AD. This suggests that the age at which a person is able to reduce their cholesterol influences their risk of developing AD. If the reduction in cholesterol is due to changes in diet, exercise or from using cholesterol-lowering medications, then this can provide insight into when interventions that target high cholesterol may have the most lasting effects for cognitive functioning later in life.

The above examples demonstrate that the concepts of the life course perspective are useful tools for conceptualizing future research. These two examples, however, would still be categorized as life span research because neither example took into account the socio-cultural context of the life span, which is necessary for a life course study. A life course study of the relationship between cholesterol and AD would need to include data that incorporates the social and cultural factors that influence cholesterol levels and cognitive functioning. These factors may include government mandates on displaying nutritional information on restaurant menus, regulations on the amount of trans-fats in food, or changes in Food and Drug Administration guidelines for cholesterol medications. These social changes influence the behavior of individuals and may contribute to secular changes in cholesterol levels and AD incidence and prevalence as a result of overall improved vascular health at the population level. A challenge to a life course study on the relationship between cholesterol and AD is this research requires individual level (e.g. age, cholesterol, cognitive function) and population level (e.g. income inequality, unemployment rate, access to medical care) data that have been collected simultaneously. Merging population and individual level data can create appropriate data sets to examine the influence that social and cultural factors may have on the relationship between cholesterol and cognitive functioning during old age. This area of research could advance the
current understanding of AD from a public policy perspective by examining how social and cultural characteristics influence the cognitive and vascular health of older adults.

**Conclusion**

Much of the public’s perception of research is driven by how results are presented by large media outlets. Popular news sources, such as the *New York Times* and *Time* Magazine, have columns dedicated to summarizing current research on potentially significant discoveries in regards to diagnosing and treating various diseases, and things people can incorporate into their daily routines to decrease their risk for developing a certain disease or condition. While disseminating current research to the general public via large media outlets is important for keeping people informed, it is easy to become confused or misled when results that seemingly conflict with prior research are presented. Therefore, it is important to always consider how the public may perceive findings from research and how results fit with the public’s perception of health and aging. This is particularly relevant to this dissertation research because there is a strong perception among the general public that cholesterol is detrimental to health because of the established relationship between high cholesterol and heart disease. This makes it necessary to critique the dissertation research, and other epidemiological studies that have examined the relationship between cholesterol and AD, within the context of the public’s perception towards cholesterol, health, and aging.

This dissertation research presents limited evidence that older adults diagnosed with AD maintain higher cholesterol from midlife to late life compared to older adults without dementia, and that lower cholesterol during midlife is associated with higher cognition during old age. These findings generally support the public health narrative that cholesterol is detrimental to health and that controlling cholesterol through dietary changes, exercise, and cholesterol lowering medications may decrease the risk for adverse health outcomes during old age. An informed member of the general public may counter with the argument that they have read reports that suggest older adults diagnosed with AD have lower cholesterol compared to older adults without...
dementia and a drop in cholesterol is a risk factor for AD. This may lead a person to make the conclusion that maintaining higher levels of cholesterol protects against AD and may be hesitant to lower their cholesterol. This conflict can be resolved by providing contextual information on the aging process and the normative and pathological changes that occur with advancing age. Aging is characterized by normative declines in physiological and cognitive domains that, collectively, contribute to a prolonged and progressive decline in functioning and quality of life. As a person approaches death, however, these declines accelerate in what has been described as a terminal drop or terminal decline (Gerstorf et al., 2010; Siegler, 1975). A plausible explanation for the observed relationship between low cholesterol and AD is that AD or symptomatic treatments for disease symptoms exacerbate this terminal decline by negatively affecting systems involved in cholesterol homeostasis, such as liver function (Giambattistelli et al., 2012; Squitti et al., 2007), cholesterol metabolism (Kolsch et al., 2010; Kolsch et al., 2004), and appetite (Ikeda, Brown, Holland, Fukuhara, & Hodges, 2002). Therefore, older adults who exhibit an unintended drop in cholesterol may be at a greater risk for AD compared to older adults who intentionally lowered their cholesterol through dietary changes, physical exercise, or with cholesterol lowering medications.

