CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	The effects of centrally acting ACE inhibitors on the rate of cognitive and functional decline in dementia: a KDD approach
Authors	Gao, Yang
Publication date	2014
Original Citation	Gao, Y. 2014. The effects of centrally acting ACE inhibitors on the rate of cognitive and functional decline in dementia: a KDD approach. PhD Thesis, University College Cork.
Type of publication	Doctoral thesis
Rights	© 2014, Yang Gao. - http://creativecommons.org/licenses/by-nc-nd/3.0/
Download date	2026-11-04 16:34:40
Item downloaded from	https://hdl.handle.net/10468/2626



UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

CENTRE FOR GERONTOLOGY AND REHABILITATION,
BUSINESS INFORMATION SYSTEMS



ucc
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

The Effects of Centrally Acting ACE Inhibitors on the Rate of Cognitive and Functional Decline in Dementia: A KDD Approach

Yang Gao

MSc. Applied Science

MSc. Commerce (Business Information Systems)

A Thesis Submitted for the Degree of Doctor of Philosophy of the National University of Ireland, Cork.

Research Supervisors: Prof. D. William Molloy and Dr. David Sammon
Head of Department: Prof. D. William Molloy and Prof. Ciaran Murphy.

September 2014

Declaration

The author hereby declares that, except where duly acknowledged, this thesis is entirely his own work and has not been submitted for any degree in the National University of Ireland, or in any other University.

CONTENTS

LIST OF TABLES ..... **VI**
LIST OF FIGURES ..... **VIII**
ACKNOWLEDGEMENTS ..... **IX**
ABSTRACT ..... **XI**
CHAPTER 1 INTRODUCTION **1**
1.1 Introduction 1
1.2 Global Realities of Cognitive Impairment 1
1.3 Research Objectives and Questions 3
1.3.1 Research Question One 6
1.3.2 Research Question Two 8
1.3.3 Research Question Three 9
1.4 Legitimisation of the Research Work 11
1.5 Overview of the Chapters 15
CHAPTER 2 BACKGROUND **18**
2.1 Introduction 18
2.2 Prevalence of Dementia 18
2.3 Cost of Dementia 20
2.4 Dementia, AD, Vascular, Mixed Dementia and MCI 21
2.4.1 Mild Cognitive Impairment (MCI) 22
2.4.2 Types of Dementia 23
2.4.2.1 Alzheimer's Disease (AD) 24
2.4.2.2 Vascular Dementia (VaD) 25
2.4.2.3 Mixed Dementia 25
2.4.3 Who is at Risk from Dementia 26
2.5 Treatment of Dementia 28
2.5.1 Pharmacological 28
2.5.1.1 Drugs for Symptomatic Control 28
2.5.1.2 Disease Modifying Drugs 29
2.5.1.2.1 Drugs Interfering with Aβ Deposition 31
2.5.1.2.2 Drugs Interfering with Tau Deposition 32
2.5.2 Non-pharmacological Treatment 33

2.6 Summary 34
CHAPTER 3 RESEARCH METHODOLOGY: CLINICAL DATASETS AND METHODS OF ANALYSIS 36
3.1 Introduction 36
3.2 Knowledge Discovery 36
3.2.1 Principles of Knowledge Discovery 36
3.2.2 KDD (Knowledge Discovery in Databases) Definition 37
3.2.3 KDD Process 38
3.3 Data Analysis 42
3.3.1 Statistics as Data Mining Methods 43
3.3.2 Data Analysis in the Medical Area 46
3.4 Clinical Databases 52
3.4.1 Introduction 52
3.4.2 The Geriatric Assessment Tool (GAT) Database 53
3.4.2.1 Overview of the GAT Database 53
3.4.2.2 Demographics of Patients in the GAT Database 56
3.4.3 The Doxycycline and Rifampin for Alzheimer's Disease (DARAD) Trial Database 58
3.4.3.1 Overview of the DARAD Database 58
3.4.3.2 Patients Demographics in DARAD 59
3.4.4 Q*mci* Validation Database 60
3.4.4.1 Overview of Q*mci* Validation Database 60
3.4.4.2 Patient Demographics in Q*mci* Validation Database 61
3.5 Key Instruments in the Three Clinical Databases 63
3.5.1 Introduction 63
3.5.2 Clinical Dementia Rating Scale (CDR) 64
3.5.3 Standardised Alzheimer's Disease Assessment Scale-Cognitive Subscale (SADAS-cog) 64
3.5.4 The Standardised Mini-Mental State Examination (SMMSE) 65
3.5.5 The Quick Mild Cognitive Impairment (Q*mci*) Screen 66
3.5.6 Geriatric Depression Scale (GDS) 67
3.5.7 Lawton-Brody Scale (ADL) and Q*adl* 68
3.5.8 Dysfunctional Behaviour Rating Scale (DBRI) 69

3.5.9 Cornell Scale for Depression in Dementia (CSDD) 69
3.6 Analytical Methods..... 69
3.6.1 Data Analysis in Medical Research 69
3.6.1.1 Experimental Design (Obtaining Data)..... 70
3.6.1.2 Descriptive Statistics (Exploring, Summarizing and Presenting Data) 70
3.6.1.3 Tests of Statistical Significance 71
3.6.2 Statistical Methods..... 72
3.6.2.1 Distribution Tests for Normality 73
3.6.2.2 Comparing Test 75
3.6.2.3 Measure of Associations..... 78
3.6.2.4 One-way Analysis of Variance (one-way ANOVA).. 82
3.6.2.5 Multivariate Analysis of Variance (MANOVA) 83
3.6.2.6 Diagnostic Tests 84
3.6.3 The Use of Data Analysis Methods 90
3.7 Conclusion 93
CHAPTER 4 QUICK MILD COGNITIVE IMPAIRMENT (Q*mci*) 95
4.1 Introduction 95
4.2 Research Motivation..... 95
4.3 Existing Cognitive Screening Instruments 96
4.3.1 Mini-Mental State Examination (MMSE)..... 97
4.3.2 Montreal Cognitive Assessment 97
4.3.3 The AB Cognitive Screen 135 97
4.4 Developing the Quick Mild Cognitive Impairment screen (Q*mci*)..... 98
4.4.1 Initial development of the Q*mci* 98
4.4.2 Validation of the Q*mci* 99
4.5 Developing the Q*mci* Cut Offs..... 103
4.5.1 Rationale for Developing Cut-offs for the Q*mci* 103
4.5.2 Methods for Developing the Cut-off Scores 103
4.5.3 Developing Cut-off Scores..... 107
4.5.4 Results for the Q*mci* Cut-off Scores 107
4.5.4 Discussion of the Q*mci* Cut-off Scores..... 110
4.6 Comparison of the Q*mci* with Other Cognitive Tests 111

4.7 Conclusion and Rationale for Using the Q*mci* 112
CHAPTER 5 DRUG ANALYSIS 114
5.1 Introduction 114
5.2 Background 115
5.2.1 Anti-hypertensive Agents for Cognition in Dementia 115
5.2.1.1 Anti-hypertensive Agents and Dementia..... 116
5.2.1.2 Centrally-acting ACE–Is and Cognition..... 117
5.2.2 Anti-hypertensive Agents and ADL Function in Dementia 118
5.3 Effects of CACE-Is on the Rate of Cognitive Decline in Dementia (*Study One: CACE Study in GAT Database*) 120
5.3.1 Introduction 120
5.3.2 Data Pre-processing – Subjects Selection 121
5.3.3 Data Analysis..... 122
5.3.4 Results 123
5.3.4.1 Baseline Characteristics 123
5.3.4.2 Rate of Decline 125
5.3.5 Conclusion..... 127
5.4 Effects of CACE-Is on Functional Decline in Patients with Alzheimer's Disease (*Study Two: CACE Study in DARAD Database*) 129
5.4.1 Introduction 129
5.4.2 Data Pre-processing – Subjects Selection 130
5.4.3 Data Analysis..... 130
5.4.4 Results 131
5.4.4.1 Baseline Demographics 131
5.4.4.2 Rate of Decline 133
5.4.5 Conclusion..... 134
5.5 CACE-Is and Functional Decline in Dementia: Do They Affect Instrumental or Basic ADLs (*Study Three: CACE Study in GAT and DARAD Databases Combined*)..... 138
5.5.1 Introduction 138
5.5.2 Data Pre-processing – Subjects Selection 139
5.5.3 Data Analysis..... 140

5.5.4 Results 141
5.5.4.1 Baseline Characteristics 141
5.5.4.2 Rate of Decline 143
5.5.5 Conclusion 146
5.6 Conclusion 148
CHAPTER 6 CONCLUSIONS 153
6.1 Introduction 153
6.2 Research Background: Databases and Outcome Measures 153
6.2.1 The Databases 155
6.2.2 The Outcome Measures 156
6.3 Research Objective and Research Questions 156
6.4 Contributions and Results 159
6.4.1 Research Contribution One 161
6.4.1.1 Study One: CACE Study in GAT Database 161
6.4.1.2 Study Two: CACE Study in DARAD Database 162
6.4.1.3 Study Three: CACE Study in GAT and DARAD Databases Combined 163
6.4.2 Research Contribution Two 164
6.4.3 Research Contribution Three 168
6.5 Research Limitations 171
6.6 Summaries, Suggestions and Future Work 172
REFERENCES 176
APPENDIX 201
A. Publication List 201
B. Published Journals 204
C. The BMJ Open paper Press Release List 241
D. Key Instruments for this Research 245

LIST OF TABLES

Table 1. 1 Research Questions Guiding this Study 5
Table 1. 2 Publications Associated with this Research Study 13
Table 2. 1 Risk Factors for Vascular Dementia and Alzheimer's Disease 26
Table 3. 1 Various Representations of the KDD Process 39
Table 3. 2 The Phases in the Knowledge Discovery in Databases (KDD) Process 41
Table 3. 3 Data Mining and Statistical Methods in Medical and Bioinformatics Research 49
Table 3. 4 Data Mining and Statistical Method Types in Medical and Bioinformatics Research 50
Table 3. 5 The Research Studies Using the GAT, DARAD and Q*mci* Validation Databases 52
Table 3. 6 Baseline Demographics and Outcome Measure Scores for GAT Patients 57
Table 3. 7 Baseline Demographics, Baseline (BL) and End-Point (EP) Scores for DARAD Patients 60
Table 3. 8 Patients Demographics in Q*mci* Validation Database 62
Table 3. 9 Key Instruments in the Three Clinical Databases 63
Table 3. 10 SMMSE Scoring Table 66
Table 3. 11 Q*mci* Scoring Table 67
Table 3. 12 The List of the Statistical Tests Used in the Research 72
Table 3. 13 Positive and Negative Distribution Matrix for Diagnosis Tests 85
Table 3. 14 The Use of Statistical Methods in the Studies of this Research 91
Table 4. 1 Comparison of the ABCS 135 and the Q*mci* Screening Test 99
Table 4. 2 The Total Q*mci*, SMMSE, ABCS 135 and Q*mci* Subtest Median Scores with IQR (Q1 = 1st Quartile, Q3 = 3rd Quartile) by Diagnosis 102
Table 4. 3 Baseline Demographics for Q*mci* Patients in GAT, DARAD, and Q*mci* Validation Databases 105
Table 4. 4 Q*mci* cut-off Scores with Sensitivity and Specificity Grouped by Age and Education Comparing Patients with NC to CI and those with Dementia Compared to the Rest 108

Table 5. 1 Baseline Characteristics of CACE-I, NoCACE-I and NewCACE-I Patients 124
Table 5. 2 Baseline and End-Point (Last Visit) SMMSE and Q*mci* Scores 125
Table 5. 3 Comparison of Differences in Q*mci* and SMMSE Scores between Baseline and End-Point 126
Table 5. 4 Differences in Baseline Demographic Characteristics and Outcome Measures between CACE-I Group to NoCACE-I Group 132
Table 5. 5 Comparison of the Rate of Decline, from Baseline to One Year, between CACE-I and NoCACE-I Patients 134
Table 5. 6 Baseline Characteristics for CACE-I, Perindopril, Other CACE-I and NoCACE-I Patients (BP=blood pressure) 142
Table 5. 7 Comparison of Six-Month Cognitive and Functional Rate of Decline in CACE-I, NoCACE-I, Perindopril and Other CACE-I Patients 144
Table 5. 8 Comparison of differences in rates of change in basic and instrumental activities of daily living (ADL) between CACE-I, NoCACE-I, perindopril and Other CACE-I groups 146
Table 6. 1 Three Research Questions 158
Table 6. 2 The Map on Research Questions, Studies and Contributions 160
Table 6. 3 Key Characteristics for Cognitive Screening Instruments 166

LIST OF FIGURES

Figure 2. 1 Natural History of Cognitive Decline 21
Figure 2. 2 Types of Dementia 23
Figure 3. 1 The General KDD Process……38
Figure 3. 2 Data Mining Categories..... 44
Figure 3. 3 Statistics and Data Mining Tasks 45
Figure 3. 4 The Top Five Most Popular Methods in Biotech/Medical in 2008 47
Figure 3. 5 Distribution of Diagnoses in the GAT Database..... 55
Figure 3. 6 Standard Normal Distribution Curve 73
Figure 3. 7 a) Positively Skewed Distributions. b) Negatively Skewed Distributions 74
Figure 3. 8 An Example of ROC Curve..... 87
Figure 3. 9 ROC Curve 88
Figure 4. 1 Flow Chart Demonstrating the Recruitment of Patients from the Three Databases……...106
Figure 4. 2 Distribution of the Q*mci* Cut-off Scores for all Patients and Four Subgroups Stratified by Age and Education, Based on Sensitivity and Specificity of each Score..... 109
Figure 5. 1 Flow Chart Demonstrates the Breakdown of the Patients Who were Included in the GAT Database…… 122
Figure 5. 2 Flow Diagram for CACE-I and NoCACE-I Patients in DARAD Database 133
Figure 5. 3 Flow Chart for Patients in GAT and DARAD Databases 140
Figure 6. 1. Data Process Steps in CDAF.....169

ACKNOWLEDGEMENTS

This thesis, the outcome of an intellectual journey over the past three years, would not have been possible without the support of many people. Herein, I wish to convey my most sincere thanks to those who have helped me in various ways throughout the years.

First and foremost, I would like to express my sincerest appreciation to my supervisor, Professor D. William Molloy, not only for his wisdom, motivation and enthusiasm for research, but also for giving me this opportunity to participate in international scientific research fields. I truly appreciate his valuable guidance, inspiration and encouragement. He promoted my vision in data analysis, and built a solid foundation for my career. I want to thank him for always keeping his door open and helping with scientific problems and, when necessary, assisting me to overcome seemingly unsolvable problems. He is not only my academic mentor but also my spiritual mentor.

I also would like to thank my co-supervisor, Dr. David Sammon, who was also my Masters co-supervisor in 2007. Without his guidance and persistent help, this dissertation would not have been possible. I want to thank him for his patience, commitment and great support. He is always standing by my side whenever I need to talk things out. He is one of the most trustworthy people in my life.

I am very grateful to the members of my PhD examination committee, Professor Declan Lyons (external examiner) and Professor Ciaran Murphy (internal examiner), who reviewed in great detail the research work presented in this dissertation and ensured that the formal defense of my work was both challenging and enjoyable. Their comments were very helpful and insightful.

Big thanks also go to my CGR colleagues, especially Dr. Ronan O'Caoimh,

with whom I prepared and co-authored several publications.

Finally, I want to thank my dearest families with all my heart. Words are too pale to express all my gratitude to my parents, Peng Gao and Wanyun Guo, my beautiful wife, Meng Li and my younger sister, Shan Gao. I would like to dedicate all my contributions to you. Love you forever.

ABSTRACT

Alzheimer's Disease and other dementias are one of the most challenging illnesses confronting countries with ageing populations. Treatment options for dementia are limited, and the costs are significant. There is a growing need to develop new treatments for dementia, especially for the elderly. There is also growing evidence that centrally acting angiotensin converting enzyme (ACE) inhibitors, which cross the blood-brain barrier, are associated with a reduced rate of cognitive and functional decline in dementia, especially in Alzheimer's disease (AD).

The aim of this research is to investigate the effects of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive and functional decline in dementia, using a three phased KDD process. KDD, as a scientific way to process and analysis clinical data, is used to find useful insights from a variety of clinical databases. The data used are from three clinic databases: Geriatric Assessment Tool (GAT), the Doxycycline and Rifampin for Alzheimer's Disease (DARAD), and the Q*mci* validation databases, which were derived from several different geriatric clinics in Canada.

This research involves patients diagnosed with AD, vascular or mixed dementia only. Patients were included if baseline and end-point (at least six months apart) Standardised Mini-Mental State Examination (SMMSE), Quick Mild Cognitive Impairment (Q*mci*) or Activities Daily Living (ADL) scores were available. Basically, the rates of change are compared between patients taking CACE-Is, and those not currently treated with CACE-Is.

The results suggest that there is a statistically significant difference in the rate of decline in cognitive and functional scores between CACE-I and NoCACE-I patients. This research also validates that the Q*mci,* a new short assessment test, has potential to replace the current popular screening tests for cognition in the clinic and clinical trials.

CHAPTER 1 INTRODUCTION

"A lion doesn't concern himself with the opinion of a sheep."

1.1 Introduction

This chapter provides an overview of the PhD research[1]. It introduces the global realities of cognitive impairment, and the need to develop new treatments for CI (cognitive impairment), especially for the elderly. This chapter also presents a description of the objectives for this research. In order to better locate the objectives, three research questions are raised. Finally, this chapter concludes with a presentation of the publications based on this research, and introduces the subsequent chapters.

1.2 Global Realities of Cognitive Impairment

Cognitive impairment (CI), also called cognitive deficit, is an inclusive term to describe when a person has trouble learning, concentrating, remembering, or making decisions, that impact their daily life (Coren, 2003). It ranges from mild to severe. Mild cognitive impairment (MCI) is a clinical state of cognitive functioning, between age associated memory impairment and dementia (Chertkow, 2002). Petersen and colleagues (Petersen et al., 1999) characterised MCI as a certain degree memory impairment type, referred to as amnestic MCI in subsequent years. Most MCI patients progress to dementia, eventually. The symptoms of cognitive impairment include memory loss, frequently asking the same question or repeating the same story over and over, not recognising familiar people and places, changes in mood or behaviour, vision problems, trouble exercising judgment, difficulty planning and carrying out tasks (Petersen et al., 2001).

[1] This PhD study commenced in April 2011. The research is co-supervised through the Centre for Gerontology and Rehabilitation (CGR), within the School of Medicine, and Business information Systems, within the College of Business and Law in UCC.

CI is a global problem. Take Alzheimer's Disease (AD) as an example, the global prevalence of AD had raised to more than 35 million people in 2010, and was the seventh leading cause of death in the United States (Prince et al., 2013). The prevalence varies among many different factors, including age, co-morbidities, genetics, and education level. The treatment of dementia is also very expensive, for example, the global annual cost of dementia was estimated at US$315 billion in 2009 (Dartigues, 2009). In recent decades, the focus has been on the fact that dementia can lead to unemployment and financial worries for families (Allen et al., 2009). There is no way to definitively diagnose AD without performing an autopsy.

Dementia is defined as the significant loss of cognitive abilities severe enough to interfere with social functioning[2]. It can result from various diseases that cause damage to brain cells. There are many different types of dementia, each with its own cause and symptoms. AD is the most common form of dementia, caused by the build-up of beta amyloid plaques in the brain (Association, 2010).

At present, it appears that none of the disease-modifying drugs in development prevent or cure Alzheimer's (Mount and Downton, 2006). Donepezil, Galantamine, and Rivastigmine are cholinesterase inhibitors, and commonly used to treat dementia. They inhibit acetylcholinesterase, and increase the level of acetylcholine, which helps nerve cells communicate. These drugs may temporarily improve mental function in people with dementia, but do not slow the progression of dementia[3]. Another drug, Memantine, can be used with acetylcholinesterase inhibitors, although the research evidence is not convincing about the efficacy of this treatment, with some studies showing positive effects, while others contradict these findings (Reisberg et al., 2003). With this in mind, there will be a great need for a treatment of dementia in the coming years, to prevent or slow progress of dementia among the increasing number of dementia individuals.

[2] http://www.medterms.com/script/main/art.asp?articlekey=2940

[3] http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/delirium_and_dementia/dementia.html

Angiotensin Converting Enzyme Inhibitors, one of the first anti-hypertensives to be studied in dementia (Brunnström et al., 2009), may slow down the rate of decline in dementia (Sink et al., 2009). The goal in this research studies is to explore the effects of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive and functional decline in dementia patients using data analysis methods and techniques, to find a new approach to treat dementia.

1.3 Research Objectives and Questions

The impetus of this research was the growing evidence that centrally acting angiotensin-converting enzyme (ACE) inhibitors, which cross the blood-brain barrier, are associated with reduced rates of cognitive and functional decline in dementia, especially in Alzheimer's disease (AD). The objective of this research is "*to investigate the effects of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive and functional decline in dementia, using a three phased Knowledge Discovery in Databases (KDD) process*". This research also compares and validates the Quick Mild Cognitive Impairment (Q*mci*) test, a new and more efficient cognitive screening tool, as one of the key measures for cognition, with the other popular used screening tools, such as Standardised Mini-Mental State Examination (SMMSE) and Standardised Alzheimer's Disease Assessment Scale-Cognitive Subscale (SADAS-cog).

The findings of this research are based on the analysis of a variety of clinical databases from Canada. The data analysis is part of a three phased KDD process. Data are structured and warehoused in Oracle 11g. They are prepared by using Structured Query Language (SQL), and analysed using SPSS (Statistical Package for the Social Sciences) 18. The findings of this research not only focus on applying useful data analysis strategies and methods on geriatric clinical databases, but also have an even greater importance in obtaining interesting information to provide decision support to doctors and future academic research direction. This research raises the

following questions:

RQ1: *What are the key outcome instruments for measuring the rate of cognitive decline in dementia?*

RQ2: *What are the effects of centrally acting ACE-Is on reducing the rate of cognitive decline in dementia?*

RQ3: *What are the effects of centrally acting ACE-Is on reducing the rate of ADL (Activities of Daily Living) decline in dementia?*

The research questions that are central to achieving the research aim are identified and described in Table 1.1.

Table 1. 1 Research Questions Guiding this Study

Research Objective	*To investigate the effects of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive and functional decline in dementia, using a three phased Knowledge Discovery in Databases (KDD) process.*		
Research Questions	**RQ1**	**RQ2**	**RQ3**
Purpose (what?)	To define the key outcome instruments for measuring the rate of cognitive decline in dementia.	To prove that centrally acting ACE-Is may reduce the rate of cognitive decline in dementia.	To prove that centrally acting ACE-Is may reduce the rate of functional decline in dementia.
Motivation (why?)	1. To distinguish the memory loss types. 2. Reliable and more sensitive instruments are required. 3. Short instruments are required.	1. BP control is associated with rate of cognitive decline. 2. There is little data on the effects of CACE-Is on the rate of cognitive decline in dementia.	1. Hypertension may affect the risk of decline in ADL score in dementia. 2. Few studies have investigated whether ACE-Is affect ADLs
Results (How?)	1. Develop a short and simple instrument. 2. Enhance the properties of the test to differentiate NC from MCI. 3. Prove that Q*mci* strongly correlates with SADAS-cog. 4. Prove that Q*mci* has superior sensitivity and specificity for differentiating MCI from NC and dementia compared to the SMMSE, the ABCS 135, and MoCA.	1. Prove that the use of CACE-Is is associated with a reduced rate of cognitive decline in dementia. 2. Prove that cognitive scores may improve in the first six months after CACE-I treatment.	1. Prove that CACE-Is are associated with a reduced rate of functional decline in dementia. 2. Prove that CACE-Is may have more beneficial effects on instrumental ADLs. 3. Prove that patients taking perindopril had a significant reduction in rate of functional decline.

These research questions are answered below in order to satisfy the research objectives:

1.3.1 Research Question One

What are the key outcome instruments for measuring the rate of cognitive decline in dementia?

The purpose of this research question is to define the key outcome instruments for measuring the rate of cognitive decline in dementia. Screening instruments are required by clinicians to reliably diagnose MCI and differentiate between normal cognition, MCI, and dementia. Adults with memory loss present a challenge to clinicians, who must determine if the memory changes are part of normal aging, are consistent with mild cognitive impairment (MCI) or early dementia. MCI is characterised by a subjective decline in memory without a change in functional ability (Ivnik et al., 1992, Smith et al., 1996, Iqbal et al., 2003, Petersen, 2001). People with MCI typically complain of memory loss but have relatively normal general cognitive function. They maintain independence in instrumental activities of daily living (IADL) e.g. cooking, finances, driving and some can still function in their occupational activities. Since most patients with MCI go on to develop dementia (Morris et al., 2001), especially Alzheimer's disease, when people present with memory loss, it is important to differentiate between age associated memory impairment, MCI and dementia, as treatment choices differ. Meanwhile, researchers and clinicians require short instruments that are reliable, valid, and responsive to change across a wide range of cognitive function. They need multiple standardised scoring formats that measure changes early (high ceiling) and in the later stages of dementia (low floor) (O'Caoimh et al., 2013b).

The current instruments available to diagnose MCI, for example, the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (Rosen et al., 1984, Standish et al., 1996) and the Clinical Dementia

Rating (CDR) scale (Hughes et al., 1982), are not feasible for use by family doctors or other clinicians in the clinical setting because they take too long to administer. The Mini Mental State Examination (MMSE) (Folstein et al., 1975), a widely used screening test for cognitive impairment, is used primarily to screen patients with cognitive impairment to quantify cognitive deficits, identify dementia and follow cognitive progression over time. The Standardised Mini-Mental State Examination (SMMSE) (Molloy et al., 1991a, Molloy and Standish, 1997b, Mitchell, 2009) has explicit guidelines for administration and scoring and improved inter-rater reliability compared to the traditional MMSE. Although it is sufficiently specific for dementia, the SMMSE is less sensitive in distinguishing between normal cognition, MCI and dementia.

Under this situation, new instruments are required that have a higher ceiling and that are not as dependent on education. The AB Cognitive Screen 135 (ABCS 135) was developed to address this need (Molloy et al., 2005). The ABCS 135 is more sensitive in differentiating NC from dementia, and more importantly, MCI from dementia than the SMMSE. It is a short screening test, administered in 3–5 minutes. However, the subtests of orientation, registration and clock drawing in ABCS 135 did not enhance the discriminatory properties of the test in differentiating NC from MCI. For this reason, the Quick Mild Cognitive Impairment (Q*mci*) screen was developed to enhance the sensitivity of the ABCS 135.

The Quick Mild Cognitive Impairment screen (Q*mci*) is a new screening test for cognitive impairment (CI), that was developed as a rapid, valid and reliable tool (O'Caoimh et al., 2012a). It is scored out of 100 points and has a median administration time of four minutes (O'Caoimh et al., 2013a). The Q*mci* was derived from the ABCS 135 (Molloy et al., 2005, Standish et al., 2007), by reweighting its subtests and adding LM (O'Caoimh et al., 2012a). It has superior sensitivity and specificity for differentiating MCI from normal cognition and dementia compared to

the SMMSE, the ABCS 135 (O'Caoimh et al., 2012a), and MoCA (Montreal Cognitive Assessment). It also correlates with the standardised Alzheimer`s Disease Assessment Scale-cognitive section (SADAS-cog), Clinical Dementia Rating (CDR) scale and the Lawton-Brody activities of daily living scale (O'Caoimh et al., 2013b). In this research, as the widely use of SMMSE, we used both SMMSE and Q*mci*, as the key outcome instruments to measure the rate of cognitive decline in dementia.

1.3.2 Research Question Two

What are the effects of centrally acting ACE-Is on reducing the rate of cognitive decline in dementia?

The purpose of this question is to prove that centrally acting ACE-Is may reduce the rate of cognitive decline in dementia. ACE-Is were one of the first anti-hypertensives to be studied, particularly in AD, the most prevalent form of dementia (Brunnström et al., 2009). Blood pressure (BP) control is associated with both a reduced incidence of cognitive impairment (CI) and rate of cognitive decline (Whitmer et al., 2005). Independent of the BP lowering properties, ACE-Is affect the renin angiotensin system so they could reduce dementia risk (Kehoe and Passmore, 2012). Centrally acting ACE-Is (CACE-Is), a sub-group of ACE-Is, that cross the blood–brain barrier, may have a greater impact than those that do not.

Outside of clinical trials, there is little data on the effects of CACE-Is on the rate of cognitive decline in patients with dementia. Given this, we compared rates of cognitive decline between those taking CACE-Is, to those not currently receiving (NoCACE-I) and to those newly started (first six months) on CACE treatment (NewCACE-I), in patients with dementia, from the GAT (Geriatric Assessment Tool) database. Data were collected in memory clinics in two university hospitals in Ontario, Canada. The GAT database contains over 8,000 individual assessments

from 1,749 people, aged 41 to 104 years of age. Two cognitive screening tests, the Standardised Mini-Mental State Examination (SMMSE) and the Quick Mild Cognitive Impairment (Q*mci*) scores are used as the key cognitive measures for this research. Both tests were administered to patients by trained raters (clinic nurses), blind to the diagnosis, prior to each assessment to monitor progression. Only patients with AD, vascular or mixed dementias (Alzheimer's-vascular) were included in this analysis. Of these, patients were included if baseline and end-point (at least six months apart) SMMSE or Q*mci* screen scores were available. Change between baseline and end-point (last visit) scores were standardised at six months to facilitate comparison between all groups. The change scores were calculated as the formula: Rate of decline = (Baseline score – End-point score)/Duration in months.

The findings demonstrated that, there was a statistically significance difference, in the median, six-month, rate of decline in cognitive scores between CACE-I and NoCACE-I patients. There was a similar, non-significant change in SMMSE scores. For persons receiving NewCACE-Is, median SMMSE scores improved in the first six months of treatment compared to persons established on CACE-Is and NoCACE over the same period. These results suggest that cognitive scores may improve in the first six months of CACE-Is treatment and provide further evidence that use of CACE is associated with a reduction in the rate of deterioration in patients with dementia.

1.3.3 Research Question Three

What are the effects of centrally acting ACE-Is on reducing the rate of ADL (Activities of Daily Living) decline in dementia?

The purpose of this question is to prove that centrally acting ACE-Is may reduce the rate of functional decline in dementia. There is growing evidence shows that, impaired activities of daily living (ADL) affect functional independence and patient quality of life (Liu et al., 1991).

Hypertension may increase the risk of decline in IADLs (Instrumental ADL score) (Caskie et al., 2010) in patients with dementia (Stuck et al., 1999). Data from recent observational studies suggests that beta-blockers (Rosenberg et al., 2008a) may slow functional decline in patients with AD. However, few studies have investigated whether ACE-Is affect ADLs.

ACE-Is may slow functional decline by improving endothelial function, increasing muscle blood flow and reducing inflammation and glucose delivery to cardiac and skeletal muscle (Onder et al., 2002). Available evidence suggests that ACE-Is are associated with lower falls risk (Sumukadas et al., 2007, Wong et al., 2013), increase muscle strength (Sumukadas et al., 2007) and improve exercise tolerance (Sumukadas et al., 2007), in older adults with normal cognition. However, other observational studies suggest that exposure to ACE-Is is associated with increased dependency in ADLs (Sink et al., 2009), and studies investigating ACE genotypes, some of which might mimic or have comparable biological ACE activity to ACE-Is, had conflicting results on functional decline in older adults, with both increased (Seripa et al., 2011) and decreased disability (Kritchevsky et al., 2005) observed. Given this, we compared the rates of decline in patients with Alzheimer's disease (AD) receiving CACE-Is to those not currently treated with CACE-Is (NoCACE-I), in patients with mild to moderate AD, from the DARAD database. There were 406 patients in total, with mild to moderate AD in the DARAD database. All patients were aged 50 years or more. They were subdivided into a CACE-I group (patients currently prescribed centrally acting ACE-Is), and a NoCACE-I group not currently receiving CACE-Is, irrespective of BP readings, diagnosis of hypertension or receipt of other anti-hypertensives. The average 12-month rate of change in outcomes, measured as the difference between baseline and 12-month scores, were compared between patients receiving CACE-Is and the NoCACE-I group.

While few research studies have investigated if CACE-Is differentially affect IADLs or BADLs. Another study was undertaken to compare the rates of IADLs and BADLs decline, in older adults with established dementia, taking CACE-Is (CACE-I) and perindopril in particular, to those not currently prescribed CACE-Is (NoCACE-I). The CACE-I group were divided into two sub-groups: Perindopril and an 'other CACE-I' groups. Data in this study were pooled from the GAT and DARAD databases. The outcome measures analysed in this study were the SMMSE, Q*mci* and a shortened version of the Lawton-Brody ADL scale. Similar to the previous study, only patients with AD, vascular or mixed AD-vascular dementia, aged 50 years or more, were included. We compared differences in the rate of change in Q*mci*, SMMSE and ADL scores, from baseline (the time point when cognitive scores were first available) to end-point (the time point when cognitive scores were last available), between CACE-I, perindopril, other CACE-I and NoCACE-I groups.

The findings in these two studies showed that, there was a significant reduction in the rate of decline in total ADL scores in patients taking CACE-Is, compared to those who were not (NoCACE-I group). CACE-Is may have more beneficial effects on IADLs (Gao et al.). Patients taking perindopril had a significant reduction in their rate of decline in BADL scores compared to the NoCACE-I and other CACE-I groups. The results suggest that perindopril may be superior to other CACE-Is, with a relatively larger difference in median rates of functional decline over six months, compared to those not currently receiving CACE-Is.

1.4 Legitimisation of the Research Work

There were seven studies comprising this research study, five were published, and two were still in preparation. All of the studies were published in peer reviewed medical journals. Some of the studies, such as

"*CACE study in GAT database*", were published in a journal, and were also presented at a conference. Table 1.2 lists the studies, including their publications, current status for each publication, and the chapters in this thesis where they feature.

Table 1. 2 Publications Associated with this Research Study

Study names	Publication Reference	Status	Publication Output	Impact Factor (year)	Thesis Sections
Qmci vs SMMSE	(O'Caoimh et al., 2012a)	published	Age and Ageing	3.816 (2012)	Chapter Four: Q*mci*
	(O'Caoimh et al., 2012b)	published	Irish Journal of Medical Science	0.506 (2012)	Chapter Four: Q*mci*
Qmci subtests	(O'Caoimh et al., 2013a)	published	Age and Ageing	3.816 (2012)	Chapter Four: Q*mci*
Qmci vs SADAS	(O'Caoimh et al., 2013b)	published	Journal of Clinical Epidemiology	5.332 (2012)	Chapter Four: Q*mci*
Study One: *CACE study in GAT database*	(Gao et al., 2013a)	published	BMJ Open	1.583 (2013)	Chapter Five: Drug analysis
	(Gao et al., 2013b)	published	Irish Gerontological Society meeting 2013	N/A	Chapter Five: Drug analysis
Study Two: *CACE study in DARAD database*	(O'Caoimh et al., 2014)	published	Journal of Alzheimer's Disease	4.17 (2012)	Chapter Five: Drug analysis
Qmci cut offs	(O'Caoimh et al.)	In preparation	JAMA	29.978 (2012)	Chapter Four: Q*mci*
Study Three: *CACE study in GAT and DARAD databases combined*	(Gao et al.)	In preparation			Chapter Five: Drug analysis

The *Qmci vs SMMSE* study compares the sensitivity and specificity of the Q*mci* with the Standardised Mini-Mental State Examination (SMMSE) and ABCS 135 (AB Cognitive screen 135), in their ability to differentiate NC, MCI and dementia. The objective was to prove that, the Q*mci* is more sensitive than the SMMSE in differentiating MCI and NC, making it a useful test, for MCI in clinical practice, especially for older adults. The *Qmci subtests* study compares the sensitivity and specificity of the subtests of the Q*mci* to determine which best discriminated between NC, MCI and dementia. The aim was to determine the contribution each subtest of the Q*mci* makes, to its sensitivity and specificity, in differentiating MCI from NC and dementia, to refine and shorten the instrument. The *Qmci vs SADAS* study compared the Q*mci* screening test with the SADAS-cog (Standardised Alzheimer's Disease Assessment Scale-cognitive subscale) as outcome measures in clinical trials. The Q*mci* correlated strongly and significantly with the SADAS-cog. The results suggest that clinicians and investigators can substitute the shorter Q*mci* for the SADAS-cog. The *Qmci cut offs* study defined Q*mci* cut-off scores for patients with symptomatic memory loss, and determines the extent to which these require adjustment for age and education.

The *CACE study in GAT database* study compared the rates of cognitive decline in clinic patients with dementia receiving CACE-Is (CACE-I) with those not currently treated with CACE-Is (NoCACE-I), and with those who started CACE-Is, during their first six months of treatment (NewCACE-I). Data was extracted from the GAT (Geriatric Assessment Tool) database. The results suggest cognitive scores may improve in the first six months after CACE-I treatment, and use of CACE-Is is associated with a reduced rate of cognitive decline in patients with dementia.

The *CACE study in DARAD database* study compared rates of decline in patients with Alzheimer's disease (AD) receiving CACE-Is to NoCACE-I patients. The data were from the DARAD (Doxycycline and Rifampicin for Alzheimer's Disease) database. The findings found that CACE-Is, and perindopril in particular, are associated with a reduced rate of functional

decline in patients with AD, without associated changes in behaviour. The *CACE study in GAT and DARAD databases combined* study compared rates of cognitive and functional decline in patients with dementia receiving CACE-Is to NoCACE-I, using a combination of two research databases, namely the GAT and DARAD databases. This study found that CACE-Is are associated with a small but significant reduction in the rate of decline in ADLs, particularly instrumental ADLs, in dementia patients.

1.5 Overview of the Chapters

Chapter Two provides background by reviewing the prevalence and costs of dementia in geriatrics for treatment and health care. It introduces and defines dementia, specifically Alzheimer's Disease (AD), Vascular, mixed dementia and MCI (Mild Cognitive Impairment). The chapter concludes with an illustration of the treatment for different types of dementia, including the symptomatic pharmacological and non-pharmacological treatments.

Chapter Three conveys a better understanding of the research methodology for this research. It introduces Knowledge Discovery in Databases (KDD), statistics and data mining with regard to the associated technologies and relevant processes. This chapter illustrates the position of data analysis within the KDD process, and includes the innovation of knowledge discovery, KDD definition and process, and KDD application areas. Statistics and data mining technologies, which are the core step of the KDD process (data analysis), are introduced in this chapter. Three databases were used in this research: GAT, DARAD and Q*mci* validation databases. The key instruments in these databases are introduced as outcome measures. The last part of the chapter presents a comprehensive overview of the analytical methods, including how to conduct medical research which requires the use of data analysis (e.g. statistics) throughout the research process, and introduces the statistical methods used in this research across the various studies.

Chapter Four introduces the Quick Mild Cognitive Impairment Screen Test (Q*mci*), as one of the key outcome measures for the research. Firstly, it introduces the existing cognitive screening instruments. As a new rapid cognitive screening test, Q*mci* is more sensitive in differentiating NC from dementia, and more importantly, MCI from dementia than the SMMSE and Montreal Cognitive Assessment (MoCA). It is also correlated strongly with the SADAS-cog and both were equally responsive to deterioration. This chapter also discusses which subtests of Q*mci* discriminate best between normal, MCI and dementia. Finally, this chapter defines the Q*mci* cut off scores, and the cut off scores extent to which these require adjustment for age and education. The analysis demonstrating the scientific validity and utility of the Q*mci* is based on the KDD (Knowledge Discovery in Databases) process, and assessed by different statistical methods.

Chapter Five reviews the effects of centrally acting Angiotension Converting Enzyme Inhibitors (CACE-Is) on the rate of cognitive and ADL decline in patients with dementia. Data from two large geriatric medicine clinic databases (GAT and DARAD), were pooled together for the more robust outcomes. At first, this chapter discusses the association between anti-hypertensive agents, especially CACE-Is, and dementia (on cognition and function). Three studies were applied to compare the rates of cognitive and functional decline in clinic patients with dementia, receiving CACE-Is (CACE-I), to those not currently treated with CACE-Is (NoCACE-I). The first study (Study One) compares rates of cognitive decline in clinic patients with dementia, receiving CACE-Is (CACE-I group), to patients not prescribed CACE-Is (NoCACE-I group). The second study (Study Two) compares rates of functional and neuropsychological (depression and behaviour) decline in dementia, between CACE-I group and NoCACE-I group. The third study (Study Three) combines the two databases together. It looks at the effects of CACE-Is, especially perindopril, on the rates of basic ADLs (Activities Daily Living scores) and instrumental ADLs decline, in dementia.

Chapter Six summarises all the results and findings of the research. The chapter provides a brief overview of the studies, including published work based on the results of this research. Then the databases and outcome measures used in this research are presented. Contributions to practice and theory from the research work are discussed, with potential benefits of the studies. Finally, it concludes with recommendations for future work.

CHAPTER 2 BACKGROUND

2.1 Introduction

This chapter discusses the natural history of cognitive impairment (CI), including age associated memory loss, mild cognitive impairment (MCI), dementia and its subtypes. The prevalence, diagnosis, prognosis, treatment and impact, particularly the current use of anti-hypertensives in the prevention and management of disease progression are discussed.

Dementia is a term for the loss in mental ability that is severe enough to interfere with the person's ability to perform his/her activities of daily living (ADL). It affects a wide range of cognitive functions, including memory, attention, language, and problem solving. Dementia normally occurs in people aged over 60 and has a 5% - 7% prevalence of case in society in most world regions (Prince et al., 2013). As populations age worldwide, the prevalence of dementia will increase. Dementia is however, not a single disease, but a syndrome that includes many different subtypes, each with distinct signs and symptoms. Symptoms are generally present for at least six month before a diagnosis can be made[4]. To date, no agents have been developed that prevent, modify or reverse dementia, and available treatments for dementia are predominantly symptomatic.

2.2 Prevalence of Dementia

In both the developed and developing world, populations are ageing. A report from the Department of Economic and Social Affairs in the United Nations in 2002 stated that, population ageing is an "unprecedented" situation, in the history of humanity[5]. In most European and North American societies, population aging is occurring because of three demographic

[4] http://www.mdguidelines.com/%20dementia/definition
[5] http://www.un.org/esa/population/publications/worldageing19502050/

trends — a change from high fertility, high mortality rates in Phase One of agricultural societies, to relatively high fertility but low mortality rates in Phase Two of industrialised societies, to the final stage of low fertility and low mortality rates of the post-industrial era (Moody, 2006, Chu, 1997, Zhan, 2013). There is also an increase in dependency ratios, with a smaller percentage of workers supporting a greater number of people in retirement. It will in addition, directly impact upon economic growth. This demographic trend is accelerating since the middle of the last century (Uhlenberg, 2013).

By 2050, the number of people aged 60 and above will rise to 1.25 billion, and will account for 22 percent of the total world population (Prince et al., 2013). This rise will cause an increase in the prevalence on dementia. The rising numbers have prompted governments to start specific strategies to handle the crisis. The probability of developing dementia doubles every five years after the age of 60, such that those over 60 have a prevalence of between five and eight percent. As age is the greatest risk factor for dementia, the prevalence of dementia increases to between 18 to 30 percent among those aged over 80 (depending on the geographical region). In people aged over 85 years or older, the prevalence on dementia increases to about 30% (Salloway et al., 2008). Combining this demographic shift with the increasing prevalence of dementia, means that the number of people with dementia will double every twenty years (Prince et al., 2013).

Dementia is a general term, to describe any progressive neurodegenerative condition that results in loss of cognitive and functional ability, and in the end causes a loss of independence (Korczyn et al., 2012). The disease not only affects patients and their loved ones, but also impacts upon society and governments.

In Canada, where the data analysed as part of this work originated, similar demographic trends are evident. In 2011, 747,000 Canadians had cognitive impairment, representing 14.9 percent of Canadians aged 65 and above. By

2031 that number is expected to reach 1.4 million people[6]. In the United States of America, 4.7 million individuals over 65 years had AD dementia in 2010; the number with dementia is expected to increase to 13.8 million by 2050 (Hebert et al., 2013a).

2.3 Cost of Dementia

One of the problems associated with the increased prevalence of dementia is the growing associated economic cost. This financial burden takes a toll on governments and families. It is difficult to accurately estimate the cost of dementia. Dementia seldom comes alone, but is often associated with other diseases. Family provide up to 80% of care, a phenomenon called "informal" care. There is little accurate data on the extent of informal care provided or the direct and indirect costs of such care (e.g. loss of work due to caring duties) (Hurd et al., 2013). The total estimated worldwide costs of dementia were 422 billion dollars in 2009, an increase of 34 percent from 2005, a figure equivalent to one percent of the global gross domestic product. The greatest increase in costs were found in developing countries (Wimo et al., 2010). A recent study from the USA found that annual costs attributed exclusively to dementia were estimated at between 41,000 to 56,000 dollars per case. The biggest portion of these costs (75 to 84 percent) can be attributed to nursing care, followed by the cost of medical treatment. The cost of dementia care is one of the biggest contributions to societal financial burden (109 billion annually in the US) and dementia costs were significantly higher than the direct societal costs of other conditions including cancer (77 billion) and heart disease (102 billion) (Hurd et al., 2013).

6 http://www.alzheimer.ca/en/niagara/Get-involved/Raise-your-voice/A-new-way-of-looking-at-dementia

2.4 Dementia, AD, Vascular, Mixed Dementia and MCI

The onset of dementia is slow and usually takes several years (depending on the type of dementia) before it is recognised and/or diagnosed. In the early stages, it often goes unrecognised as there is enormous variation in presentation and the first signs are subtle. Furthermore, the first warning signs (e.g. forgetfulness, change in personality, misplacing things) are often wrongly associated with other factors (e.g. stress or age) and not every doctor is trained to detect these important warning signs (Gauthier et al., 2006).

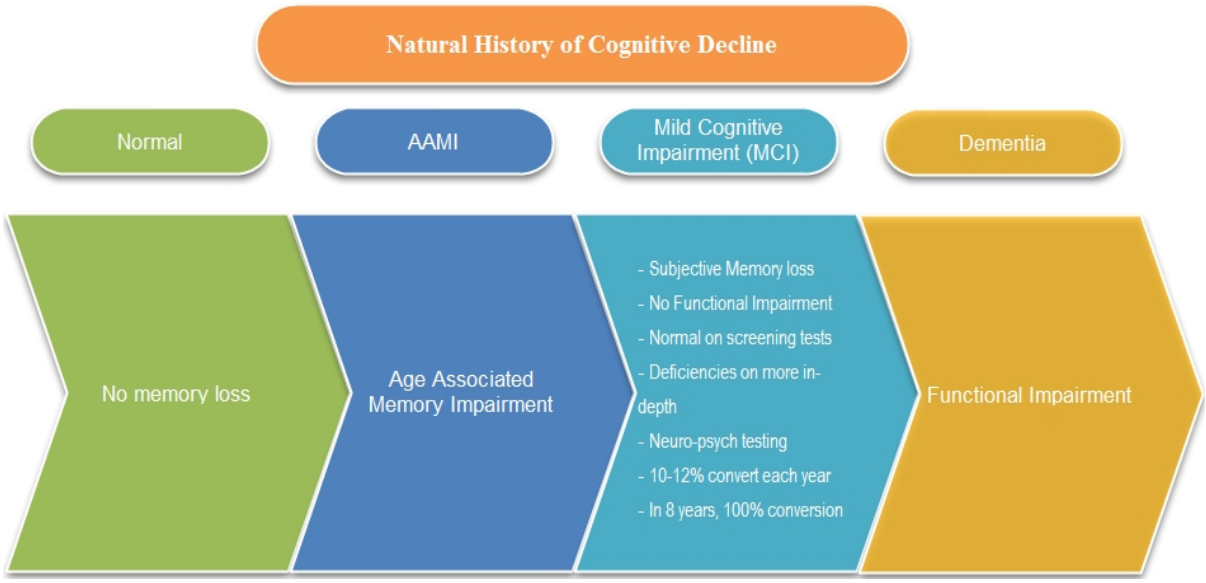


Figure 2. 1 Natural History of Cognitive Decline

Figure 2.1 demonstrates the natural history of cognitive decline. The first stage occurs as people are getting older, and is associated with normal age appropriate memory loss (Christensen, 2001). As we age, neuronal cell loss develops. This is "Age Associated Memory Impairment" (AAMI) (Crook et al., 1986, O'Brien and Levy, 1992). The next stage is Mild Cognitive Impairment (MCI), a common condition that has been recognised as a prodrome to dementia (Morris et al., 2001).