This dissertation research focused on the relationships between longitudinal trajectories of cholesterol, AD and cognitive functioning later in life. This research also explored the utility of creating summary scores of cognitive functioning that were based on cognitive performance on individual subtests of a neuropsychological battery to differentiate between subjects with normal cognition, cognitive impairment and dementia. The results from the dissertation research indicate that a summary score that provides equal weight to subtests of a neuropsychological battery is better able to differentiate between subjects that have been classified as having normal cognition, ILMTB, MDITB, and dementia. There were subtle differences in the longitudinal trajectories of total cholesterol, HDL cholesterol and total/HDL ratio from midlife to late life according to AD status. The potential significance of these differences should be interpreted with caution, as they
may not be clinically meaningful. There was not strong visual evidence for a relationship between subject-specific trajectories of total cholesterol from midlife to late life and cognition later in life, but older adults in the highest quartile for cognitive functioning had slightly lower total cholesterol at approximately 55 years of age.

The results of the dissertation research brought to light important research questions on the relationship between longitudinal trajectories of cholesterol, AD and cognitive functioning later in life. Future research should utilize a life course perspective to determine if the timing in which a decline in cholesterol occurs is associated with AD and cognitive functioning later in life. Furthermore, a life course perspective may also be able to provide insight into if perceptions of the future risk of AD and poor cognitive functioning influences present health behaviors. Studying the relationship between cholesterol, AD and cognitive functioning may generate evidence that can be applied to develop targeted interventions to improve the overall health of adults across the life span.
References


159


hypercholesterolemia (the CURVES study). *The American journal of cardiology, 81*(5), 582-587.


24S-hydroxycholesterol from the brain into the circulation. *Proceedings of the National Academy of Sciences of the United States of America, 93*(18), 9799-9804.


Vita

Brian Downer
University of Kentucky
Graduate Center for Gerontology
J525 KY Clinic
740 South Limestone
Lexington, KY 40536

Phone: (859) 218-0148
Email: brian.downer3@uky.edu

CURRENT POSITION
July 2010-present: Graduate Research Assistant, ABD
University of Kentucky, Lexington KY: Graduate Center for Gerontology

RESEARCH INTERESTS
Vascular risk factors for Alzheimer’s disease, gene by environment interactions, cognitive aging.

TEACHING INTERESTS
Epidemiology of aging, chronic diseases of aging, application of quantitative methods in aging research

EDUCATION
Aug 2010-present  Doctoral student, Gerontology
University of Kentucky, Lexington KY

Feb 15 2013  Doctoral Candidate in Gerontology
University of Kentucky, Lexington KY

Feb 2011  Graduate Certificate in Applied Statistics
University of Kentucky

Aug 2006-May 2010  B.S. Psychology
Biology minor
Aquinas College, Grand Rapids MI

Jan 2006-May 2006  Undeclared
Muskegon Community College, Muskegon MI

Aug 2005-Dec 2005  Undeclared
University of Arizona, Tucson AZ

PROFESSIONAL EXPERIENCE
Aug 2013-May 2014  Teaching Assistant
GRN 250 Growing Old in Today’s World
Supervisor: Graham Rowles, PhD
Jan 2013-May 2013  Teaching Assistant  
CPH 738 Statistical Genetics  
Supervisor: David Fardo, PhD

Jan 2012-May 2012  Teaching Assistant  
CPH 738 Statistical Genetics  
Supervisor: David Fardo, PhD

May 2009-Sep. 2009  Internship  
Behavioral Resources and Institute for Neuropsychological Services  
Supervisor: Michael Wolff, PhD; Rochelle Manor, PhD

PUBLICATIONS

Published Manuscripts


Invited Manuscripts


Published Reports

http://www.ca.uky.edu/agc/pubs/fcs7/fcs7200/fcs7200.PDF.

http://www.ca.uky.edu/agc/pubs/fcs7/fcs7201/fcs7201.PDF

http://www.ca.uky.edu/agc/pubs/fcs7/fcs7202/fcs7202.PDF

http://www.ca.uky.edu/agc/pubs/fcs7/fcs7203/fcs7203.PDF
http://www.ca.uky.edu/agc/pubs/fcs7/fcs7204/fcs7204.PDF

http://www.ca.uky.edu/agc/pubs/fcs7/fcs7205/fcs7205.PDF

**Manuscripts Under Review/Revision**


**Manuscripts in Preparation**
Downer, B., Jiang, Y., Zanjani, F., & Fardo, F. The Differential Effects of Midlife and Late Life Alcohol Consumption on Cognitive Functioning and Regional Brain Volumes among Older Adults.