2.4.1 Mild Cognitive Impairment (MCI)

MCI is regarded as a precursor of dementia, and is defined as the presence of greater cognitive decline than would be expected for an individual at a particular age, with an educational level. People with MCI continue to function independently and by definition have no functional impairment. People with dementia differ in that they usually have more significant cognitive deficits and present with impairment in activities of daily functioning (Gauthier et al., 2006). The chance of developing Alzheimer's disease (AD), the most common dementia subtype, after a diagnosis of MCI, is 11-33% over the next two years (Ritchie, 2004). Using the same clinical criteria and taking into account the medical history of memory loss, the progression rate can rise from 41% after one year to 64% after two years (Geslani et al., 2005). Thus, on average, 10-12 % of patients with MCI convert to dementia each year (Bowen et al., 1997, Tierney et al., 1996a, Tierney et al., 1996b). If followed over a prolonged period of time, almost all will develop dementia within eight years of diagnosis (Morris et al., 2001).

To diagnose patients correctly with MCI, it is necessary to distinguish between normal aging and dementia. As MCI progresses, the risk of getting a prompt diagnosis of dementia provides an opportunity to initiate treatment early. People with MCI typically complain of memory loss, but have relatively normal general cognitive function. They maintain independence in instrumental activities of daily living (IADL), e.g. cooking, finances, and driving, and some can still function in their occupational activities. Typically, a history of memory loss for persons with MCI is corroborated by family members (Molloy et al., 2005). If MCI can be reliably diagnosed, it may be possible to start interventions that could prevent progression and conversion to dementia. Short and simple clinical screening tools to differentiate MCI from normal cognition and (or) early dementia, facilitate diagnosis (Molloy et al., 2005). A number of these have been developed and are discussed in detail below.

2.4.2 Types of Dementia

Dementia can broadly be divided into two different types; cortical and sub-cortical dementia. Cortical dementia only affects the outer layers of the cortex. The most common types are AD and Creutzfeld-Jacob Dementia[7]. The symptoms generally include short-term memory loss, difficulty with word recall and understanding the meaning of words (aphasia). Subcortical dementia, on the other hand, affects the structures below the cortex. Examples include Parkinson's disease dementia (PDD) and vascular dementia (VaD). Symptoms are different to the cortical dementias, with early personality change and slowing in executive and motor function, while language and memory are relatively well preserved in the initial stages. Figure 2.2 shows the distribution of the different types of dementia. A description of the three most common forms and those included in the analysis: AD, VaD and mixed (AD-VaD) dementia, is provided below.

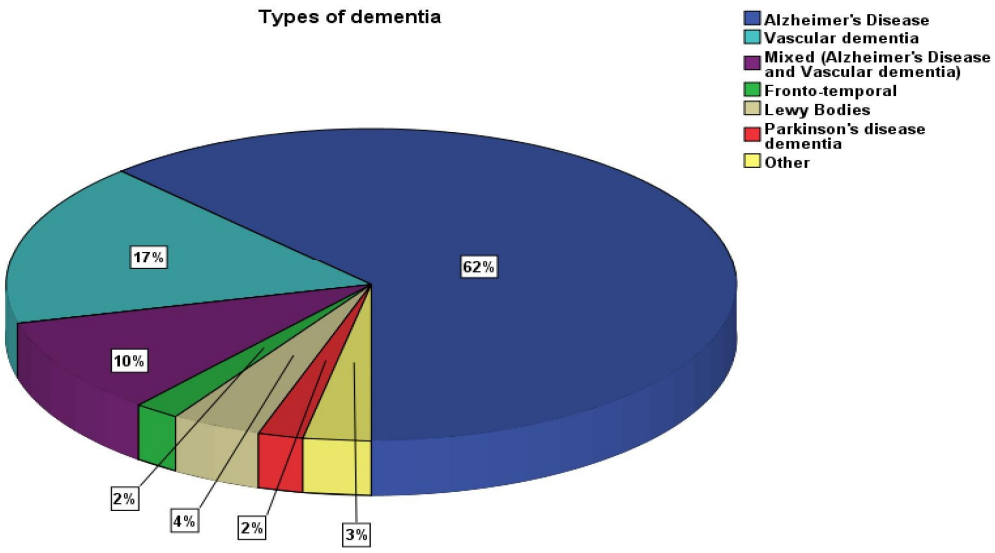


Figure 2. 2 Types of Dementia

[7] http://alzheimers.about.com/od/typesofdementia/a/cortical_sub.htm

2.4.2.1 Alzheimer's Disease (AD)

The most common form of dementia is AD, accounting for up to 50 percent of all dementia cases (Prince et al., 2013). AD is a cortical dementia, characterised by degeneration of brain tissue and a progressive loss of mental functions[8].

Symptoms of the disease progress to a point where the patient is totally dependent on the care of others. In the early stages, people find it more difficult to remember certain words and to think abstractly. Insomnia, not being able to sleep, and a change in the normal behaviour are also often early signs. As the disease progresses, it becomes difficult to remember recent events (short term memory loss). Normal day-to-day activities are increasingly difficult and require help from others. About half of patients develop a psychosis, paranoia, delusions and/or hallucinations at some point during the condition. By the end-stage of AD, patients usually cannot walk, eat or talk anymore and need full-time care. Once this stage is reached, most people die within some months[9]. The exact progression is unpredictable and there is a wide variation in the course of the disease, with an average duration of six to twelve years (Brodaty et al., 2012). The disease is typically diagnosed by a physician, who assesses the symptoms, described by the patient and his/her caregivers, performs a physical examination and cognitive testing with short screening tests such as the Standardised Mini-Mental State Examination (SMMSE). Usually Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI) scans and blood tests are performed to support the clinical diagnosis and rule out an alternative cause. A definite diagnosis of dementia can only be confirmed after death, with an analysis of brain tissue.

[8] http://alzheimers.about.com/od/typesofdementia/a/cortical_sub.htm

[9] http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/delirium_and_dementia/dementia.html

2.4.2.2 Vascular Dementia (VaD)

VaD is the second most common form of dementia (Prince et al., 2013), and frequently co-exists with AD. This condition is called mixed dementia. Patients with VaD have neuronal degeneration caused by progressive ischaemic secondary to a reduced or blocked cerebral blood supply. A series of strokes, large or small, can cause VaD. As small, micro thromboembolic strokes are not always clinically evident, VaD can develop silently (Korczyn et al., 2012). Unlike AD, where the progression is gradual, VaD can worsen suddenly or remain stable for a long time. The symptoms of VaD are similar to AD, but generally it does not affect speech and memory to the same extent. It is characterised by a change of personality and a slowing of thought processes. The symptoms vary depending on where the stroke occurred in the brain, and can lead to comorbid symptoms, including loss of vision, paralysis of arms or legs and/or depression[10]. Due to a higher comorbidity profile, patients with VaD may have more rapid progression with a lower mean survival time, five years compared to seven years for AD (Korczyn et al., 2012). The diagnosis of VaD is made in those with symptoms of dementia, with prominent cardiovascular risk factors and the presence of stroke or stroke like symptoms. While cerebral ischeamic changes, ranging from small vessel disease to large vessel territory strokes, can be seen on CT or MRI, the diagnosis is never definitive during life.

2.4.2.3 Mixed Dementia

When the symptoms signs and pathology of both VaD and AD occur together this is referred to as "mixed" dementia. A definite diagnosis of mixed dementia is difficult due, on the one hand, to unclear diagnostic criteria for the disease and, on the other hand, a need to do a post mortem examination. The fact that an autopsy is necessary to confirm the diagnosis, makes it hard to estimate the exact prevalence and incidence. Mixed dementia is much more common than was previously realised, as autopsy

10 http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/delirium_and_dementia/dementia.html

studies have shown a prevalence, as high as 54% of cases, suffering from dementia (Langa et al., 2004). As with VaD, it might be possible to prevent the disease by diminishing the vascular risk factors and preventing strokes. Current treatment for mixed dementia uses the same drug therapy as AD, including memantine and cholinesterase inhibitors (donepezil, galantamine and rivastigmine)[11].

2.4.3 Who is at Risk from Dementia

Table 2. 1 Risk Factors for Vascular Dementia and Alzheimer's Disease (after: Korczyn et al., 2012)

Risk factors for both VaD and AD	**Risk factors for AD**
Age	Female gender
Midlife diabetes mellitus	
Midlife hypertension	
Coronary artery disease	
Midlife hypercholesterolaemia	Apolipoprotein E status
High dietary saturated fat and cholesterol	Head trauma
Hyperhomocysteinaemia	
Obesity	
Metabolic syndrome	
Arteriosclerosis	
Smoking	
Poor education	

Table 2.1 shows the risk factors that contribute to dementia. There is overlap between the risk factors of VaD and AD. In recent years, there is growing recognition that VaD and AD may not be two separate entitles, but share a lot of disease pathology (Korczyn et al., 2012).

11 http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/delirium_and_dementia/dementia.html

In general, age remains the strongest risk factor for dementia. Most cases of AD are seen in older adults, ages 65 years or above. Between the ages of 65 and 74, approximately 5% of people have AD. For those over 85, the risk increases to 30-50%. While the onset usually starts after 65 years, there are rare cases of early-onset AD, starting as early as 30, that account for about 5% of all AD cases. The exact cause of sporadic AD is unclear, while young onset AD is usually familial (Finckh et al., 2000).

There may be a connection between educational level and the risk of developing AD. People with fewer years of education seem to be at higher risk (Association, 2010). The exact cause for this relationship is unknown, but it is theorised that a higher education level leads to the formation of more synaptic connections in the brain. This creates a "synaptic reserve" in the brain, enabling patients to compensate for the loss of neurons as the disease progresses.

There are also several modifiable risk factors for dementia. Type two diabetes mellitus, in midlife, and the presence of strokes have been found to increase the chance of AD and VaD (Patterson et al., 2007). Higher levels of cholesterol during midlife also increases the risk of AD and VaD (Patterson et al., 2007), as well as coronary artery disease (arteriosclerosis) (Korczyn et al., 2012). When it comes to lifestyle and diet, drinking moderate amounts of red wine and eating fish and seafood both are preventive, while a diet full of saturated fats can increase the chance of developing dementia (Patterson et al., 2007). Physical activity, especially during later stages of the life helps delay/prevent AD, possibly because it lowers the rate of obesity, which is a risk factor in itself (Cheng et al., 2013). Spending a longer time in formal education (more than 15 years compared to 12 years) decreases the chance for VaD and AD (Patterson et al., 2007). Smoking may increase the chance of dementia, even though this is debated in the literature (Patterson et al., 2007).

Looking exclusively at AD, females are at a greater risk of developing the disease such that over a lifetime 16% of women will develop AD compared

to only six percent of men of the same age. The presence of apolipoprotein (APO) E2 gene protects against the development of AD, while APOE4 increase the chance of dementia (Launer et al., 1999). Head trauma also contributes to the development of AD, especially in the presence of the APOE4 gene (Patterson et al., 2007).

2.5 Treatment of Dementia

Treatment of dementia can broadly be divided into pharmacological and non-pharmacological management.

2.5.1 Pharmacological

2.5.1.1 Drugs for Symptomatic Control

Medications in the treatment of dementia can be divided into two groups, one targeting disease progression, the other targeting symptoms[12].

Cholinesterase inhibitors and N-Methyl D-Aspartamate receptor (NMDA) antagonists are the two most widely used medications that target the symptoms of dementia. The currently available cholinesterase inhibitors are donepezil, galantamine and rivastigmine. These drugs increase the level of the neurotransmitter acetylcholine in the brain. The effectiveness of the drugs varies between patients, with up to one-third of patients having no benefit. In addition, side-effects are common, including nausea, weight loss and worsening confusion. NMDA-antagonists, like memantine are used in later stages of the disease and can be used in combination with the cholinesterase inhibitors (Qaseem et al., 2008).

Antipsychotic drugs (like haloperidol, aripiprazole, risperidone or quetiapine) are used to manage the behavioural and psychological symptoms of dementia (BPSD) such as agitation, delusions, hallucinations

12 http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/delirium_and_dementia/dementia.html

and aggression, especially in the later stages of the disease. These however, increase stoke risk and should be used with caution (Douglas and Smeeth, 2008). Anticonvulsants (like gabapentin or carbamazepine) may also be used as mood stabilisers. Their effectiveness however is unclear and individual non-pharmacological treatments should be used first (Qaseem et al., 2008).

Dietary supplements, such as vitamin B12 pills, lecithin or ginkgo biloba extracts have been tried extensively in previous years, but have little value in treating dementia[13].

2.5.1.2 Disease Modifying Drugs

The fact that Alzheimer's takes so long to develop suggests that, it may be possible to design drugs that work early in the disease process, to delay symptom onset and disability[14]. For that reason, researchers have been testing a number of "disease-modifying" drugs that target the earliest biological changes in Alzheimer's. However, to date, there is no cure for dementia and few disease modifying drug treatments have been developed to manage dementia patients.

Studies have revealed that the two hallmark brain lesions in Alzheimer's — amyloid deposits and intracellular neurofibrillary tangles (NFTs) — appear decades before telltale clinical symptoms such as memory impairment. The production of Aβ, which is a crucial step in AD pathogenesis, is the result of cleavage of APP (Griffin, 2006). Aβ forms highly insoluble and proteolysis-resistant fibrils known as senile plaques. NFTs are composed of the tau protein (Galimberti and Scarpini, 2011). Tau is relatively abundant in neurons, but is present in all nucleated cells and functions physiologically to bind microtubules and stabilise microtubule assembly for polymerisation.

---

[13] http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/delirium_and_dementia/dementia.html

[14] http://www.health.harvard.edu/newsweek/Disease-modifying-drugs-for-Alzheimers.htm

The disease-modifying drugs, in development, target much earlier biological abnormalities, especially the sequence of events that contribute to the development of amyloid plaques. Plaque formation begins when a brain protein, amyloid precursor protein (APP), is broken down into peptides by various enzymes, known as secretases. The plaques consist of several forms of beta-amyloid peptides, some relatively benign, others more toxic.

Usually the most toxic beta-amyloid peptide, Aβ42, makes up less than 5% of beta-amyloid load in the brain. However, a combination of genetic and environmental factors may tip the balance toward greater Aβ42 production. According to a leading theory about Alzheimer's (Wang et al., 2012), these sets of biological events will lead to buildup of toxic beta-amyloid plaque around neurons, which effect memory and cognition.

The disease-modifying drugs in development work in different ways, but all seek either to decrease production of toxic beta-amyloid peptides or to prevent them from accumulating in the brain. The ultimate aim is to find whether — by blocking plaque — these drugs can delay cognitive or functional decline in people with Alzheimer's.

The treatment of a dementia depends on the type of dementia the patient has. For example, a patient with vascular dementia will be treated to control cerebrovascular risk factors, such as high blood pressure and elevated cholesterol levels. Alzheimer's disease, the most common form of dementia, can be treated using drugs like acetylcholinesterase inhibitors that increase acetylcholine. There are four main acetylcholinesterase inhibitors on the market – donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), and tacrine (Cognex) (Farlow, 2002). These drugs are used for AD and mixed dementias. Donepezil is now also approved for severe AD. Tacrine was the first drug approved for AD in 1993, but it is rarely used, due to hepatotoxicity (Galimberti and Scarpini, 2011). However, those drugs only slightly alleviate symptoms, and do nothing significant to prevent

disease progression[15].

A fifth drug used for treating Alzheimer's disease (usually in moderate to severe stages) is Memantine. Memantine is different than the other group of drugs. It works by blocking glutamate, which is produced in excessive amounts in brain cells damaged by Alzheimer's disease. Memantine can be used with acetylcholinesterase inhibitors, although the research evidence is not convincing about the efficacy of this treatment with some studies yet, showing positive side effects while others contradict these findings (Reisberg et al., 2003).

2.5.1.2.1 Drugs Interfering with Aβ Deposition

- **Gamma-secretase Inhibitors**

LY450139 is a Gamma-secretase inhibitor for the treatment of Alzheimer's disease (Henley et al., 2009). However, LY450139 and other nonselective agents may cause serious side effects that would counterbalance any benefit for people with Alzheimer's (Bergmans and De Strooper, 2010). Some researchers believe that more selective gamma-secretase inhibitors, in early development, may prove to be better options as disease modifiers (Van Dam and De Deyn, 2006). Selective Aβ42-lowering agents specifically lower Aβ42 levels in the brain. The first drug in this class to reach late-stage testing is tarenflurbil (Flurizan). The drug modulates gamma-secretase activity by shifting production away from Aβ42, without interfering with other proteins.

- **Anti-aggregation Agent**

The most studied anti-amyloid aggregation agent is tramiprosate (AlzhemedTM, Neurochem Inc.) (Wright, 2006). Tramiprosate (Alzhemed) prevents Aβ42 peptides from sticking together (one theory being that this is the stage at which they become particularly toxic). Although a phase II study generated optimism, researchers announced at the Alzheimer's Association International Conference on Prevention of

[15] http://www.health.harvard.edu/newsweek/Disease-modifying-drugs-for-Alzheimers.htm

Dementia in June 2007 (Sullivan, 2007), that results of a phase III study were hard to interpret. At the time of writing this thesis, nothing has been published about it yet.

- **Vaccines**

A few safer Alzheimer's vaccines are under development. One agent, bapineuzumab, a monoclonal antibody, targets and clears beta-amyloid. In Europe, 30 participants are also undergoing brain scans to determine whether the drug is clearing amyloid plaque deposits[16]. A phase III study has not yet started. Another passive immunisation agent, intravenous immunoglobulin, is in phase II trials for Alzheimer's. Because this substance is already FDA-approved to treat people with immune deficiencies, its safety profile is well known. Whether it will be effective as a disease modifying agent in Alzheimer's, remains to be seen. Researchers are hopeful, however, because intravenous immunoglobulin has both anti-amyloid and anti-inflammatory properties, that may be helpful in Alzheimer's.

2.5.1.2.2 Drugs Interfering with Tau Deposition

By 2050 there will be 600 million people with significant tau pathology but not all with AD (Woodward, 2012). Anti-tau therapy could have widespread application for those affected, including people with AD, some frontotemporal lobar degenerations and mild cognitive impairment (Gong et al., 2010). Tau immunotherapy has not progressed beyond animal models, but it appears promising and human trials are starting. A tau-blocking compound, named methylthioninium chloride (MTC), is being tested (TauRx Therapeutics, RemberTM). MTC interferes with tau aggregation by acting on self-aggregating truncated tau fragments (Wischik et al., 1996). A phase III trial was planned, but the reformulation needs to be studied further.

Several phosphorylation inhibitors, as well as drugs that dephosphorylate tau, have been developed. None have undergone extensive human testing.

[16] http://www.health.harvard.edu/newsweek/Disease-modifying-drugs-for-Alzheimers.htm

Lithium and memantine affect tau phosphorylation, but have not yet shown convincing disease-modifying effects. Metformin induces tau phosphatase 2A activity, but has not been trialed as a specific dementia therapy (Woodward, 2012).

2.5.2 Non-pharmacological Treatment

Since drug treatments have not proved particularly beneficial and carry the risk of side effects, non-pharmacological treatments are an important adjunct. Exercise can improve quality of life, although the effectiveness of this intervention is not yet proven. Review papers show mixed results with little consistent evidence for or against particular intervention strategies (Kurz, 2013, O'Neil et al., 2011). The problem is that most studies are poorly designed, with small sample sizes or no control groups, making it difficult to determine if the success of the intervention is because of a increased attention on the patient. The research interventions are also usually individually-designed, making it hard to compare the effects universally and create practical guidelines (Kurz, 2013).

Interventions can be divided into five main categories:

- treatments to enhance cognitive performance,
- to enhance well-being,
- to improve behavioural symptoms,
- to improve activities of daily living
- give support to patients (Kurz, 2013).

There is increased evidence for greater effectiveness when combining two or more interventions together (Karp et al., 2006). Focusing on cognitive performance, there is evidence for a slower rate of decline and a decreased risk of dementia when elderly patients do cognitive exercises on a regular basis (Cheng et al., 2013). The most effective treatments to improve the well being of patients with dementia seem to be activity-therapy and reminiscence-therapy. Activity-therapy methods stimulating activities in their every day life, include activities such as baking, going for walks or going shopping etc (Kurz, 2013). Reminiscence therapy includes activities

specifically talking about events from the past or listening to music that may trigger memories, or writing a biography.

For the management of the BPSD there is evidence that stimulation-oriented approaches (e.g. massage therapy, aroma therapy and light therapy) are more beneficial than emotional approaches (e.g. animal therapy and stimulated care). Exercise therapy, in itself, has not been evaluated in clinical trials; however there is evidence that regular exercise increases sleeping time and decrease the risk of falls (O'Neil et al., 2011). It increases the quality of life for patients with dementia and provides opportunities for caregivers and their families to receive training on how to deal with the demands of caring for a family member with dementia (Kurz, 2013). In summary, it can be concluded that there are some benefit to non-pharmacological treatments, although a greater evidence base needs to be established.

2.6 Summary

This chapter describes the background of dementia and its early stage (MCI), including the prevalence, risk factors, costs and treatment. Dementia is not a single disease, but instead a group of diseases or, in some cases, injury, that can cause a change in a person's intellect, thinking skills, such as memory or language, personality or social behaviour. People will often equate dementia with Alzheimer's Disease, but Alzheimer's is just one type of dementia. The onset and course of dementia is dependent upon the type of disease causing the symptoms. Some dementias are progressive and primarily managed by changes the environment; others can be medically treated and reversed.

Patients with dementia use more healthcare services and typically require more expensive care. Using AD as an example, AD progresses gradually and can last for decades. There are three main stages of the disease, each with its own challenges and symptoms. By identifying the current stage of the disease, physicians can predict what symptoms can be expected in the future and possible courses of treatment. Each case of AD presents with a

unique set of symptoms, varying in severity.

For most dementias, there is no cure, but there are treatments available to help slow the progression of disease. Changes to the patient's environment are essential in the management of depression. Maintenance of a healthy active lifestyle is also important. One of the main aims of this PhD research is to examine the effect of a specific treatment, centrally acting angiotensin converting enzyme inhibitors (CACE-Is) in the management of CI and on the rate of cognitive, functional and neuropsychological decline in patients with dementia.

CHAPTER 3 RESEARCH METHODOLOGY: CLINICAL DATASETS AND METHODS OF ANALYSIS

3.1 Introduction

The purpose of this chapter is to introduce the KDD (Knowledge Discovery in Databases) process, and data analysis techniques used in this research, with regard to the associated technologies and relevant processes. The first section describes how KDD can be used to analyse data, while further examining the role that data analysis plays in the KDD process. The second section explains the principle of data analysis, and the relationship between statistics and data mining. The third section describes the three geriatric clinical databases, including the clinical characteristics of the patients that populate these databases, used as the data source for this PhD research. It also discusses the outcome measures used to assess the rate of cognitive and functional decline. The last section details the data analysis techniques used to examine these databases.

3.2 Knowledge Discovery

3.2.1 Principles of Knowledge Discovery

In knowledge discovery, it is important to understand the overall approach, before one attempts to extract useful knowledge from data (Klösgen and Zytkow, 2002). Simply applying any algorithms or models for data analysis is not sufficient for a successful project/study (Elo and Kyngäs, 2008). Discovering knowledge should meet the following principles:

- The outputs must be useful for the user/owner of the data. The ultimate result leads to the success of a project/study. Only the application with a well-defined process model will at the end of a project/study be valid, useful, traceable, and understandable (Cios et al., 1998).
- A well-defined knowledge discovery model should have a logical structure, which can be described to decision makers, in order for them

to understand the need and value behind information (Matheus et al., 1993).

- Knowledge discovery projects should include careful planning and scheduling, instead of directly running a model on the data, especially data from the real world (Peng et al., 2008).

A widely used and well-known framework, called KDD (Knowledge Discovery in Databases) (c.f. Fayyad et al., 1996b), is often applied to formalise the process model. It has attracted a great deal of attention in the information industry, due to the need for turning large amounts of data into useful information and knowledge.

3.2.2 KDD (Knowledge Discovery in Databases) Definition

Today, data is being collected and accumulated at a dramatic pace, across a wide variety of fields, where it is stored in many different kinds of databases and information repositories. There is an urgent need for a new generation of techniques to assist people to extract useful information from these databases. In order to do this, it is important to follow a theoretical and systematic process. Knowledge Discovery in Database (KDD) refers to the broad multi-step process of finding knowledge in data, and emphasises the high-level application of particular data manipulation and data mining methods (Piatetsky-Shapiro, 1991). It provides scientific ways to extract implicit, previously unknown, and potentially useful information from raw data (Fayyad et al., 1996d). Knowledge discovery uses data mining, statistical and machine learning techniques that have evolved through a synergy in artificial intelligence, computer science, statistics, and other related fields (Mitchell, 1997). The overall goal of the KDD process is to extract knowledge from data in the context of large databases.

One of the most popular KDD definitions is: "*the nontrivial process of identifying valid, novel, potentially useful, and ultimately understandable patterns in data*" (Fayyad et al., 1996a) (p. 30). It has been widely applied to problems across many areas, for example, health care (c.f. Abbott, 2000).

3.2.3 KDD Process

The KDD process is interactive and iterative, involving numerous steps with many decisions made by the user. It is an evolutionary process, with its own lifecycle and is a means to an end, not an end in and of itself (Holmes, 2014). Numerous tools exist for this endeavor, many coming from statistics and data mining. The overall KDD process (Figure 3.1) includes the evaluation and possible interpretation of the "mined" patterns to determine which patterns may be considered "new knowledge".

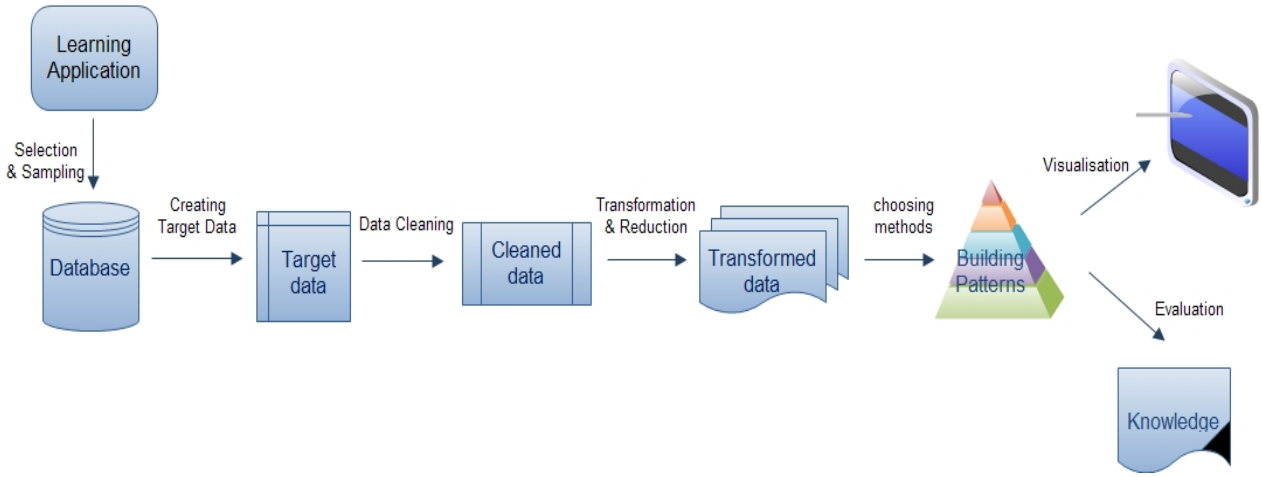


Figure 3. 1 The General KDD Process (after: Fayyad et al., 1996b)

The KDD process is best understood in three phases – *the process before data analysis*, *data analysis* and *the process after data analysis*. Han *et al*. (Han and Kamber, 2001) and Tan *et al*. (Tan, 2007) named the phase before data analysis with a more generic term – *Data Pre-processing*. It gathers all the necessary preparation steps before data analysis, including *Data Cleaning*, *Data Integration*, *Data Selection* and *Data Transformation*. Similarly, they called the phase after data analysis - *Data Post-processing*, as it includes *Visualisation* and *Pattern Evaluation*. While various researchers use these various terms in their studies, all of the sub-steps can be summarised into the three main phases (see Table 3.1).

Table 3. 1 Various Representations of the KDD Process

KDD main phases / References	Data pre-processing					Data analysis		Data post-processing			No. of Citations
(Fayyad et al., 1996a)	Learning Application	Data Selection and sampling	Creating a target dataset	Data cleaning	Data reduction and transformation	Choosing methods	Applying models	Visualisation	Pattern Evaluation		5,778
(Han and Kamber, 2001)		Data integration	Concept generation	Data Cleaning	Data reduction	Data mining		Data presentation			20,676
(Cios et al., 2007)	Business understanding	Data understanding		Data preparation		Modeling			Evaluation	Deployment	9
(Renu et al., 2013)		Splitting Algorithm	Obtain primary object types		Conversion Algorithm	Data mining			Evaluation		1

Even though there are different ways to describe the KDD process, some steps within a phase can be merged, based on project and requirements, for example, in *data pre-processing*, data cleaning and data reduction can both be forged together, and called data preparation (c.f. Cios et al., 2007). This merging activity illustrates the flexibility of the KDD process, but this discussion is outside the scope of this research. We use Fayyad's (Fayyad et al., 1996a) model as an example to introduce the KDD steps. The model consists of nine steps, which are outlined in Table 3.2.

Table 3. 2 The Phases in the Knowledge Discovery in Databases (KDD) Process (after: Fayyad et al., 1996a)

Phases	Steps	Description
Data pre-processing	Learning application	Includes relevant prior knowledge and the goals of the application.
	Data selection and sampling	Where data relevant to the analysis task are retrieved from the database.
	Creating a target dataset	Includes selecting a dataset or focusing on a subset of variables or data samples on which discovery is to be performed.
	Data cleaning	Includes basic operations, such as removing noise or outliers if appropriate, collecting the necessary information to model or account for noise, deciding on strategies for handling missing data fields, and accounting for time sequence information and known changes. Finally, a few more issues need to be decided, such as data types, schema, and mapping of missing and unknown values.
	Data reduction and transformation	Includes finding useful features to represent the data and using dimensional reduction or transformation methods to reduce the effective number of variables under consideration or to find invariant representations for the data.
Data analysis	Choosing methods	Includes selecting method(s) to be used for searching for patterns in the data, such as deciding which models and parameters may be appropriate and matching a particular data analysis techniques with the overall criteria of the KDD process (e.g., the user may be more interested in understanding the model than in its predictive capabilities).
	Applying models	An essential process where intelligent methods are applied in order to extract data patterns, including statistics, data mining and machine learning methods.
Data post-processing	Visualisation	Interpreting the discovered patterns and possibly returning to any of the previous steps, as well as possible visualisation of the extracted patterns, removing redundant or irrelevant patterns, and translating the useful ones into terms understandable by the users.
	Pattern Evaluation	To identify the truly interesting patterns representing knowledge. Pattern evaluation incorporates knowledge into the performance system, taking actions based on the information obtained, or simply documenting it and reporting it to interested parties, as well as checking for and resolving potential conflicts with previously extracted knowledge.

As can be seen in Table 3.2, the first five steps comprise the pre-processing phase, the steps of choosing the data analysis model and applying models represent the data analysis phase. The KDD process can involve iteration and/or loops between any two steps (Tan, 2007). The data analysis step may interact with the user or a knowledge base. The relevant patterns are presented to the user, and may be stored as new knowledge (Han and Kamber, 2001). Overall, the largest effort involved and the most important

phase in KDD processing is data analysis.

In summary, the KDD process involves using the database along with any required selection, cleaning, sampling, and transformations of it; applying data analysis methods (algorithms) to enumerate patterns from it; and evaluating the outcome (models) to identify the subset of the enumerated patterns deemed knowledge. Data analysis is the core phase in KDD, which consists of applying different methods (i.e. statistics or data mining) that, under acceptable computational efficiency limitations, produce a particular enumeration of patterns (or models) over the data. The next section will introduce the relationships between statistics and data mining in this data analysis phase.

3.3 Data Analysis

Data analysis is about looking for patterns (Fayyad et al., 1996c). There is nothing new about this – people have been seeking patterns for thousands of years (Ellis, 1993). Farmers try to find patterns when growing crops, hunters seek patterns in animal behaviour, and parents watch for patterns in their children, etc. Similarly, a data scientist discovers the patterns from real world data, and encapsulates these in theories that can be used for predicting what will happen in new situations. Today, vast amounts of data is being collected and warehoused, such as web/e-commerce data, purchasing items in stores, bank/credit card transactions and so on. These trends are broadly known as ‘big data’, and new software, technology and tools are needed to cope with the high volume, variety, and velocity of this big data (Howe et al., 2008). Data mining, as one of the most popular technologies, is about solving problems by analysing data already present in databases (Witten and Frank, 2005).

3.3.1 Statistics as Data Mining Methods

In theory, KDD refers to the overall process of discovering useful knowledge from data. As shown in Table 3.1, data mining is one of the steps in the knowledge discovery process, included in the data analysis phase, and involves the extraction of hidden information from a dataset. It is a broad field that combines techniques from different areas in computer science and statistics (Chakrabarti et al., 2004). This term is used mainly by statisticians, database researchers, and more recently by Information Systems (IS) and business communities (Fayyad et al., 1996b). Data mining assists data analysts with finding patterns and relationships in the data (Edelstein, 1999), however, it does not tell people the value of the patterns to the organisation. Furthermore, the patterns uncovered by data mining must be verified in the real world (Edelstein, 1999).

In general, data mining methods can be divided into two categories: *descriptive* and *predictive* (Han et al., 2006). *Descriptive* mining tasks characterise the general properties of the data in the database. It includes Classification, Regression and Deviation, etc. *Predictive* mining tasks perform inference on the current data in order to make predictions. It includes Clustering, the Association Rule and Sequential Patterns, etc (see Figure 3.2).

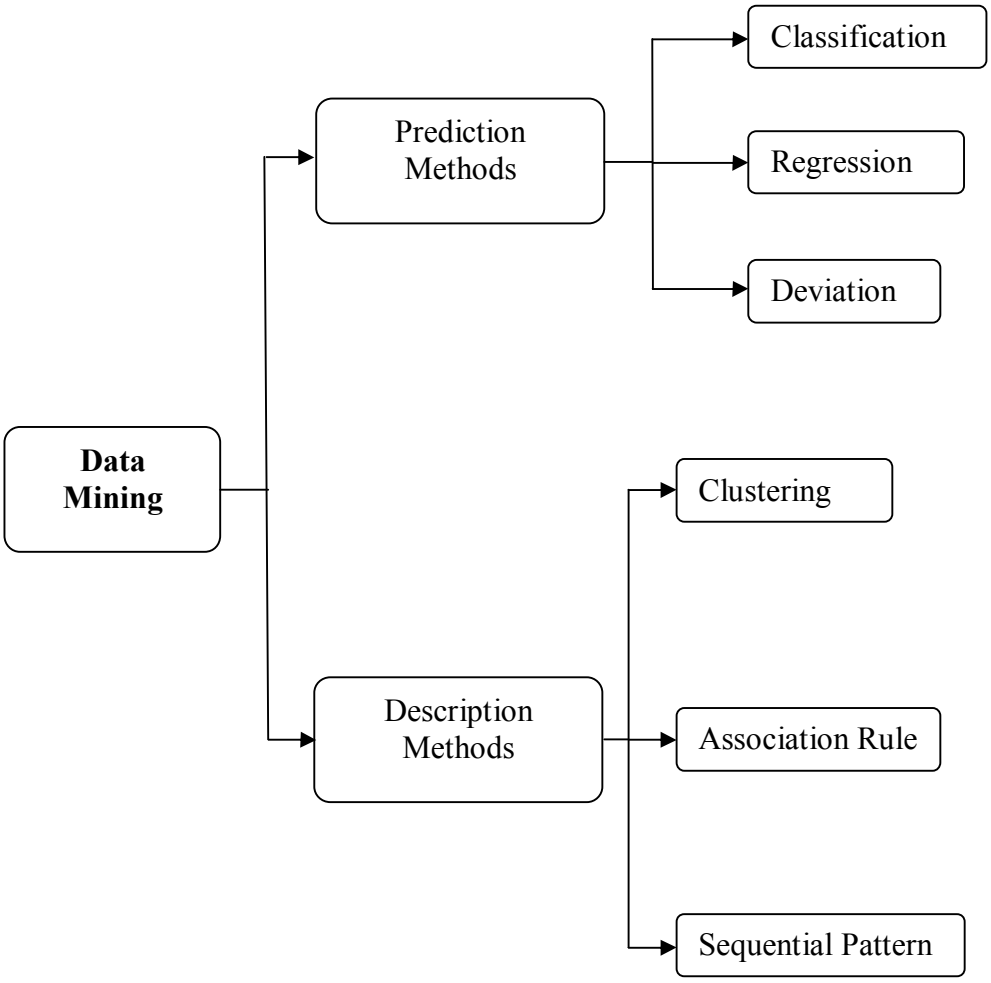


Figure 3. 2 Data Mining Categories (source: Han et al., 2006)

Prediction Methods use some variables to predict unknown or future values of other variables (Tan, 2007). *Classification* maps a data item into one of the predefined classes (Srivathsa, 2011). Classification problems aim to identify the characteristics that indicate the group to which each case belongs. This pattern can be used both to understand the existing data and to predict how new instances will behave. *Regression* analysis is a statistical method that is most often used for numeric prediction (Han et al., 2006). It predicts a value of a given continuous variable based on the other variables, assuming a linear or nonlinear model of dependency. *Deviation Detection* is also known as *Anomaly Detection*. It also detects significant deviations from normal behaviour (Tan, 2007). The overall goal is to discover all objects that are different from the others.

Descriptive models are the "unsupervised learning" functions (Larose, 2006). These functions do not predict a target value, but focus more on the intrinsic structure, relations, interconnectedness, etc. of the data. The aim is to find human-interpretable patterns that describe the data (Tan, 2007). *Clustering* techniques apply when there is no class to be predicted but rather when the instances are to be divided into natural groups (Witten and Frank, 2005). Mining base on the *Association Rule* finds interesting associations and/or correlation relationships among large sets of data items (Rajak and Gupta, 2008). To find the rules, it needs to execute the rule-induction procedure for every possible combination of attributes, with every possible combination of values. Hence, a single association rule often predicts the value of more than one attribute (Witten and Frank, 2005). *Sequential Pattern Discovery* is essentially a time-ordered association (Tan, 2007). It is the process of extracting previously unknown, valid, and understandable information from large databases.

However, some statistical methods are considered part of data mining (Hill and Lewicki, 2006). Some, like statistical prediction methods of different types of regressions and correlation analysis, are now considered as an integral part of data mining research and applications (Piatetsky-Shapiro et al., 1996). Another example, comparing classifiers based on ROC curves are statistical methods, but also belong to Evaluation of Classification, a type of classification method, in data mining (Chakrabarti et al., 2004).

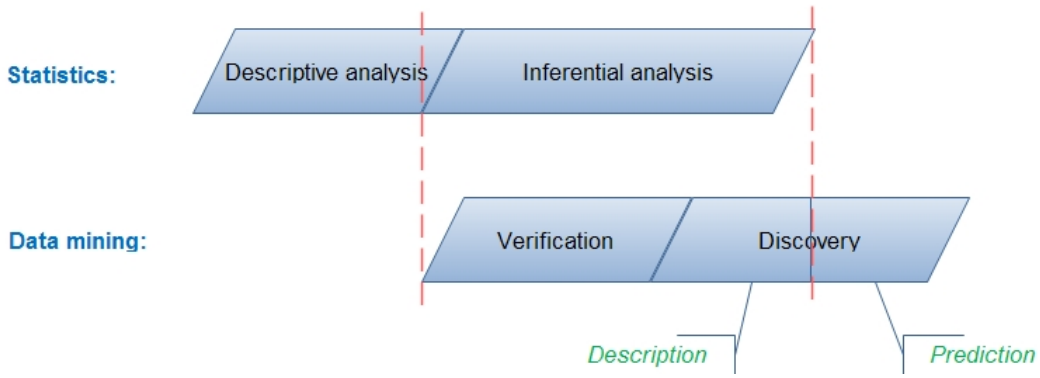


Figure 3. 3 Statistics and Data Mining Tasks

It can be argued that in the strictest sense, the definition of "statistics" and their techniques are not data mining. However, as shown in Figure 3.3, statistics consist of two main parts, *descriptive* and *inferential* analysis. The methodology for organising and summarising the data for the sample is called descriptive statistics. When these summaries are attempted to be used in order to draw conclusions about an entire population, the employment is called statistical inference (Anderson, 1996).

Furthermore, the primary goal of data mining is verification and discovery (Xiao, 1998). Like statistics, the data mining verification goal is designed to confirm the user's hypothesis. Data mining of a discovery goal is designed to automatically find new patterns for the user. The discovery goal can be further subdivided into *prediction*, where the system finds patterns for the purpose of predicting future behaviour of some entities; and *description*, where the system finds patterns to present them to a user in a human-understandable form.

In summary, due to the complexity of the stored data, and of the data interrelations, in the context of data mining, description tends to be more important than prediction. That means that data mining techniques are usually not used without the use of statistics, however, data mining discovers more than statistics does. Statistics emphasise descriptive analysis more than data mining, and they are at the core of data mining - helping to distinguish between random noise and significant findings, and providing a theory for estimating probabilities of predictions, etc (Piatetsky-Shapiro et al., 1996).

3.3.2 Data Analysis in the Medical Area

The medical area is a knowledge-intensive domain, in which neither data gathering nor data analysis can be successful without using knowledge on both the problem domain and the data analysis process. Over the last few years, the term "knowledge discovery" has been more and more used in medical literature (Prather et al., 1997, Bellazzi and Zupan, 2008, Epstein,

2010). This means the usefulness of integrating data analysis with decision support techniques (Mallach, 2000, Mladenic, 2003) to promote the construction of effective decision criteria and models supporting decision making and planning in public heath care.

In 2008, a survey was conducted by KDnuggets.com[17], one of the most influential data mining and KDD websites in the world. See Figure 3.4. The most popular method in the medical area was Regression.

Biotech/ Medical:	
1	Regression/ Forecasting
2	Clustering/ Segmentation
3	Classification
4	Association rules
5	Time sequences

Figure 3. 4 The Top Five Most Popular Methods in Biotech/Medical in 2008

Table 3.3 and 3.4 present the results of a literature review exploring the types of data analysis techniques most frequently used in the medical area. In total 49 articles were reviewed, and 26 were considered applicable to this research. All of the articles are in the medical/bioinformatics area and using Knowledge Discovery in Databases or data mining techniques. They were randomly selected by referring to concepts, like "KDD in medical" or "data mining in health care", in their titles and abstracts. However, some of the articles were excluded as they were not an appropriate fit for this research. For example, in some instances, they were borrowing the technical terminology instead of actually using data analysis techniques. In some instances, they were just reporting on the analytical tools they developed, and didn't mention which methods the tools supported.

[17] http://www.kdnuggets.com/polls/2007/analysis_applications_more_in_2008.htm

Data mining methods have been widely applied in medical and bioinformatics area. See Table 3.3. The data mining methods in these studies were used individually or combined with other methods. For example, Khan *et al.* (Khan et al., 2008) only used decision trees, a data mining model, in an oral medicine study (study number 12); yet Ferreira *et al.* (Ferreira et al., 2012) used data mining methods (decision trees and Naïve Bayes), and statistical methods (ROC curves, Chi-square test and diagnostic tests) to improve diagnosis in neonatal jaundice (study number 5). There are six studies that applied the KDD process, and data mining methods are used in all of these six studies. Overall, there were 18 studies (70%) combining data mining and statistical methods. It means that, in data analysis, statistics are closely used with data mining methods. In these 18 studies, data were described by using statistical methods, during the knowledge discovery process. Thus, we could note that data mining can learn from statistics – to a large extent, statistics is fundamental to what data mining is really trying to achieve. It is also worth mentioning that this literature reviewed focuses on generic research studies, which means that these data analysis methods could be applied in different areas of medical and bio-informatics research.

Table 3. 3 Data Mining and Statistical Methods in Medical and Bioinformatics Research

Study No.	Authors	Area of Research	Contribution Focus	Data Mining Methods	Statistical methods	KDD study
1	(Tsumoto et al., 2013)	Improvement of hospital management	clinic manager	√		
2	(Hebert et al., 2013)	AD prevalence	geriatrician	√	√	
3	(Wong et al., 2013)	Cardiovascular medications	geriatrician and pharmacist	√	√	
4	(Hajjar et al., 2012)	Drug analysis in dementia	geriatrician and pharmacist	√	√	
5	(Ferreira et al., 2012)	Diagnosis in neonatal	clinical practitioners	√	√	
6	(Gagliardi, 2011)	Knowledge extraction	diagnostic practitioners	√	√	√
7	(Zhang et al., 2011)	Cognitive impairment	geriatrician	√	√	
8	(Dong et al., 2011a)	Drug analysis in dementia	geriatrician and pharmacist	√	√	
9	(Chen and Herskovits, 2010)	Dementia	geriatrician	√	√	
10	(Smith et al., 2009)	Cancer	cancer researcher	√	√	
11	(Sink et al., 2009)	Drug analysis in dementia	geriatrician and pharmacist	√	√	
12	(Khan et al., 2008)	Oral medicine	pharmacist	√		
13	(Mullins et al., 2006)	Introduce a new DM approach	clinical researchers	√		
14	(Inza et al., 2004)	Gene selection	bioinformatician	√		
15	(Robles et al., 2004)	Protein research	bioinformatician	√	√	
16	(Weber et al., 2004)	Analysis of gene expression	bioinformatician	√	√	
17	(Roy Walker et al., 2004)	Dementia	geriatrician and bioinformatician	√	√	
18	(Tan et al., 2003)	Improvement of clinical practice	clinical practitioners	√		√
19	(Goodwin et al., 2003)	Preterm birth risk	nursing practitioner	√		√
20	(Lee and Abbott, 2003)	Knowledge discovery for nurse researchers	nurse practitioner	√	√	√
21	(Mitnitski et al., 2003)	Dementia	geriatrician	√	√	√
22	(Ganzert et al., 2002)	Respiratory treatment	clinical practitioners	√	√	
23	(Tsumoto, 2000)	Knowledge discovery and evaluation	outpatient clinic	√		
24	(Lavrac et al., 2000)	Intelligent analytical methods	physicians	√		√
25	(Tierney et al., 1997)	Mortality risk	clinical practitioners	√	√	
26	(Standish et al., 1996)	Cognitive screen test	geriatrician	√	√	
Sum				**26**	**18**	**6**

Table 3. 4 Data Mining and Statistical Method Types in Medical and Bioinformatics Research

Article No.	Data Mining Methods		Statistical Methods				
	Predictive mining	Descriptive mining	Regression	Diagnostic tests	Chi-square test	ROC curves	Comparing tests
1		√					
2	√		√				
3	√		√		√		
4	√		√		√		
5	√			√	√	√	
6	√			√			
7	√			√		√	
8	√		√				√
9	√		√				
10	√			√			
11	√		√				√
12	√						
13	√						
14	√	√					
15	√			√			√
16	√		√				
17		√					√
18	√						
19	√						
20	√			√		√	
21	√				√		
22	√		√			√	
23		√					
24	√	√					
25	√		√			√	
26	√					√	√
Sum	**23**	**5**	**9**	**6**	**4**	**6**	**5**

Of the 26 articles selected, most of the medical studies (n=23) were using predictive mining methods, 88%, and five studies used description methods (19%). See Table 3.4. Also two studies used both prediction and description methods. For those studies using predictive mining methods, there were 14 studies using a variety of classification methods, and nine studies using regression analysis. Classification methods are getting more and more popular in medical research. Decision Trees and Bayesian analysis were often used as the classification methods. Of these, Decision Trees were always combined with other data mining methods, such as Naïve Bayes or neural networks etc. Regression analysis is the most popular statistical method (n=9) in these studies. This literature review confirmed the survey results from KDnuggets, that regression was the most frequently used data analysis method in the medical area. Additionally, there were ten geriatrics studies in the literature reviewed, which were focused on dementia. All of them were using both data mining and statistical methods, as shown in Table 3.3. The most popular data mining/statistical method was also regression. Thus, regression analysis is a key analytical method in this type of research.