**PROFESSIONAL PRESENTATIONS**


Downer, B., Zanjani, F., & Fardo, D. (2012). *Alcohol Consumption, APOE Genotypes and Longitudinal Change in Memory of Older Adults*. Presented (paper) at the University of Kentucky College of Public Health Research Day, Lexington, Kentucky, United States


RESEARCH SUPPORT
2012-present Research Challenge Trust Fund Assistantship, University of Kentucky

2010-2012 Memory Banking: Extension-based Intervention for Caregiving in Rural Communities:

  Role: Research Assistant
  Principal Investigators: Zanjani, Hosier, Watkins

  Purpose: Examine how the proposed intervention, Memory Banking, can affect risk factors related to the Caregiving process, using an extension-based training and dissemination model.

  Funding Source: United States Department of Agriculture Cooperative State Research and Extension Service [2009-45048-05575] UK - HEEL
  Budgeted Amount: $100,000

Additional Trainings and Workshops
Oct 2013 Writing Strategies for the NIH F31/F32 (Graduate Students/Postdocs) Fellowship Application: University of Kentucky

Oct 2013 Making Lectures Engaging and Interactive: University of Kentucky

June 2012 Grant Writer’s Seminars and Workshops “Write Winning Career Development Award Proposals”: University of Kentucky

HONORS AND AWARDS
2013 First place, University of Kentucky College of Public Health Research Day
2012 Grantmakers in Aging Fellow
2012 Second place, University of Kentucky College of Public Health Research Day
2012 The Donovan Scholarship in Gerontology
2011 The Everett and Anne Lee Student Gerontology Award
2010 University of Kentucky Dean’s Scholarship
2006-2010 Dean’s List Aquinas College, Grand Rapids MI

MEMBERSHIPS
American Society on Aging
Gerontological Society of America
Emerging Scholars and Professionals Organization
International Society to Advance Alzheimer’s Research and Treatment
Sigma Phi Omega, the National Academic Honor & Professional Society in Gerontology

SERVICE
National
June 2013-present Association for Gerontology in Higher Education Conference Site Selection Committee

Jan 2013-present Student Chair Designee, Association for Gerontology in Higher Education
June 2013 – present  Association for Gerontology in Higher Education Publications and Resources Committee

Department, College, and University
April 2012-Feb 2013  Vice President Sigma Phi Omega, Gamma Mu Chapter, University of Kentucky

May 2012-May 2013  Summer Series on Aging Conference Committee Member

March 2012-Feb 2013  Senior Student Representative of Administrative Council, University of Kentucky Graduate Center for Gerontology

May 2011-2012  Treasurer of Sigma Phi Omega, Gamma Mu Chapter, University of Kentucky

Feb 2011-present  Graduate Center for Gerontology Student Affairs committee

Feb 2011-March 2012  Junior Student Representative of Administrative Council, University of Kentucky Graduate Center for Gerontology

Aug 2008-May 2010  Psychology club: President  Aquinas College, Grand Rapids, Michigan

Community
May 2011, 2013  Meeting the Challenges and Opportunities of Aging Conference: Volunteer

Jan 2010-June 2010  Alzheimer’s Association Memory Walk Committee Member  Team recruitment subcommittee member, Grand Rapids, Michigan

June 2008  Habitat for Humanity, Spring Lake, Michigan

Scientific reviews
2014  American Journal of Alzheimer’s Disease and Other Dementias: Journal Reviewer

2014  The Journal of Nutrition, Health and Aging: Journal Reviewer

2013  Association for Gerontology in Higher Education Annual Conference: Abstracts Reviewer

2013  Genes, Brain and Behavior: Journal Reviewer

2012  Aging and Mental Health: Journal Reviewer