However, no matter how much data mining is applied in medical research, statistics, especially biostatistics (called medical statistics in UK), has played an integral role in modern medicine in everything from analysing data to determining if a treatment will work to developing clinical trials. Virtually any medical research study uses biostatistics from beginning to end. It becomes the foundation of data analysis in medical research. The University of North Carolina's Gillings School of Global Public Health defines biostatistics as "*the science of obtaining, analysing and interpreting data in order to understand and improve human health*"[18]. Statistics help researchers make sense of all the data collected to decide whether a treatment is working or to find factors that contribute to diseases. This research study will apply a variety of data analysis methods, especially statistical methods, some of which were used as data mining methods, to build models and discover useful information from clinical databases. For

[18] http://sph.unc.edu/bios/biostatistics/

example, multivariate regression analysis was used to compare end point cognitive and functional scores. The next section will list the data sources used in this research – the three main databases and their key instruments, and how they were used in each study.

3.4 Clinical Databases

3.4.1 Introduction

For the purpose of this research, the data came from three clinical databases: the Geriatric Assessment Tool (GAT), the Doxycycline and Rifampin for Alzheimer's Disease (DARAD), and the Q*mci* Validation databases. These data were collected from a variety of geriatric medicine clinics or trials in Canada. This section introduces these databases, including their background, uses, the variables, and patients' baseline demographics.

Table 3. 5 The Research Studies Using the GAT, DARAD and Q*mci* Validation Databases

Database name / Studies	GAT	DARAD	Q*mci* Validation
Q*mci* cut offs	√	√	√
Q*mci* subtests			√
Q*mci* vs SMMSE			√
Q*mci* vs SADAS		√	
CACE study in GAT database	√		
CACE study in DARAD database		√	
CACE study in GAT and DARAD databases combined	√	√	

Table 3.5 demonstrates how the three databases were used in different studies for this research. The GAT database was used in the Q*mci* cut offs study along with the DARAD and the Q*mci* Validation databases for a greater sample size. The GAT was also used in comparing the rate of cognitive decline between patients taking CACE-Is (Centrally Acting Angiotensin Converting Enzyme Inhibitors) and those not currently treated with CACE-Is. Combined with the DARAD database, those data were used to study the effect of CACE-Is on the rate of cognitive and ADL (activities of daily living) decline. The DARAD database was used in the Q*mci* cut offs, and Q*mci* versus SADAS studies. It was also used in finding the differences in the rate of ADL decline between CACE-I and NoCACE-I patients. Combined with the GAT database, the DARAD database was used in comparing the rate of cognitive and ADL decline for patients taking different CACE-I drugs. The data from the Q*mci* Validation database was used in the Q*mci* cut offs, Q*mci* subtests, and Q*mci* versus SMMSE studies.

3.4.2 The Geriatric Assessment Tool (GAT) Database

3.4.2.1 Overview of the GAT Database

The GAT is a customised web-based software application that automates a clinician's entire outpatient review, summarising the findings in a discharge letter and recording data in a database. GAT data were collected in outpatient geriatric medicine clinics in two university hospitals in Ontario, Canada between 1999 and 2010. The database contains over 8,000 individual assessments from 1,749 people, aged 41 to 104 years of age. Of these, 1,728 people have diagnosis recorded. It manages patients, assessment visits, medications, caregivers, doctors, users and automates the doctor's Geriatric Clinic. Specifically, the GAT records patient visits, manages patient records, schedules appointments, manages doctor records, manages caregiver records, administers staff, prints consultations (eliminating the need for dictation), records potential study candidates, billing and more.

This database contains observational data, collected in a “real world” setting, where treatments were administered on the basis of clinical judgment. It includes basic demographic data (age, gender, educational level, medical conditions, diagnosis and laboratory findings etc.) and in the case of subjects suspected of having memory loss, the results of two cognitive screening tests, the Standardised Mini-Mental State Examination (SMMSE) (Molloy et al., 1991a) and the Quick Mild Cognitive Impairment screen (Q*mci*) (O'Caoimh et al., 2012a, Molloy et al., 2005). Both tests were administered to patients by trained raters (clinic nurses), blind to the diagnosis, and prior to each assessment to monitor progression. A Quick Activities of Daily Living Score (Q*adl*) test is also available in GAT, for patients assessed from 2001 to 2009.

The GAT database includes patients with possible or probable AD, VaD, mixed dementia (AD-VaD), Lewy Body Dementia (LBD), frontotemporal dementia (FTD), Parkinson Disease (PDD), normal cognition (NC), MCI, patients with depression (with and without comorbid CI), alcohol, post-traumatic dementia (PTD), PTD with depression, and post anaesthesia dementia (PAD). The majority of the dementia patients in the GAT database have AD, vascular and mixed dementia. The distribution of these diagnoses is shown in Figure 3.5. In this research, AD, vascular and mixed dementia were included (yellow tagged in Figure 3.5), as they have the similar symptoms. Although the database contains data on patients with a wide variety of dementia subtypes, only individuals with subjective memory loss, such as possible or probable Alzheimer’s Disease (AD), vascular and mixed dementia subtypes were included in this analysis, as those diagnoses have similar symptoms.

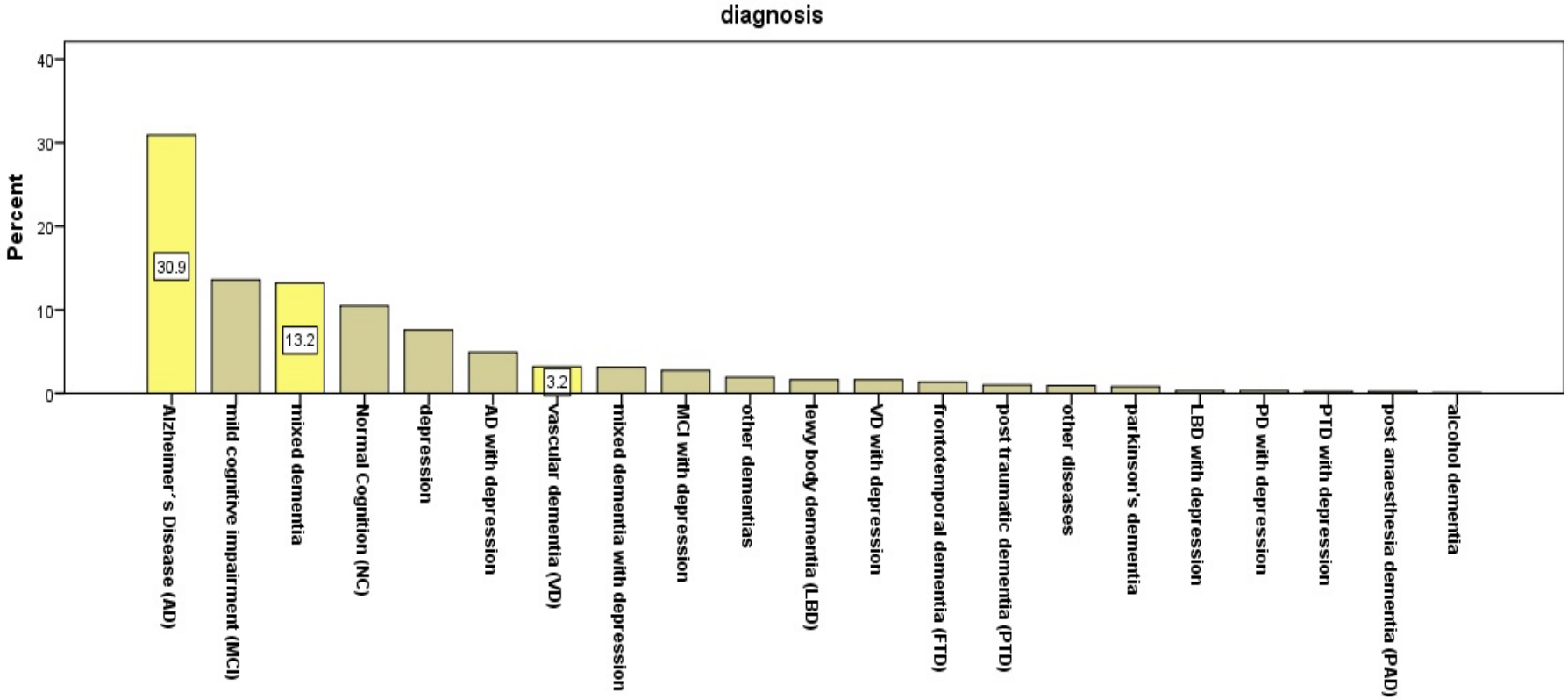


Figure 3. 5 Distribution of Diagnoses in the GAT Database

3.4.2.2 Demographics of Patients in the GAT Database

Each subject included in the GAT database underwent a comprehensive work-up, including physical history, examination and laboratory investigations, and each was diagnosed as having either NC, MCI or dementia with or without comorbid depression. Dementia was diagnosed by a consultant physician using National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (McKhann et al., 1984) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (Association and DSM-IV., 1994). MCI was defined by clinical criteria where subjects presented with subjective and corroborated memory loss, without loss of function. The results of cognitive testing were not used to confirm the diagnosis. Controls were subjects presenting with subjective memory loss with NC. Depression was also diagnosed clinically and screened using the Geriatric Depression Scale (score > 7) (Brink et al., 1982).

Table 3. 6 Baseline Demographics and Outcome Measure Scores for GAT Patients

	Total	Dementia	MCI	Normal	Depression
Number	1728	817	235	181	137
Age (mean ± SD)	75.3 ±9.8	77.9 ±8.1	74.7 ±9.3	73.9 ±10.3	68.9 ±11.3
Male (%)	46.7%	50.3%	48.5%	47.2%	29.4%
Education (mean ± SD)	11.4 ±4.1	10.9 ±4.0	11.4 ±4.2	13.3 ±4.3	12.5 ±4.1
Systolic BP in mmHg (mean ± SD)	133.3 ±17.7	133.7 ±17.9	135.6 ±19.2	131.5 ±14.4	133.1 ±19.3
Diastolic BP in mmHg (mean ± SD)	71.6 ±10.8	71.8 ±11.0	72.0 ±10.2	71.5 ±10.7	71.1 ±10.6
SMMSE median baseline score (IQR)	25 (7)	22 (7)	28 (3)	29 (2)	29 (3)
Q*mci* median baseline score (IQR)	49 (27)	38 (22)	57 (15)	69 (18)	64 (18)
Q*adl* median baseline score (IQR)	4 (15)	10 (19)	0 (2)	0 (9.5)	2 (4)

Table 3.6 shows the baseline characteristics and outcome measure scores, for patients included from 1,728 total patient numbers and divided according to diagnosis. There was no significant difference on age, gender, education, blood pressure in dementia, MCI, normal and depression groups. SMMSE and Q*mci*, the cognitive outcome measures, are scored out of 30 and 100 respectively, with higher scores suggesting greater cognition. The functional outcome measure, Q*adl* (Quick activities of daily living test), is scored out of 90, with higher scores suggesting worse independence.

3.4.3 The Doxycycline and Rifampin for Alzheimer's Disease (DARAD) Trial Database

3.4.3.1 Overview of the DARAD Database

The DARAD was a multi-centre, blinded, randomised, 2x2 factorial control trial conducted in Canada between 2006 and 2010. The DARAD database included subjects with mild to moderate AD, recruited from 14 Canadian centres, including Toronto, Hamilton, Halifax and Edmonton, on the basis of National Institute of Neurological and Communicative Disorders and Stroke criteria. All patients were aged over or equal to 50 years old, Standardised Mini-Mental State Examination (SMMSE) score from 14 to 26, having sufficient English literacy to complete standardised testing, and having a consenting caregiver to monitor the patient and report on their behaviour. These subjects received detailed work-up and had cognitive assessments performed every three months for one year (Molloy et al., 2012).

The original objective of the DARAD trial was to compare two antibiotics, rifampacin and doxycycline to placebo, over a one-year period. Cognition, function, mood and behaviour were scored. The primary outcomes were a measure of cognition, the SADAS-cog (Standish et al., 1996) and a measure of global function – the Clinical Dementia Rating (CDR) (Hughes et al., 1982). Secondary outcomes included the Standardised Mini-mental State Examination (SMMSE) (Molloy et al., 1991a), Quick Mild Cognitive Impairment Test (Q*mci*) (Molloy et al., 2005, O'Caoimh et al., 2012a), activities of daily living (ADL) function measured by the Lawton Scale (Self-maintenance, 1969), behaviour measured by the Dysfunctionsal Behaviour Rating Scale (Molloy et al., 1991b), the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988), and depression measured by Geriatric Depression Scale (Yesavage et al., 1983, Shiekh and Yesavage, 1986). The DBRI has two sub-tests, behavioural frequency and difficulty/response (DBRIF and DBRIR). These tests are described briefly in Section 3.5.

The SADAS-cog, CDR-SB, Q*mci*, Lawton-Brody ADL Scale and DBRI scores were available at one, three, six, nine and twelve months (end-point). The SMMSE score was recorded at screening and end-point, the GDS score at baseline and end-point and the CSDD score at baseline, six-months and end-point only.

3.4.3.2 Patients Demographics in DARAD

An initial power calculation estimated that 500 patients would be sufficient to detect a three points difference in the SADAS-cog with significance level 0.05, assuming a standard deviation of change of 9.8, allowing for 10% dropout. In total, 406 patients with mild to moderate AD (SMMSE scores between 14 and 26) were included in the DARAD study, conducted from 2006 to 2010. All patients were aged 50 years or more, and met the National Institute of Neurological Disorders and Stroke (NINCDS) criteria for AD. Not all the patients took all the nine tests. Patients were stratified on centre, age, gender, SMMSE score, use of cholinesterase inhibitors, site and NMDA agonists, using a computer randomisation programme. Patients returned for interval assessment at three, six, nine and twelve months and were contacted by phone once per month.

Physical exams and laboratory screening were carried out and patient/caregiver reports were elicited at each visit to monitor patient safety. Adverse events (AE) were assessed at each visit by asking the patient and caregiver about any sickness or untoward physical event the patient had experienced since the previous visit. When patients reported adverse events, the local investigator assessed the probability of the relationship of the AE to the study medication based on the patient's medical history, family reports, the chronology related to the study and the known safety profiles of doxycycline and rifampin. The investigator made this determination blinded to the treatment allocation. Serious adverse events (deaths, hospitalisations, cancer, etc.) were reported to the local research ethics boards as well as to the central monitoring site. Regular safety reports were also submitted to the

Data Monitoring Committee (DMC) which operated at arms-length from the research group and had access to the treatment allocation via the unblinded medication manager. Table 3.7 presents the baseline demographics, baseline and end point scores for each outcome measures for patients included in the DARAD trial.

Table 3. 7 Baseline Demographics, Baseline (BL) and End-Point (EP) Scores for DARAD Patients

Number		406	Age		77.8 (7.1)	Male %		50.7%
Education		12.3 (3.5)	BP systolic		134.3 (16.0)	BP diastolic		73.1 (10.2)
Q*mci*	BL	39 (19)	ADL	BL	51 (9)	CDR-SB	BL	5.5 (4)
	EP	33 (22)		EP	47 (12)		EP	8 (6)
CSDD	BL	3 (4)	DBRIF	BL	4 (10)	DBRIR	BL	13 (11)
	EP	4 (5)		EP	5 (16)		EP	14.5 (15)
GDS	BL	1 (3)	SADAS	BL	20 (10)	SMMSE	BL	23 (5)
	EP	1 (3)		EP	24.5 (17)		EP	21 (7)

The patients in the DARAD database had mild to moderate AD. There were no significant difference between their age, gender, education and blood pressure. In outcome measures, Q*mci*, ADL and SMMSE with higher scores suggest better condition; CDR-SB, CSDD, DBRIF, DBRIR, GDS and SADAS with higher scores suggest worse condition.

3.4.4 Q*mci* Validation Database

3.4.4.1 Overview of Q*mci* Validation Database

The Q*mci* database includes patients recruited from four memory clinics in Ontario Canada, (Hamilton, Paris, Niagara Falls and Grand Bend). The

assessments were done on patients and families during clinic. This was a highly selected population, created to validate the Q*mci* (O'Caoimh et al., 2012a, O'Caoimh et al., 2013a). It only included subjects aged 55 years or more, referred for assessment of cognition. Subjects with LBD, PDD and depression were excluded. Normal controls in this database included caregivers and families attending with patients. Those with subjective memory loss, but normal cognition or with alternative causes of memory loss such as hypothyroidism, were excluded.

3.4.4.2 Patient Demographics in Q*mci* Validation Database

This database contained 965 patients, recording their age, gender, education, diagnosis, stages of dementia and three cognitive tests (Q*mci*, SMMSE and ABCS135). There were mainly three diagnosis types in this database. Normal controls were selected by convenience sampling. All caregivers, or those attending with the subjects, were asked if they themselves had memory problems. Those without memory problems were invited to participate as normal controls. A diagnosis of MCI was made by a consultant geriatrician if patients had recent, subjective but corroborated memory loss, without obvious loss of social or occupational function. A diagnosis of dementia was based on NINCDS (McKhann et al., 1984) and DSM-IV criteria (First, 1994). Dementia severity was correlated with the Reisberg FAST scale (Reisberg, 1987). Dementia patients were divided into three sub-groups, based on stages: mild, moderate and severe dementia. The baseline demographics are presented in Table 3.8.

Table 3. 8 Patients Demographics in Q*mci* Validation Database

Group	N	Mean Age	Gender (% male)	Mean Education (years)	Median Q*mci* (IQR)	Median SMMSE (IQR)	Median ABCS135 (IQR)
Normal	630	67.4	40.3%	13.8	76 (14)	29 (2)	116 (12)
MCI	154	73.6	50%	12.2	62 (15)	28 (2)	102 (17)
Dementia Total	181	78.1	46.1%	11.0	36 (22)	22 (2)	70 (38)
Mild dementia	129	78.3	44.3%	11.2	40 (17)	23 (5)	75 (27)
Moderate dementia	31	76	48.5%	10.4	17 (27)	15 (9)	37 (51)
Severe dementia	7	75.3	71.4%	10.3	3 (7)	8 (4)	8 (23)

Table 3.8 shows the baseline characteristics and three cognitive test scores. There was no significant difference in age, gender, and education between the dementia, MCI, and normal groups. Q*mci*, SMMSE and ABCS135, the cognitive outcome measures, are scored out of 100, 30 and 135 respectively, with higher scores suggesting greater cognition. The majority (78%) of dementia cases were mild (n = 141). Removing moderate and severe cases did not affect sensitivity (O'Caoimh et al., 2012a). These cognitive tests were performed in random order, by trained raters, blind to the diagnosis and prior to the assessment.

3.5 Key Instruments in the Three Clinical Databases

3.5.1 Introduction

This section introduces all the key instruments/measures for dementia patients used in this research; they are contained in the GAT, DARAD and Q*mci* Validation databases. These instruments measured cognition, function, depression, and behaviour profiles in the dementia patients: SADAS-cog (Standish et al., 1996), SMMSE (Molloy et al., 1991a), and Q*mci* (Molloy et al., 2005, O'Caoimh et al., 2012b) were the measurements for cognition; Lawton-Brody ADL (ADL) (Self-maintenance, 1969) and Q*adl* were the measurements for function; GDS (Yesavage et al., 1983, Shiekh and Yesavage, 1986) and CSDD (Alexopoulos et al., 1988) were the measurements for depression; DBRI (Molloy et al., 1991b) measured behaviours on patients' frequency and response to each behaviour as caregivers' burden; CDR (Hughes et al., 1982) was used as a scale to quantify the severity of dementia. Table 3.9 describes these instruments in the three databases.

Table 3. 9 Key Instruments in the Three Clinical Databases

Database name / Instruments	GAT	DARAD	Q*mci* Validation
CDR		√	
SADAS-cog		√	
SMMSE	√	√	
Q*mci*	√	√	√
GDS	√	√	
ADL/ Q*adl*	√	√	
DBRI		√	
CSDD		√	

The databases also include the subtest scores for these instruments. Most of these instruments are widely employed in clinics today. Some of them, like SADAS-cog, are the accepted gold standard for measuring cognition in dementia (Rosen et al., 1984). All of the screening tools are attached in Appendix.

3.5.2 Clinical Dementia Rating Scale (CDR)

The Clinical Dementia Rating Scale (CDR) is a clinician-rated instrument that stages dementia, tracking the progression of cognitive and functional decline. It measures memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR may be scored in two ways: the global CDR scored our of three points (Morris, 1993), and the CDR sum of boxes (CDR-SB) technique (Ferris et al., 1997). In this study, the CDR-SB scores ranged from 0 - 18 (most severe), with a score of zero indicating no impairment, scores of 0.5-4.0 denote possible impairment, and 4.5-9.0, 9.5-15.5 and 16.0-18.0 suggest mild, moderate and severe impairment respectively. CDR was performed at baseline and follow-up. The CDR has excellent inter-rater reliability (0.89) and correlates significantly with the Short Portable Mental Status Questionnaire (0.74) and the Blessed Dementia Scale (0.84) cognitive tests ($P < 0.0001$) (Davis et al., 1990).

3.5.3 Standardised Alzheimer's Disease Assessment Scale-Cognitive Subscale (SADAS-cog)

The Alzheimer's Disease Assessment Scale-cognitive section (ADAS-cog) (Rosen et al., 1984) is the accepted standard for measuring cognition in clinical trials in dementia. It has 11 domains measuring word recall, object naming, command following, construction and ideational praxis, orientation, word recognition, language, speech comprehension, word finding and recall. Total scores range from 0 to 70 with higher scores (>18) suggesting greater cognitive impairment. The minimal important change has been determined to be approximately four points, representing a change at six month period.

Many regulatory authorities, including the US Food and Drug Administration, require evidence of such change at six months to confirm the benefit of any new medication (McKhann et al., 1984, Matthews et al., 2000, Aisen et al., 2003).

The ADAS-cog, although comprehensive and useful at different stages of dementia, has limitations. It is long, requires training, and there are concerns about the instruments' inter-rater reliability (Connor and Sabbagh, 2008). It also has a ceiling effect, limiting usefulness in the initial stages of dementia (Mohs et al., 1997). To overcome these problems, the Standardised Alzheimer's Disease Assessment Scale-cognitive section (SADAS-cog) was created with clearly defined administration and scoring guidelines, which showed improved inter-rater reliability (Standish et al., 1996). It can be administered in approximately 45 minutes (O'Caoimh et al., 2013b).

3.5.4 The Standardised Mini-Mental State Examination (SMMSE)

This is a widely used short mental status instrument that scores cognition and includes orientation, registration, concentration, short-term memory, language and visual-spatial ability, taking approximately 10 minutes to administer. Originally MMSE was developed by Folstein, et al. (Folstein et al., 1975) to distinguish depression from dementia. The SMMSE has explicit guidelines for administration and scoring and improved inter rater reliability, compared with the traditional MMSE (Molloy et al., 2005). It is used extensively as a reliable measure of dementia severity. The test/retest reliability is 0.89 and the inter rater reliability is 0.83. The scale is responsive to change and correlates well (0.70-0.90) with other cognitive screening instruments (Kane et al., 2000). Table 3.10 presents the scoring of the different domains in the SMMSE.

Table 3. 10 SMMSE Scoring Table

SMMSE test	**Score**
Orientation	5
Registration	5
Concentration	5
Short-term recall	6
Naming familiar items	2
Repeating a common expression	1
The ability to read and follow written instructions	1
Write a sentence	1
Construct a diagram	1
Follow a three step verbal command	3
Total	*30*

The SMMSE is scored out of 30 points. People who are well-educated, have normal cognition, complain of memory loss, or have diagnosed MCI will usually score above 26 (Molloy et al., 1991a, Molloy et al., 2005). Mild, moderate and servere dementia patients will usually score between 20 – 25, 10 – 19, 0 – 10, respectively (Vertesi et al., 2001).

3.5.5 The Quick Mild Cognitive Impairment (Q*mci*) Screen

The Q*mci* is a short (three to five minutes) cognitive screen with six subtests measuring five cognitive domains: orientation (five questions), registration (five-word registration), delayed recall, visual-spatial ability (clock drawing), verbal fluency (naming animals in one minute) and logical memory (immediate verbal recall of a short story). It is scored out of 100 points, with higher scores suggesting greater cognitive abilities. Table 3.11 presents the points weightings of the six subtests. The Q*mci* is sensitive to early cognitive changes and was developed specifically to differentiate

between normal cognition, MCI and dementia. The Q*mci* shows a statistically significant difference between normal cognition and MCI. This difference is significant regardless of patients' age or education. The Q*mci* has superior accuracy for detecting MCI compared to the SMMSE (O'Caoimh et al., 2012a).

Table 3. 11 Q*mci* Scoring Table

Q*mci* subtests	**Score**
Orientation	10
Registration	5
Clock drawing	15
Delayed recall	20
Verbal fluency	20
Logical Memory	30
Total	*100*

Q*mci* cut offs are sensitive to patients' age and education. For all patients, the optimal cut-off score for identifying cognitive impairment is ≤60; sensitivity of 89%, specificity 86%, and area under the curve (AUC) 0.95. A score ≤50 has 84% sensitivity, 79% specificity, AUC 0.89 for detecting dementia (O'Caoimh et al.).

3.5.6 Geriatric Depression Scale (GDS)

The Geriatric Depression Scale (GDS) (Yesavage et al., 1983) is a clinician-administered measure of depression. It has two accepted forms, the long form with 30 questions, and a short form with 15 questions. The GDS-30 was originally validated with standard research diagnostic criteria for depression. With a cut off point of 11/30, it has a sensitivity of 84% and specificity of 95% for depression. Test retest reliability is satisfactory with a correlation of 0.85. The 15 GDS-SF item was used in DARAD, scored from 0 to 15 with a score ≥5 suggesting depression (Marc et al., 2008). While the performance of the GDS is compromised by severe cognitive impairment (approximately 20 or less out of 30 on the MMSE), this scale is considered

suitable as a brief screen for depression in patients with mild to moderate patients with dementia (da Costa et al., 2008).

3.5.7 Lawton-Brody Scale (ADL) and Q*adl*

Lawton-Brody Scale is a well established instrument for measuring the performance of instrumental and basic activities of daily living (ADLs) (Spilker, 1990, Lawton, 1970). It combines both basic (Physical Self-Maintenance Scale) and instrumental (Lawton Scale) ADLs, covering 14 subtests, scored from 14 to 65 points, with higher scores suggesting greater independence. It consists of items that may be performed by either women or men (ability to use telephone, toileting, feeding themselves, dressing, grooming, walking, bathing, shopping, food preparation, housekeeping, laundry, mode of transportation, medication administration and handling finances). Administration is either by self report (Self-maintenance, 1969) or by a caregiver. The inter rater reliability is 0.85, and the coefficient of reliability is 0.96 for men and 0.93 for women.

The Q*adl* test is a shortened version of the Lawton-Brody ADL scale. It contains 10 subtests, scored by patients' caregivers, indicate how the patient manages his/her "*activities of daily living*", and how s/he functions every day. It also includes how s/he manages medications, handles money (pay bills, shop, etc), uses the telephone, prepares food, grooms (hair, shaving, nails, etc.), bathes (bath, shower), walks, toilets (urine/feces), transfers (e.g bed to chair), and feeds themselves (eat and drink). Each subtest has two questions: what is the level of care required, and how much of a problem this is. Each "*level of the care*" question is scored from zero to five points, with higher scores suggesting more dependence. Each question for "problem" is scored from zero to four, with higher scores suggesting worse problem. The Q*adl* has excellent inter-rater reliability (Caoimh et al., 2012).

3.5.8 Dysfunctional Behaviour Rating Scale (DBRI)

The Dysfunctional Behaviour Rating Scale (DBRI) measures 25 behaviours according to their frequency (DBRI frequency, from 'never' to 'greater than five times per day') and scores caregiver burden for each behaviour (DBRI reaction, impact from 'no problem' to 'great deal of a problem'). The questions are answered by a caregiver or other informant, who is familiar with the patient. The inter-rater reliability of the DBRI is 0.75. Validity of the DBRI as compared to the Behavioural Problem Checklist (BPC) total score is 0.71. The DBRI is a specific, reliable and valid caregiver-reported measure of dysfunctional behaviour in cognitively impaired elderly patients living in the community.

3.5.9 Cornell Scale for Depression in Dementia (CSDD)

CSDD was specifically developed to assess signs and symptoms of major depression in patients with dementia. It has 19 items that use the information from an interview with patient and caregiver. CSDD ratings are significantly related to clinical diagnoses of depression in elderly people, with or without dementia (Vida et al., 1994, Ownby et al., 2001). It has a 19-item scale, range of 0-39: normal <6, probable depression 10-17, definite depression ≥18.

3.6 Analytical Methods

This section focuses on the analytical methods used in the core part of KDD process (data analysis), within the medical area. It explains how to use descriptive statistics to understand and report on medical data, and introduces the statistical methods used in this research across the various studies.

3.6.1 Data Analysis in Medical Research

Nowadays, clinical medicine is facing the challenge of interpreting a growing volume of data recorded as part of clinical practice. Large clinical

and administration databases are now common, as hospital information systems become more sophisticated, capturing patient case mix. Enormous amounts of information are collected continuously by monitoring physiological parameters of patients (Tan et al., 2003) and can be used for medical research and to improve hospital management. The analysis of medical data will be a keystone to planning future healthcare (Auffray et al., 2009). Data analysis of quantitative and qualitative research must be performed and reported according to scholarly conventions. The purpose of this section is to introduce the concepts of data analysis in medical research.

3.6.1.1 Experimental Design (Obtaining Data)

Data collection is one of the key parts in the research process. The collection methods will directly impact on data analysis at a later stage (Peacock and Peacock, 2010). Research questions determine which variables are needed for analysis. During the design of collection forms, variables associated with the outcomes should be considered. Coding allows non-numerical or numerical data in categories to be used in analysis. Some data analysis packages can analyse non-numerical data, but it is easier to assign a number to each category. Hence, the coding should be designed at the time when form is made, so that it can be built into the form. A special code is used for missing data or not-applicable (n/a) value. For example, for a yes/no question, number one represents yes, zero represents no, and nine could be used to indicate a missing value. It is not allowable to fill in a casual number like 999 or 222 for an unknown answer, as those numbers are also representing an amount. One variable should not contain two or more kinds of data types. For the last example, if number one is chosen to represent yes, and zero represents no, then the missing value should be represented by a number, e.g. “9”, not a character, such as “blank”.

3.6.1.2 Descriptive Statistics (Exploring, Summarizing and Presenting Data)

In statistics, a population is studied, and usually the set of observations

represents a *sample* from the entire collection of possible data known as a *population* (Peacock and Peacock, 2010). It is important that the population being sampled is well-defined to ensure that the sample drawn will be representative and useful to describe it. Summarising data is helpful in checking data quality as well as for presenting findings to others. The first step in analysing data should begin by presenting and describing the information contained in it. This is completed by employing a set of techniques more commonly known as *descriptive statistics* or *exploratory data analysis* (Hartwig, 1979). These tools are primarily concerned with summarising and exploring data to detect errors and assess patterns. Generally, this involves ordering and presenting the collected measurements in the form of tables; graphs such as pie charts, bar charts and histograms; and numerical summaries.

3.6.1.3 Tests of Statistical Significance

A significance test uses data from a sample to show the Likelihood that a hypothesis about a population is true. If the hypothesis being tested is not true, then the opposite hypothesis must be true. A measure of the evidence for/against the hypothesis is provided by a *p* value. The *null hypothesis* (Fisher, 1935) is the basic hypothesis which usually is expanded in the form 'there is no difference' or 'there is no association'. The corresponding *alternative hypothesis* is that 'there is a difference' or 'there is an association'. For example, for the question of "if a new treatment can reduce blood pressure better than the existing one", the *null hypothesis* means that blood pressure is the same between the two groups; the *alternative hypothesis* means that blood pressure is different in the two groups. In scientific and medical research, null hypothesis play a major role in testing the significance of differences in treatment and control groups. A p value < 0.05 indicates statistical significance (means that there is less than a 5% chance that this difference was due to chance), which is an integral part of hypothesis testing used as an important value judgment. In statistics, a result is considered significant, because it has been predicted as unlikely to have occurred by chance alone, not because it is important or meaningful (Wilcox,

1996).

3.6.2 Statistical Methods

The purpose of this section is to introduce the different statistical methods used in this research. Table 3.12 presents the list of the tests.

Table 3. 12 The List of the Statistical Tests Used in the Research

<table>
<tr><th colspan="2">Types of methods</th><th>Test names</th></tr>
<tr><td colspan="2">Distribution tests for normality</td><td>The Shapiro-Wilk Test</td></tr>
<tr><td rowspan="3">Comparing test</td><td rowspan="2">Parametric methods</td><td>Two-Sample t-Test</td></tr>
<tr><td>Paired t-test</td></tr>
<tr><td>Non-parametric methods</td><td>Mann-Whitley U test</td></tr>
<tr><td rowspan="4">Measure of associations</td><td rowspan="2">Correlation Coefficient</td><td>Pearson’s Correlation Coefficient</td></tr>
<tr><td>Spearman’s Rank Correlation Coefficient</td></tr>
<tr><td colspan="2">Simple Linear Regression</td></tr>
<tr><td colspan="2">Chi-Square Test</td></tr>
<tr><td colspan="2" rowspan="2">Analysis of variance</td><td>One-way Analysis of variance (one-way ANOVA)</td></tr>
<tr><td>Multivariate analysis of variance (MANOVA)</td></tr>
<tr><td colspan="2" rowspan="2">Diagnostic tests</td><td>Receiver Operating Characteristic (ROC) curve</td></tr>
<tr><td>Youden’s index and Likelihood ratios</td></tr>
</table>

The tests listed in Table 3.12 were the methods applied in this research, some of the other tests for the similar purpose, for example, the Kolmogorov-Smirnov test for normality distribution, will not be considered. The next sections will introduce the theory of the tests, and the conditions where they could be applied.

3.6.2.1 Distribution Tests for Normality

The normal distribution is the most important and most widely used distribution in statistics for quantitative data. Data needs to be determined as normal distributed or non-normal distributed, before parametrical or non-parametrical tests are executed. Parametric methods are often used while the data are normal distributed, and where they are not true of the raw data, which usually are not normal distributed. There are situations in which even transformed data may not satisfy the assumptions of normal, however, and in these cases it may be inappropriate to use traditional (parametric) methods of analysis. Non-parametric methods (Noether, 1967) provide an alternative series of statistical methods that require no or very limited assumptions to be made about the data. There is a wide range of methods that can be used in different circumstances, but some of the more commonly used are the non-parametric alternatives to the t-tests (Whitley and Ball, 2002).

Sometimes, the normal distribution is called the "bell curve", although the tonal qualities of such a bell would be less than pleasing. The normal curve was discovered by de Moivre in 1753 (Gaddum, 1945) and developed as a useful mathematical tool. Figure 3.6 presented the Standard Normal Distribution with percentages for every half of a standard deviation, and cumulative percentages.

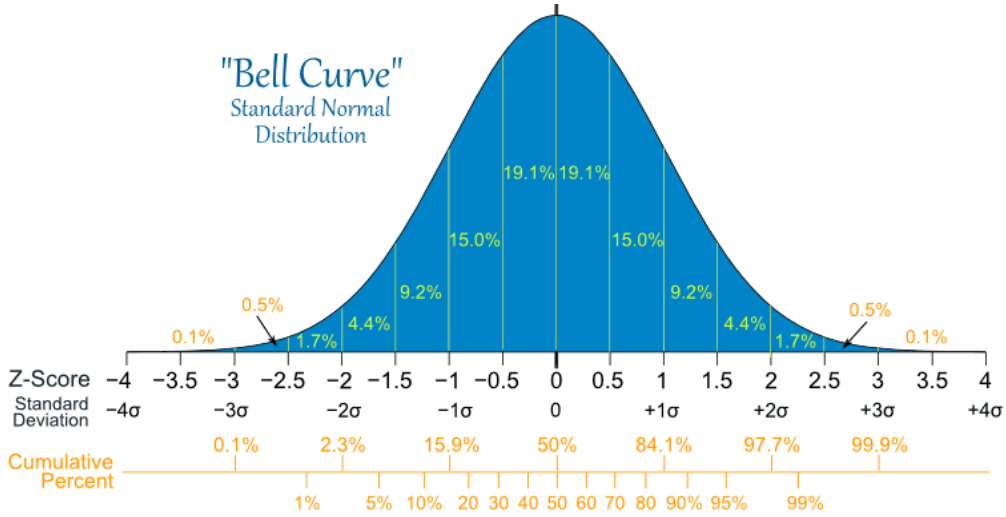


Figure 3. 6 Standard Normal Distribution Curve

The hypotheses used in testing data normality are as follows:

H0: The distribution of the data is normal.

Ha: The distribution of the data is not normal.

The normal distribution is characterised by the following mathematical function:

$$f_x(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$ (Adams, 1974)

Where x is the co-ordinate on the x-axis. The expected value of a normal distribution is μ. It can take on all real values. The variance is σ^2, which can only take on positive values.

If a test does not reject normality, this suggests that a parametric procedure that assumes normality (e.g., a t-test) can be safely used. Non-normal data distributions are skewed distributions which are non-parametric, with a tail. Figure 3.7 a) and b) represent the positively and negatively skewed data distributions respectively. If the longer tail occurs on the right, that is, if there are more extreme values on the right, it is said to be positively skewed or right-skewed. If the longer tail occurs on the left with more extreme values on the left of the distribution, it is said to be negatively skewed or left-skewed.

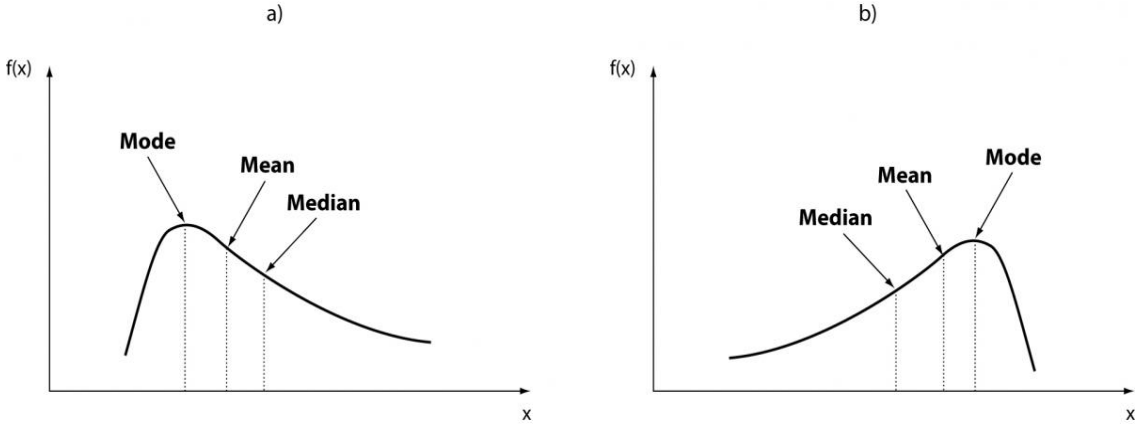


Figure 3. 7 a) Positively Skewed Distributions. b) Negatively Skewed Distributions

If data are not normally distributed, do not report the mean for the data. Describe distinctly non-normal data with the median and range or

interquartile range (Lang et al., 1998). Another way to report this type of data is by using a five-number summary consisting of the minimum, 25th percentile, 50th percentile, 75th percentile, and maximum. These five numbers are based on the boxplot.

- **The Shapiro-Wilk Test for Normality**

The Shapiro-Wilks test (Shapiro and Wilk, 1965) for normality is one of the general normality tests designed to detect all departures from normality. It calculates a *W* statistic that tests whether a random sample, x_1, x_2, ..., x_n comes from (specifically) a normal distribution . Small values of W are evidence of departure from normality and percentage points for the *W* statistic. The *W* statistic is calculated as follows:

$$W = \frac{(\sum_{i=1}^{n} a_i x_{(i)})^2}{\sum_{i=1}^{n} (x_i - \bar{x})^2}$$

where the $x_{(i)}$ are the ordered sample values (x_1 is the smallest) and the a_i are constants generated from the means, variances and covariances of the order statistics of a sample of size from a normal distribution (Pearson and Hartley, 1972).

The test rejects the hypothesis of normality when the p-value is less than or equal to 0.05. Failing the normality test allows you to state with 95% confidence the data does not fit the normal distribution. Passing the normality test only allows you to state no significant departure from normality was found. Shapiro-Wilks test was used on every study in this research for testing the normality of data, in order to choose whether parametric or non-parametric tests should be applied in the later analysis.

3.6.2.2 Comparing Test

Testing for comparison can be separated into parametric and non-parametric methods, based on the distributions of data. Methods that use distributional assumptions are called parametric methods (Altman and Bland, 2009), i.e. *t* test. Alternative methods, such as Mann-Whitney test, and rank correlation,

do not require the data to follow a particular distribution. Methods which do not require us to make distributional assumptions about the data are called non-parametric methods (Altman and Bland, 2009).

- **Two-Sample t-Test (Parametric methods)**

The two-sample (independent groups) t-test (Seize, 1977) is used to determine whether the unknown means of two populations are different from each other based on independent samples from each population. It is based on the sampling distribution of the difference of two sample means (normal distributed continuous data). Hence, a normality test for the t-test need to be run when the data has small sample size. If it is not, a similar non-parametric t-test should be used. Another consideration that should be addressed before using the t-test is whether the population variances can be considered to be equal. If they are different, the Satterthwaite approximation, available in some statistical programs, may be used (Peacock and Peacock, 2010).

The null hypotheses for the comparison of the means in a two-sample t-test is that, the two samples come from populations are the same.

The means of two samples can be tested for difference by the following formula:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_p^2}{n_1} + \frac{s_p^2}{n_2}}}$$

(Phillips, 1999)

Where $\overline{x_1}$, $\overline{x_2}$ are the means, S_p is the pooled standard deviation calculated from the groups standard deviations.

- **Paired t-test (Parametric methods)**

The paired t-test (Seize, 1977) is a methods for data in which the two samples are paired in some way. It analyses mean difference and confidence interval for the difference in a paired sample, as in a two treatment

randomised block design. It also used to compare two means that are repeated measures for the same participants - scores might be repeated across different measures or time. Similar with two sample t-test, it is based on the sampling distribution of the mean difference (normal).

The null hypothesis for the comparison of the means in a paired t-test is that, the population mean of the differences is zero.

The means of two paired samples can be tested for difference by the following formula:

$$t = \frac{\bar{d}}{S_d / \sqrt{n}}$$ (Phillips, 1999)

Where if $x_{i1} - x_{i2} = d_i$, then the mean of the difference d_i is $\bar{d}$. S_d is the standard deviation of the difference, and *n* is the sample size.

- **Mann-Whitley U test (non-parametric methods)**

The Mann-Whitley U test (Wilcoxon, 1945, Mann and Whitney, 1947) is similar with the two-sample t-test without the normality or equal variance assumption. However, the data must meet the requirement that the two samples are independent (Elliott and Woodward, 2007). Unlike the parametric test, The Mann-Whitley U test uses ranks or ordering of the data instead of the raw data values. Hence, in another word, it is designed to compare groups' medians, not means. In addition, it also can compare ordinal data from two independent groups.

The logic behind the Mann-Whitney test is to rank the data for each condition, and then see how different the two rank totals are. If there is a systematic difference between the two conditions, then most of the high ranks will belong to one condition and most of the low ranks will belong to the other one. As a result, the rank totals will be quite different. On the other hand, if the two conditions are similar, then high and low ranks will be distributed fairly evenly between the two conditions and the rank totals will be fairly similar. The Mann-Whitney test statistic "U" reflects the difference

between the two rank totals. The smaller it is (taking into account how many participants you have in each group) then the less likely it is to have occurred by chance. Note if there have small samples, the Mann-Whitney test has little power. In fact, if the total sample size is seven or less, the Mann-Whitney U test will always give a *p* value greater than 0.05, no matter how much the groups differ (Kruskal, 1957).

See the following calculation of *U* value. Both samples (having sizes N and M) are combined into one array which is sorted in ascending order. Information had been kept about which sample the element had come from. After sorting, each element is replaced by its rank (its index in array, from 1 to N+M). Then the ranks of the first sample elements are summarised and the *U*-value is calculated:

$$U = NM + \frac{N(N+1)}{2} - \sum_{x_i} Rank(x_i)$$

The null hypothesis of the Mann-Whitney U test is that, observations from one group do not tend to have a higher or lower ranking than observations from the other group.

3.6.2.3 Measure of Associations

This section describes measures and tests of associations between two categorical variables and between two numerical variables. Of these, correlation coefficient and regression (simple linear regression) are used to investigate the relationship between two variables. Chi-square test is used in sampling distribution of the test statistic.

- **Pearson's Correlation Coefficient (Correlation Coefficient)**

A Correlation Coefficient test is used to measure the strength of relationship or degree between two variables, of a supposed linear association between them. A correlation coefficient is always between -1 and +1, where -1 indicates that the points in the scatter-plot of the two variables all lie on a line that has negative slope, and a correlation coefficient of +1 indicates that

the points all lie on a line that has positive slope. Hence, in general, a positive correlation between two variables indicates that, as one of the variable increase, the other variable also tends to increase. On the contrary, if the correlation coefficient is negative, then as one variable increases, the other one tends to decrease. If there is absolutely no linear relationship then the correlation coefficient is zero.

The correlation coefficient should be employed as a descriptive measure only when scatter plot indicates that a linear relationship exists between the two variables of interests. Pearson's Correlation Coefficient (Society, 1894) measures the strength of the linear relationship between two numerical variables. It is appropriate for data that attain at least an interval level of measurement. It is independent of the scale used to measure the variables.

The hypotheses for testing the statistical significance of a Pearson's correlation coefficient are the following:

H0: There is no linear relationship between the two variables.
Ha: There is a linear relationship between the two variables.

The following test statistic is used for calculating Pearson's Correlation Coefficient:

$$T = \frac{r}{\sqrt{\frac{1-r^2}{n-2}}}$$ (Society, 1894)

Where r is the sample correlation coefficient and n is the sample size. Under the null hypothesis of no correlation, this test statistic will follow a t distribution with n-2 degrees of freedom. The t distribution is used to carry out the desired hypothesis test.

- **Spearman's Rank Correlation Coefficient (Correlation Coefficient)**

If the data consists of rank (ordinal data) or there are serious reservations about the underlying assumption of bivariate Normality, the Spearman's

Rank Correlation Coefficient (Spearman, 1904) should be used. It is the nonparametric equivalent of the parametric Spearman's Rank Correlation Coefficient, and it measures the strength of linear relationship between two categorical variables. As for Pearson's correlation coefficient, the sign of the correlation indicates the direction of the relationship while its absolute value indicates the strength of the linear association. It has the same null hypothesis with Pearson's correlation coefficient.

To compute the Spearman's Rank Correlation Coefficient, the raw scores will be substituted by their ranks, and perform the usual Pearson's correlation coefficient on the ranks. The way to calculate the rank of Spearman's Rank Correlation Coefficient is:

$$r_s = 1 - \frac{6\sum d^2}{n(n^2-1)}$$

Where d means the difference between two ranks, and n represents the simple size.

- **Simple Linear Regression**

Simple linear regression (Legendre, 1805, Gauss, 1809) is a statistical method used to examine the nature of linear relationship between one predictor (independent variable) and a single quantitative response (dependent) variable, where one predicts the outcome and the other is regarded as the outcome. In general, simple linear regression analysis produces a regression equation that can be used in prediction. A typical linear regression expression/equation involves observing a sample of paired observations in which the independent variable (X) may have been fixed at a variety of values of interest, and the dependent variable has been observed. This resulting set of observations is sometimes referred to as a training sample. It gives the equation of the best straight line through the observed data:

$$Y = a + bX + c$$

Where *Y* is the outcome, *a* is the intercept, *b* is the slope of the line, *X* is the predictor variable, and *c* is an error term with zero mean and constant variance. The equation can be used to predict the dependent variable given a value of the independent variable. In this PhD research, simple linear regression was used to determine if the linear model fit the data for correlation coefficient analysis.

- **Chi-Square Test**

The term Chi-Square (Pearson, 1900) has two distinct meanings in statistics. One meaning is, it is used to refer to a particular mathematical distribution. Another meaning of the term is, it is used to refer to a statistical test whose resulting test statistics is distributed in approximately the same way as the Chi-Square distribution (Fisher, 1924).

In general, Chi-Square Test tests for an association between two categorical variables, where each variable having only two categories is equivalent to the z test for two proportions. It is based on the Chi-Square distribution with *n* degrees of freedom, where *n* is given by (no. of rows -1) * (no. of columns -1). The Chi-Square distribution is not symmetrical. It climbs to its highest point rapidly and comes down to the horizontal axis more slowly. It is skewed to the right, starts at zero on the horizontal axis, and extends indefinitely to the right approaching the horizontal axis as it does so. There are an infinite number of Chi-Square distributions – one for each degree of freedom. As the degree of freedom increase, the shape of the Chi-Square distribution looks increasing like the normal distribution.

The Chi-Square test is always testing the null hypothesis, which states that there is no significant difference between the expected and observed result. If the data consists of two categories on the row and two categories on the column (2x2 table), then it is allowed to compare two proportions. The null hypothesis (H_o) that there is no association between the row and column variables can be restated in terms of proportions. The test statistic is given by following formula:

$$x^2 = \sum_{cells} \frac{(O-E)^2}{E}$$

Where O is the observed frequency in a given cell, and E is the expected frequency in the given cell if the null hypothesis is true. The way to calculate E, the expected frequency, is as following:

$$E = \frac{Row \quad total \quad x \quad column \quad total}{Sample \quad size}$$

3.6.2.4 One-way Analysis of Variance (one-way ANOVA)

ANOVA (Fisher, 1925) is used to assess the statistical difference between the means of two or more groups. The term "one-way" is used when there is only one independent variable. One-way ANOVA is an extension of the two-sample t-test used to determine where there are differences among more than two group means.

Differences between the group means are examined with the F-test instead of the t-test when ANOVA are used. To do so, the total variance is partitioned into two forms of variation and they are compared. One is the *variation within the groups* and the other is the *variation between the groups*. The *F-distribution* is the ratio of these two forms of variance and can be calculated as follows:

F = variance between groups (VB) / variance within groups (VW)

When the variance between the groups relative to within the groups is larger, then the F value is larger. Larger F value indicates significant differences between the groups and a high likelihood the null hypothesis will be rejected. The null hypothesis for the comparison of the means in a one-way ANOVA is that, the population means of the all groups are the same.

One-way ANOVA test works on continuous data, and the measurement variable is normally distributed within each group. Another assumption is

that the within-group variances are the same for each of the groups.

3.6.2.5 Multivariate Analysis of Variance (MANOVA)

MANOVA (multivariate analysis of variance) (Bartlett, 1939) is a statistical procedure to determine if a set of categorical predictor variables can explain the variability in a set of continuous response variables. It is also possible to include continuous predictor variables either as covariates or as true independent variables in the design. It is related to within-subject ANOVA in that both of these analyses examine multiple measurements from each case in data.

The primary purpose of MANOVA is to show that an independent variable has an overall effect on a collection of continuous dependent variables. If there are a large number of dependent variables in data, a MANOVA should be performed to see if there is any effect of the independent variables, taking into account the number of different dependent variables of examining.

If there were multiple dependent variables in data, an ANOVA could be used on each variable to examine the effect of the independent variable. However, if performing these multiple tests would increase the error rate were concerned, a MANOVA would be useful, as it is a single test of the independent variable's influence on the collection of dependent variables. In other words, MANOVA can act as protection against an inflation of error rate from performing a large number of analysis investigating the same hypothesis. If there is a significant effect of the independent variable in the MANOVA, one could then follow up that MANOVA with univariate ANOVAs (ANOVAs with a single dependent variable) (Rencher and Christensen, 2012).

Performing a MANOVA is not the same as looking for an effect on the average of the dependent variables. Therefore, it is also different from looking for a main effect of a between subjects variable within a repeated measures analysis. In truth, the dependent variables are never combined

together in MANOVA. MANOVA separately considers the effect of the independent variables on the dependent variables. It actually produces a matrix of results, which separately contains the influence of the independent variables on each of the dependent variables.

3.6.2.6 Diagnostic Tests

A diagnostic test or procedure is used in clinical practice to determine if a patient is likely to have a particular disease or situation. A diagnostic test is used in preference to a definitive 'gold standard' test, when this definitive test is expensive, or/and time-consuming, and impractical for use in routine clinical practice. It can classify individuals into two categories, such as positive or negative, diseased or non-diseased, high or low risk, etc. Diagnostic tests won't always give the 'correct' answer, it's important to be able to quantify how accurate a particular test is. There is no single statistical measurement that can summarise the accuracy, since a test result may either fail to detect a case (false negative) or falsely identify a case (false positive).

Sometimes it is not possible to determine the true diagnosis without invasive procedures, which would be harmful to the patient, so the 'gold standard' is the best diagnosis possible. There are four commonly used measures to summarise a test's performance: sensitivity (Altman and Bland, 1994a), specificity (Altman and Bland, 1994a), positive predict value (PPV) (Altman and Bland, 1994b), negative predict value (NPV) (Altman and Bland, 1994b).

Sensitivity is the proportion of true positives that are correctly identified by the test. Oppositely, specificity is the proportion of true negatives that are correctly identified by the test. See Table 3.13.

Table 3. 13 Positive and Negative Distribution Matrix for Diagnosis Tests

Disease status				
		Positive	Negative	Total
Test	Positive	*a*	*b*	*a* + *b*
	Negative	*c*	*d*	*c* + *d*
	Total	*a* + *c*	*b* + *d*	*n*

Assuming that the diagnostic tests can either be positive and negative, indicating the presence or absence of a disease. The numbers *a*, *b*, *c*, *d*, and *n* represent the amounts of true positive, true negative, false negative, true negative, and total simple size respectively. The sensitivity and specificity can be represented as follows:

Sensitivity = a/(a+c)
Specificity = d/(b+d)

Sensitivity refers to the proportion of true positives who are test positive, and specificity refers to the proportion of true negatives who are test negative. However, sensitivity and specificity are characteristics of the test, but they do not help a clinician to interpret the results of the test. PPV and NPV are useful in a clinical setting as they give the probabilities that an individual subject is truly positive given that they tested positive, or truly negative given that they tested negative. PPV and NPV depend on the prevalence of the disease (Peacock and Peacock, 2010) in the population being tested. The definition of prevalence of disease is as follows:

Prevalence of disease = (a+c)/n

Prevalence of disease indicates the proportion of all individuals who have the disease. If the sensitivity and specificity for a test are known, but the test intends to be used on different population from the one it was developed in, the PPV and NPV can be calculated using the following standard formulae based on Bayes' theorem (Todhunter, 1865, Pearson, 1907, Fisher, 1922).

$$PPV = \frac{sensitivity \times prevalence}{[sensitivity \times prevalence] + [(1 - specificity) \times (1 - prevalence)]}$$

$$NPV = \frac{specificity \times (1 - prevalence)}{[(1 - sensitivity) \times prevalence] + [specificity \times (1 - prevalence)]}$$

PPV indicates the proportion of test positives who are true positive, and NPV indicates the proportion of test negatives who are true negative.

- **Receiver Operating Characteristic (ROC) Curve**

Receiver Operating Characteristic (ROC) curves (Green and Swets, 1966) are a useful way to interpret sensitivity and specificity levels and to determine related cut scores. ROC curves are a generalisation of the set of potential combinations of sensitivity and specificity possible for predictors (Pepe et al., 2004). ROC curve analyses not only provide information about cut off scores, but also provide a natural common scale for comparing different predictors that are measured in different units, whereas the odds ratio in logistic regression analysis must be interpreted according to a unit increase in the value of the predictor, which can make comparison between predictors difficult (Pepe et al., 2004). An overall indication of the diagnostic accuracy of a ROC curve is the area under the curve (AUC). It is widely recognised as the measure of a diagnostic test's discriminatory power (Worster et al., 2006). AUC values closer to one indicate the screening measure reliably distinguishes among students with satisfactory and unsatisfactory reading performance, whereas values at .50 indicate the predictor is no better than chance (Zhou et al., 2011). As a graphical method, the AUC of ROC curve can be used to compare the sensitivity and specificity for all possible cut off scores. This allows the most appropriate cut-off to be chosen for the particular context.

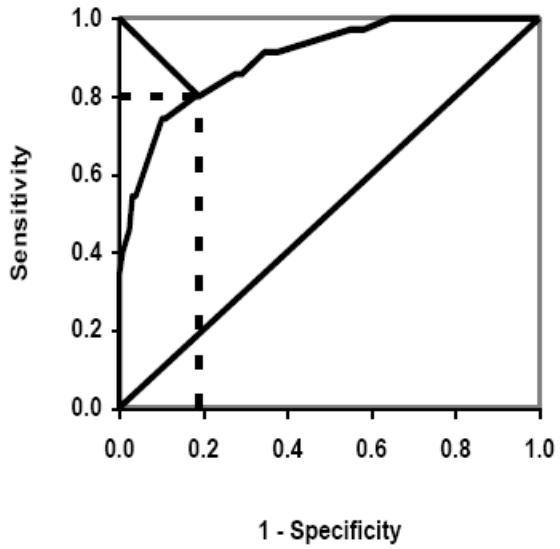


Figure 3. 8 An Example of ROC Curve

An example of ROC curve obtained by plot at different cut-offs is shown in Figure 3.8. The ROC curve is a graph of sensitivity (y-axis) vs. 1 - specificity (x-axis). It offers a graphical illustration of these trade-offs at each "cut-off" for any diagnostic test that uses a continuous variable. Ideally, the best "cut-off" value provides both the highest sensitivity and the highest specificity, easily located on the ROC curve by finding the highest point on the vertical axis and the furthest to the left on the horizontal axis (upper left corner). However, it is rare that this ideal can be achieved, so that, for example, one may opt to choose a higher sensitivity at the cost of lower specificity. It will depend on the requirement of study.

- **Youden's index and Likelihood ratios**

The Youden's index (*J*) (Youden, 1950), a function of sensitivity and specificity, is a commonly used measure of overall diagnostic effectiveness (Zou et al., 1997, Barkan, 2001). It is one of the oldest measures for diagnostic accuracy. It is used for the evaluation of overall discriminative power of a diagnostic procedure and for comparison of this test with other tests.

The Youden's index is the difference between the true positive rate and the false positive rate. This index ranges between zero and one, with values

close to one indicating that the biomarker's effectiveness is relatively large and values close to zero indicating limited effectiveness. Maximising this index allows to find, from the ROC curve, an optimal cut-off point independently from the prevalence. Figure 3.9 shows that, J is the vertical distance between the ROC curve and the first bisector (or chance line). J is defined by

$$J = \max\{sensitivity(c) + specificity(c) - 1\} \quad \text{(Youden, 1950)}$$

Where c refers to the overall cut-off points, $-\infty < c < +\infty$.

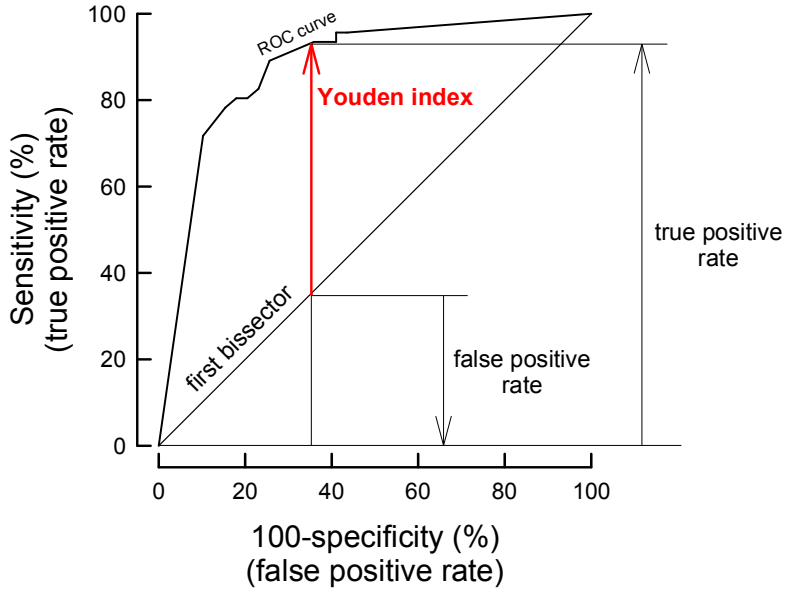


Figure 3. 9 ROC Curve

If risk of disease is an increasing function of the marker level, sensitivity decreases and specificity increases with rising c. Thus, there is a penalty, decreased specificity for increasing sensitivity too far. J occurs at the optimal cut-point for calling a patient diseased, maximising the number of correctly classified individuals (Hilden and Glasziou, 1996).

Youden's index is not affected by the disease prevalence, but it is affected by the spectrum of the disease, as are also sensitivity, specificity and

Likelihood ratios. However, Youden's index is not sensitive for differences in the sensitivity and specificity of the test, which is its main disadvantage. The consequences of a positive or negative test result may be quite different and the loss from missing a case may be greater than from overcalling a control. For example, a test with sensitivity (0.9) and specificity (0.4) has the same Youden's index (0.3) as another test with sensitivity (0.6) and specificity (0.7). If one is to assess the discriminative power of a test solely based on Youden's index, it could be mistakenly concluded that these two tests are equally effective. Hence, Likelihood ratios (Neyman and Pearson, 1931) is used to verify the results.

As an alternative statistics for summarising diagnostic accuracy, which have several particularly powerful properties that make them more useful clinically than other statistics, Likelihood ratios (LR) is defined as the ratio of expected test result in subjects with a certain state/disease to the subjects without the disease. Each test result has its own Likelihood ratio, which summarises how many times more (or less) likely patients with the disease are to have that particular result than patients without the disease. It is the ratio of the probability of the specific test result in people who do have the disease to the probability in people who do not (Deeks and Altman, 2004).

As discussed, Likelihood ratios directly link the pre-test and post-test probability of a disease in a specific patient. It shows how many times more likely particular test result is in subjects with the disease than in those without disease. When both probabilities are equal, such test is of no value and its Likelihood ratio equals one. A Likelihood ratio greater than one indicates that the test result is associated with the presence of the disease, whereas a Likelihood ratio less than one indicates that the test result is associated with the absence of disease. The further Likelihood ratios are from one the stronger the evidence for the presence or absence of disease. Likelihood ratios above 10 and below 0.1 are considered to provide strong evidence to rule in or rule out diagnoses respectively in most circumstances (Oxman et al., 1994). When tests report results as being either positive or negative the two Likelihood ratios are called the positive Likelihood ratio

(LR+) and the negative Likelihood ratio (LR-).

$$LR+ = \frac{\text{Probability of a positive test given the presence of disease}}{\text{Probability of a positive test given the absent of disease}} = \frac{sensitivity}{1 - specificity}$$

$$LR- = \frac{\text{Probability of a negative test given the presence of disease}}{\text{Probability of a negative test given the absent of disease}} = \frac{1 - sensitivity}{specificity}$$

LR+ values should be greater than one, *LR*- values should be positive fractions between zero and one. However if the *LR*+ was less than one and the *LR*- was greater than one, the definitions of a positive and negative test result would be reversed. A benefit of using Likelihood ratios over a test's predictive values is that, unlike predictive values, the Likelihood ratio depends only on sensitivity and specificity, and not on disease prevalence. Consequently, the Likelihood ratios from one study are applicable to some other clinical setting, as long as the definition of the disease is not changed. If the way of defining the disease varies, none of the calculated measures will apply in some other clinical context.

3.6.3 The Use of Data Analysis Methods

Table 3.14 shows how these methods employed in difference studies. It lists nine frequently used statistical (e.g. ROC curve) and data mining (e.g. Simple Linear Regression) methods in clinical studies. Each study applies a verity methods. Of these, distribution tests for normality, comparison methods (parametrical and non-parametrical), and Chi-Square Test are usually used for descriptive analyses in statistics. The other methods are usually used as inferential analysis in statistics.

Table 3. 14 The Use of Statistical Methods in the Studies of this Research

Methods / *Studies*	**Distribution tests for normality**	**Parametric methods for comparison**	**Non-parametric methods for comparison**	**Correlation Coefficient**	**Simple Linear Regression**	**Chi-Square Test**	**Multivariate Analysis of Variance (MANOVA)**	**Receiver Operating Characteristic (ROC) curve**	**Youden's index and Likelihood ratios**
Q*mci* cut offs (O'Caoimh et al.)	√		√			√		√	√
Q*mci* subtests (O'Caoimh et al., 2013a)	√		√	√	√	√		√	
Q*mci* vs SMMSE (O'Caoimh et al., 2012a)	√		√			√		√	
Q*mci* vs SADAS (O'Caoimh et al., 2013b)	√		√	√	√	√			
CACE study in GAT database (Gao et al., 2013a)	√		√			√	√		
CACE study in DARAD database (O'Caoimh et al., 2014)	√	√	√			√	√		
CACE study in the GAT and DARAD databases combined (Gao et al.)	√		√			√	√		

Shapiro-Wilks test, Mann-Whitney U test, and Chi-square test are widely used in all studies in this research. Shapiro-Wilks test is used for testing the normality of data, to choose whether parametric or non-parametric tests should be applied in the later analysis. Mann-Whitney U test is always used in the demographic analysis for comparing differences in the baseline characteristics between two groups in those studies. Chi-square test is used for testing the differences in baseline characteristics, for example, the comparison on gender, age or education levels between two groups, for verifying the baseline differences.

In the Q*mci* subtest study (O'Caoimh et al., 2013a), the reliability of the test was demonstrated by measuring the Q*mci* on two separate occasions. Pearson's correlation coefficient showed good test–retest correlation. In Q*mci* vs SADAS study (O'Caoimh et al., 2013b), the correlations between the Q*mci* and the SADAS-cog were calculated using the data collected at 1, 3, 6, 9, and 12 months. This showed that Q*mci* correlated strongly with the SADAS-cog and both were equally responsive to change over time. In this PhD research, simple linear regression was always jointly applied with correlation coefficient analyses, to verify if the model is linear to fit with the data in these analyses.

In The CACE studies on GAT (Gao et al., 2013a), DARAD (O'Caoimh et al., 2014), that used two databases combined (Gao et al.), multivariate analysis of variance was used to compare end point cognitive and functional scores (SMMSE, Q*mci* and ADL), adjusted for the baseline scores and characteristics (age, years of education, duration of follow-up and BP) between groups.

In the Q*mci* subtests study (O'Caoimh et al., 2013a), ROC curves were constructed to determine the sensitivity and specificity of the Q*mci* subtests. Area under the curve (AUC) was calculated for each subtest, and analysed for age and years of education. In the Q*mci* cut-off study (O'Caoimh et al.), the area under the curve (AUC) was calculated to determine the performance of the Q*mci* for the total sample and each subgroup to classify

patients as normal cognition, MCI or dementia. Youden's index and Likelihood ratios were also used in the Q*mci* cut off study. Cut-off scores were calculated using Youden's Index for each possible outcome based upon ROC curves. To provide clinical relevance to the cut-offs, Likelihood ratios of the probability of having normal cognition and CI were determined. The positive Likelihood ratio (LR+) describes how the probability of disease shifts when the finding is present.

3.7 Conclusion

The first part in this chapter explains the KDD definition and process, which refers to the overall process of determining useful knowledge from databases. It includes three main phases: data pre-processing, data analysis, and data post-processing. Data pre-processing transforms raw data into an understandable format. It prepares the real world (raw) data for further processing. Data analysis is the core phase in KDD, which applying data analysis methods (algorithms) to enumerate patterns from it. This part presents two main data analytical approaches: data mining and statistics. They are closely connected and employed together during analysis. Data post-processing evaluates the extracted knowledge, visualizes it, or merely documents it for the end user.

Then this chapter introduces the data sources used in this research – the three clinical databases: the Geriatric Assessment Tool (GAT), the Doxycycline and Rifampin for Alzheimer's Disease (DARAD), and the Q*mci* Validation databases. The key instruments of these databases, and the studies they were used are also presented. The last section in this chapter describes the specific analytical methods used in the research. The key concepts of data analysis in medical research are introduced. These methods built the core part (data analysis) for the KDD process in the research. They are not only used in the studies of the research, but also the popular data analytical methods in general medical area, especially the geriatrics research. The next two chapters, Chapter Four and Five will present and discuss those

studies, describe how the methods were applied, and present the interesting/significant findings from the analysis outcomes.

CHAPTER 4 QUICK MILD COGNITIVE IMPAIRMENT (Q*mci*)

4.1 Introduction

This chapter provides a review of the different short cognitive screens that were in the research. Along with the Standardised Mini-Mental State Examination, the Quick Mild Cognitive Impairment (Q*mci*) screen is the other cognitive outcome measure that will be analysed in this work. It then presents a comprehensive description of the Q*mci* screen, detailing the rationale for developing the test and explaining its evolution in recent studies, from a previous version called the AB Cognitive screen 135. This chapter also explains the process whereby usable cut-off scores for the Q*mci* were developed in order to be able to use this test in subsequent analyses.

This chapter will initially present data that we used to establish the sensitivity and specificity of the Q*mci* for differentiating MCI from normal cognition and dementia. It was also compared with the SMMSE and its predecessor, the ABCS 135 (O'Caoimh et al., 2012a). Finally, it will explore the development of cut-off scores between normal, MCI and dementia, and the methods employed as part of this work to develop these cut-off scores. The analysis demonstrating the scientific validity and utility of the Q*mci* is based on the KDD (Knowledge Discovery in Databases) process, and assessed by different statistical methods. These will be described in detail.

4.2 Research Motivation

Adults with memory loss present a challenge to clinicians, who must determine if memory changes are part of normal aging or are consistent with cognitive impairment (CI), mild cognitive impairment (MCI) or dementia. Screening for CI is important to allow clinicians to identify reversible causes and initiate treatment so that patients and caregivers may plan for the

future (Boise et al., 1999). Screening for CI is limited, by a lack of sensitive and specific cognitive screening tests to differentiate normal cognition (NC) and MCI from dementia (Winblad et al., 2004). The effects of age and education further complicate this. Few tests are sensitive or specific in patients with low education (Cordell et al., 2013). Clinicians need standardised scoring formats that can measure changes over the full spectrum of cognitive decline from early (high ceiling) through to the later stages of dementia (low-floor). Given this, there is a need for short cognitive screening instruments that can differentiate NC from MCI and dementia, and accurately describe transition over the full spectrum of cognitive decline.

As discussed in Chapter Two, MCI represents a heterogeneous group of disorders of memory impairment (Petersen, 2004). Individuals with MCI have variable and often subtle cognitive changes, making accurate diagnosis difficult. Although many go on to develop dementia, the rate of progression varies from person to person, mainly due to variability in the definitions used (Fisk et al., 2003) and in the diagnostic methods employed.

4.3 Existing Cognitive Screening Instruments

Several cognitive screening tests are currently used in clinical practice including the Alzheimer's Disease Assessment Scale-cognitive section (ADAS-cog) (Rosen et al., 1984), the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), the SMMSE (Molloy and Standish, 1997b), the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and the original version of the Q*mci*, the AB Cognitive Screen 135 (ABCS 135) (Standish et al., 2007). This section will explore the psychometric properties of the different tests used. As the Alzheimer's Disease Assessment Scale-cognitive section (ADAS-cog) and the Standardised Mini-Mental state Examination (SMMSE) have been introduced in Chapter 3, we will not describe them again at here.

4.3.1 Mini-Mental State Examination (MMSE)

The Folstein Mini-Mental State Examination (MMSE) (Folstein et al., 1975) is one of the most widely employed cognitive screening tools for dementia patients, who present with cognitive impairment. It is used primarily to screen patients with cognitive impairment and quantifies cognitive deficits. It is useful in identifying dementia and in following cognition over time. The Standardised Mini-Mental State Examination (SMMSE) was developed to improve the accuracy of the MMSE. The SMMSE has explicit administration and scoring guidelines, and improved inter-rater reliability than the MMSE (Molloy et al., 1991a, Molloy and Standish, 1997b). Both the MMSE and SMMSE have a limited role in identifying MCI (Mitchell, 2009), as they lack sufficient accuracy to differentiate between NC and MCI, especially in patients with high levels of education (Crum et al., 1993). These factors limit the MMSE and SMMSE as useful screening tools.

4.3.2 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is another cognitive screening tool that has grown in popularity in recent years. Unlike the MMSE, it is highly sensitive and specific at differentiating MCI from NC and dementia (Nasreddine et al., 2005). Originally validated against the MMSE (Nasreddine et al., 2005), it has since been externally validated against different cognitive tests in different cognitive disorders (Gill et al., 2008, Videnovic et al., 2010, Wong et al., 2009). It takes longer than the MMSE, at least 10 minutes (Nasreddine et al., 2005) and has floor effects, limiting its use in those with advanced dementia (O'Caoimh et al., 2013c). It has a high sensitivity but a relatively low specificity at its recommended cut-off score (<26) (Smith et al., 2007). It was originally published in 2005 and was not available for analysis in any of the databases used in this work.

4.3.3 The AB Cognitive Screen 135

The AB Cognitive Screen 135 (ABCS 135) was also developed to improve the accuracy of diagnosing MCI and mild dementia. The ABCS 135 has five

domains: orientation, registration, clock drawing, delayed recall (DR) and verbal fluency (VF) (Molloy et al., 2005). It is administered in three to five minutes and is more sensitive in differentiating NC from MCI and dementia than the SMMSE (Molloy et al., 2005). Verbal fluency and delayed recall subtests in the ABCS135 were best at distinguishing between MCI and NC (Standish et al., 2007). Both subtests have a tendency to floor when administered to patients in the later stages of dementia. Orientation and registration are not sensitive to early cognitive change, but they decline at a linear rate through the later stages, providing a measure of change in established dementia. Clock drawing is useful to differentiate MCI from early dementia and to chart progression. Age and education affect both the ABCS135 and SMMSE (Molloy et al., 2005).

Although, the ABCS 135 is quick to use and accurate (Molloy et al., 2005), subsequent analysis of its domains suggested that much of the test may be redundant (Standish et al., 2007). Analysis had suggested that although all of the domains differentiate NC and MCI from dementia, orientation, registration and clock drawing did not enhance the ability of the test to differentiate NC from MCI. For this reason, the Quick Mild Cognitive Impairment (Q*mci*) screen was developed, to enhance the sensitivity of the ABCS 135, particularly for MCI.

4.4 Developing the Quick Mild Cognitive Impairment screen (Q*mci*)

4.4.1 Initial development of the Q*mci*

The Q*mci* has the same basic structure as the ABCS 135 except that it contains an additional subtest called logical memory (LM) giving it a total of six subtests, covering five domains: orientation, registration, clock drawing, delayed recall (DR), verbal fluency (VF) (naming animals) and LM. LM tests immediate verbal recall of a short story (Wechsler, 2008) and is not affected by age or education (Lichtenberg and Christensen, 1992). With the addition of LM, the ABCS 135' scoring was also reweighted, with

its total point score reduced from 135 points to 100 points (see Table 4.1).

Table 4. 1 Comparison of the ABCS 135 and the Q*mci* Screening Test

ABCS 135	**Score**	**Q*mci***	**Score**
Orientation	25	Orientation	10
Registration	25	Registration	5
Clock drawing	30	Clock drawing	15
Delayed recall	25	Delayed recall	20
Verbal fluency	30	Verbal fluency	20
		Logical memory	30

Previous analysis of the ABCS 135 domains found that DR and VF, were more sensitive at differentiating MCI from NC than orientation, registration and clock drawing (Standish et al., 2007). Given this, these three domains were reduced by a factor of 2.5, 5 and 2, respectively. The relative weighting of VF and DR were also increased relative to the other domains. The Q*mci* tool and scoring guidelines are presented in appendix.

4.4.2 Validation of the Q*mci*

To validate the Q*mci*, we previously compared the sensitivity and specificity of the newly developed Q*mci* with its predecessor the ABCS 135 and the SMMSE to distinguish individuals with NC from those with MCI and dementia (O'Caoimh et al., 2012a). In summary, subjects were analysed from the Q*mci* database that contained data from patients attending four memory clinics in Ontario, Canada (Hamilton, Paris, Niagara Falls and Grand Bend). In the Q*mci* database, data were available for 965 subjects. Normal controls were selected by convenience sampling. Caregivers, or those attending with the subjects, without memory problems were invited to participate as normal controls. Dementia was based on NINCDS (McKhann et al., 1984) and DSM-IV criteria (First, 1994). A diagnosis of MCI was made by a consultant geriatrician in patients who had recent, subjective but corroborated memory loss, without loss of social or occupational function.

Subjects under 55 years, unable to communicate verbally in English, diagnosed with depression, Parkinson's disease or Lewy-body dementia, and those without collateral were excluded. Each subject had the SMMSE and the Q*mci* administered. The ABCS 135 was reconstituted from the Q*mci* data by removing the LM domain and reweighting to a total of 135 points. The Shapiro–Wilk test was used to test normality and found that the majority of data were non-parametric. This data were analysed using the Mann–Whitney U test. Student's t-tests compared scores for parametric data. Data were also analysed using Receiver operating characteristics (ROC) curves. Pearson Chi-squared tests were used to compare distributions when it was not possible to analyse differences in medians. Each of the Q*mci* domains were subsequently analysed and compared with the SMMSE to investigate the psychometric properties of the individual parts of the test and how these contribute to the workings of the test as a whole (O'Caoimh et al., 2013a).

In the 965 participants included, there were 551 females (57%) and 414 males (43%). Of the total included, 630 subjects had NC (65%), 154 had MCI (16%) and 181 (19%) had dementia. The median age of the total population was 70.5 years. Subjects with normal cognition had a median SMMSE score of 29, those with MCI a score of 28 and those with dementia score of 22, compared with a median Q*mci* score of 76, 62 and 36 respectively. The results and demographics are summarised with inter-quartile range (IQR) in Table 4.3.

While all three tests distinguished dementia from MCI, the Q*mci* had greater accuracy in differentiating MCI from NC and MCI from dementia. Although the Q*mci*, ABCS 135 and the SMMSE were able to distinguish MCI from NC, the Q*mci* was more sensitive with an area under the curve (AUC) of 0.86 compared with 0.83 for the ABCS 135 and 0.67 for the SMMSE. The Q*mci* was also more sensitive at differentiating MCI from dementia, AUC of 0.92 versus 0.91 for the ABCS 135 and 0.91 for the SMMSE (O'Caoimh et al., 2012a). The results from this initial work showed that the Q*mci* was more sensitive than the SMMSE and the ABCS 135 in differentiating MCI

from NC, while all three are able to distinguish NC from dementia, the Q*mci* was a valid test to use in subsequent analyses of the databases in this work. The median Q*mci*, SMMSE and ABCS 135 scores, along with the median scores for the Q*mci* domains, for subjects with either MCI and NC or MCI and dementia are presented in Table 4.2.

Table 4. 2 The Total Q*mci*, SMMSE, ABCS 135 and Q*mci* Subtest Median Scores with IQR (Q1 = 1st Quartile, Q3 = 3rd Quartile) by Diagnosis

Item	**NC median (Q3-Q1 = IQR) (*n* = 630)**	**MCI median (Q3-Q1 = IQR) (*n* = 154)**	**Dementia median (Q3-Q1 = IQR) (*n* = 181)**	***P*-value of the median diff between MCI-NC**	***P*-value of the median diff between MCI-Dementia**	**Area under the Curve (95% CI*)* NC from MCI**	**Area under the Curve (95% CI*)* MCI from D**
Q*mci* total	76 (83–69= 14)	62 (68–53=15)	36 (45–23 = 22)	$P < 0.001$	$P < 0.001$	0.86	0.92
SMMSE total	28 (29–27 = 2)	28 (29–27 = 2)	22 (25–18 = 7)	$P < 0.001$	$P < 0.001$	0.67	0.91
ABCS 135	116 (121–109=12)	102 (111–94 = 17)	70 (84–46 = 38)	$P < 0.001$	$P < 0.001$	0.82	0.91
Qmci subtests (score out of)							
Orientation (10)	10 (10–10 = 0)	10 (10–9 = 1)	7 (9–5 = 4)	$P < 0.001$	$P < 0.001$	0.57	0.88
Registration (5)	5 (5–5 = 0)	5 (5–4 = 1)	5 (5–3 = 2)	$P < 0.001$	$P = 0.002$	0.56	0.64
Clock drawing (15)	15 (15–15 = 0)	14 (15–13 = 2)	11 (14–2 = 12)	$P < 0.001$	$P < 0.001$	0.67	0.76
Delayed recall (20)	16 (20–12 = 8)	12 (16–8 = 8)	0 (8–0 = 8)	$P < 0.001$	$P < 0.001$	0.73	0.84
Verbal fluency (20)	11 (13–9 = 4)	7 (9–6 = 3)	4 (6–2 = 4)	$P < 0.001$	$P < 0.001$	0.77	0.83
Logical memory(30)	20 (24–16 = 8)	12.5 (16–10=6)	8 (10–2 = 8)	$P < 0.001$	$P < 0.001$	0.80(0.77-0.84)	0.82(0.77-0.86)

Results suggested that LM was the most accurate domain for separating MCI from NC with an AUC of 0.80, higher than the ABCS 135 (0.80) and SMMSE (0.67). The other domains, VF (0.77), and DR (0.73) registration for words (0.56), orientation (0.57) and clock drawing (0.66) were the less accurate. The ability of the tests to differentiate MCI from dementia, including the ability of the Q*mci* domains is also presented in Table 4.3.

In summary, the Q*mci* (total), ABCS 135, SMMSE and LM had similar ability to differentiate MCI from dementia, suggesting that no single test is superior in the assessment of patients with established CI. Each of the domains of the Q*mci* accurately distinguished MCI from dementia, although the best performing test was now orientation (AUC of 0.88) suggesting that different domains have different utilities depending on whether one is trying to differentiate MCI from NC or MCI from dementia.

4.5 Developing the Q*mci* Cut Offs

4.5.1 Rationale for Developing Cut-offs for the Q*mci*

The utility of screening instruments depends upon their sensitivity and specificity in the diagnosis of the condition being sought. For short cognitive screens, cut-off scores for transition points between different cognitive states are required. Cognitive tests provide a range of scores which mean that clinicians must select cut-off scores to optimize sensitivity and specificity. Useful screening instruments should be responsive to change across the cognitive spectrum, from normal cognition to MCI and dementia. Additionally, there are no published cut-offs for the Q*mci*. In order to use the test in subsequent analyses, we performed a study to define cut-off scores for the Q*mci*.

4.5.2 Methods for Developing the Cut-off Scores

In this study, we pooled three databases the Q*mci* validation database, the GAT (Geriatric Assessment Tool) database, and the DARAD (Doxycycline

And Rifampacin for Alzheimers Disease) trial database (Molloy et al., 2012), to try to develop the cut-off scores between normal, MCI and dementia. Subjects were included if their Q*mci* scores, diagnosis, age and educational level were available. Inclusion and exclusion criteria were similar to the Q*mci* Validation Database (O'Caoimh et al., 2012a). Table 4.3 presents the baseline demographic data for patients included from the three databases.

Table 4. 3 Baseline Demographics for Q*mci* Patients in GAT, DARAD, and Q*mci* Validation Databases

Database	No of Patients Available	No of assessments included	NC (n=x)	MCI (n=x)	Dementia (n=x)	Age (Mean+/-SD)	Gender (% male)	Education (Mean+/-SD)	Q*mci* score (Mean+/-SD)
DARAD	413	1,697	0	0	381	77.6 +/-7.0	49.5%	12.2+/-3.5	35.9+/-14.5
GAT	1,034	1,894	114	163	414	77.7 +/- 7.9	53.6%	11.9+/-3.9	45.7+/-20.2
Q*mci* (validation)	965	940	624	149	167	70.2+/-9.8	42.8%	13.1+/-3.6	65.6+/-19.6
Total	2,412	4,531	738	312	962	76.1+/-8.6	49.8%	12.2+/-3.7	46.2+/-21.1

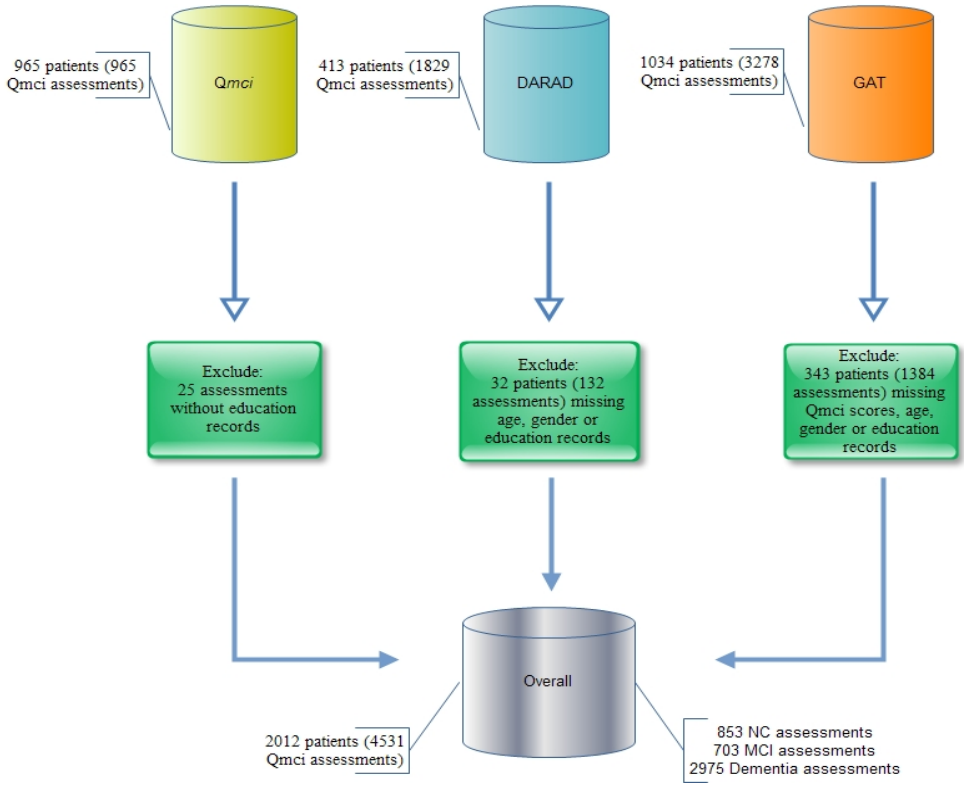


Figure 4. 1 Flow Chart Demonstrating the Recruitment of Patients from the Three Databases

The Q*mci* is scored out of 100 points. Pooled data were grouped by age and education, and the Q*mci* cut-offs were analysed for each subgroup. The cut-off for age was 75 years, as this provided the best balance in numbers between the four subgroups. Age 75 also represents the accepted age cut-off for CI using the MMSE (Ylikoski et al., 1992), above which scores must be adjusted to account for age. The cut-off for education was 12 years, as the average length of formal schooling in North America (United States and Canada) is 12 years, equivalent to leaving education after high school, between 16 and 17 years of age[19]. The population was divided according to age and education, to create four subgroups: age ≤ 75 with education ≥ 12 years, (n=1176); age ≤ 75 with education ≤ 12 years (n=611), age > 75 with education < 12 years, (n=1234); and age > 75 with education ≥ 12 years, (n=1510). Table 4.4 provides the total number, gender, mean age, education and Q*mci* scores for the total sample and the four subgroups.

[19] http://www.nationmaster.com/country-info/stats/Education/Average-years-of-schooling-of-adults

Analyses were conducted using SPSS 18.0. The Shapiro–Wilk test assessed normality, the Mann–Whitney U test compared non-parametric data, and student's t-tests compared parametric data. The Kruskal-Wallis test for comparisons between two or more groups. Youden's Index was used to estimate the best balance sensitivity and specificity at each cut-off for the Q*mci*. The area under the curve (AUC) was calculated to determine the performance of the Q*mci* for the total sample and each subgroup to classify patients as normal cognition, MCI or dementia.

4.5.3 Developing Cut-off Scores

Cut-off scores were calculated using Youden's Index (Youden, 1950) for each possible outcome based upon receiver operating characteristics (ROC) curves. These Cut-off scores were chosen to give the best balance between sensitivity and specificity. Priority was given to sensitivity, aiming for a minimum sensitivity of 85% and if possible, a specificity of 85%. We tried to balance sensitivity and specificity to maximize both, choosing scores to stretch out the point differences between the different diagnoses, maximizing the range for MCI.

To provide clinical relevance to the cut-offs, Likelihood ratios of the probability of having normal cognition and CI were determined. The positive Likelihood ratio (LR+) describes how the probability of disease shifts when the finding is present. A score of two to five suggests a small chance, five to ten moderate and >10 a large chance. The negative Likelihood ratio (LR-) describes how the probability of disease shifts when it is absent (McGee, 2002). A score of 0.2-0.5 suggests a small chance, 0.1-0.2 moderate and <0.1 a large chance.

4.5.4 Results for the Q*mci* Cut-off Scores

Baseline demographic data are provided in Table 4.4. After excluding patients with missing data, 2,012 subjects, representing 4,531 assessments, were available for analysis. Of these, 853 had NC, 703 MCI and 2975

dementia, (Figure 4.1). The median age at the time of assessment was 78 years, interquartile range (IQR) 11. The median Q*mci* score for normal cognition was 75 (IQR 15) points, for MCI 57 (IQR 20) and dementia 37 (IQR 23). The scores were significantly different in the three groups, $p<0.001$. Based upon Youden's Index, a cut-off score of 60/100 provided the best balance between sensitivity and specificity for the overall population for CI, and 50/100 for dementia. At these cut-offs of the Q*mci* had a sensitivity of 89% and specificity of 86% for CI (AUC 0.95, 95% confidence interval 0.94-0.95), and a sensitivity of 84% and specificity of 79% for dementia (AUC of 0.89, 95% confidence interval 0.88-0.90). The cut off scores for overall population and subgroups were presented in Table 4.4.

Table 4. 4 Q*mci* cut-off Scores with Sensitivity and Specificity Grouped by Age and Education Comparing Patients with NC to CI and those with Dementia Compared to the Rest

		Optimal Cut-off	Sensitivity	Specificity
Overall	*NC vs CI*	60	89%	86%
	D vs rest	50	84%	79%
Age ≤ 75 Edu < 12	*NC vs CI*	57	84%	82%
	D vs rest	47	85%	80%
Age ≤ 75 Edu ≥ 12	*NC vs CI*	67	86%	89%
	D vs rest	53	93%	81%
Age > 75 Edu < 12	*NC vs CI*	54	85%	81%
	D vs rest	42	80%	62%
Age > 75 Edu ≥ 12	*NC vs CI*	56	87%	81%
	D vs rest	47	82%	71%

Table 4.4 provides cut-off scores and sensitivity and specificity levels for NC, the threshold for CI (NC from MCI and dementia), and dementia (dementia from NC and MCI), for the overall population and four subgroups, divided according to age and education, selected using the Youden's Index. The optimal cut-off for identifying CI for older subjects (>75) with less time in formal education (<12) fell from 62 to 54 points. Sensitivity and specificity for detecting CI were highest for younger (≤ 75) subjects with more education (≥ 12), at 88% and 87% respectively and lowest for the

oldest subjects (>75) with less formal education (<12), at 85% and 81% respectively. This subgroup also had the lowest sensitivity and specificity for detecting dementia, 80% and 62%, at a cut-off of 42. The Q*mci* was most accurate at separating CI from NC for younger subjects (≤75), with more time in formal education (≥12), AUC of 0.95. The Q*mci* was least able to differentiate CI from NC (AUC of 0.89) and dementia (AUC of 0.81), in older subjects (>75) with less (<12) formal education, with sensitivities and specificities falling correspondingly. The points range between NC and dementia cut-offs, was wider for younger subjects with more formal education, 67 to 53, (14 point spread), and narrowest for older subjects with less education, 56 to 46, (nine points). The distribution of Q*mci* cut-offs for the population overall and each subgroup is illustrated in Figure 4.2.

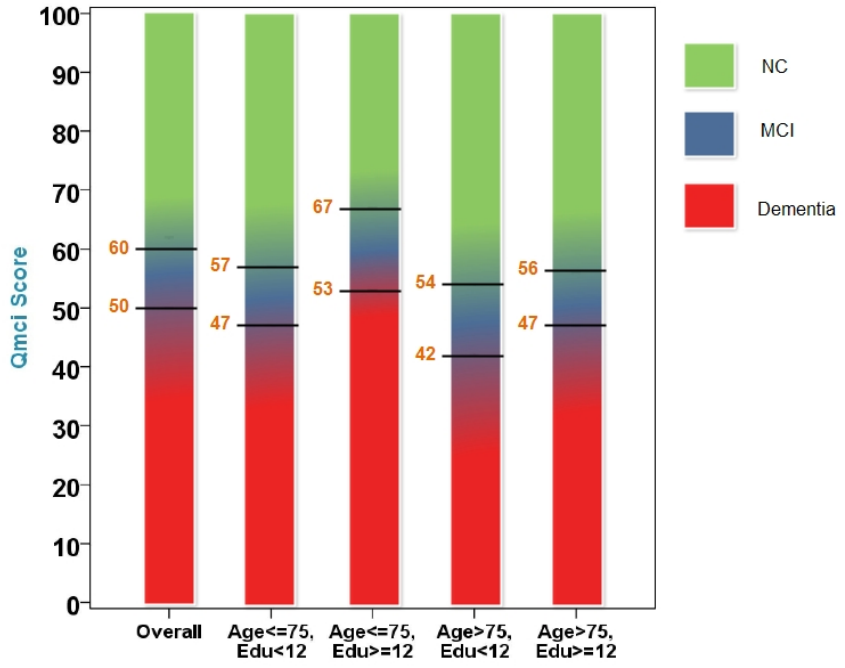


Figure 4. 2 Distribution of the Q*mci* Cut-off Scores for all Patients and Four Subgroups Stratified by Age and Education, Based on Sensitivity and Specificity of each Score

Likelihood ratios were calculated for the cut-off scores for the total population and each subgroup. Those at or below 60, the cut-off that provided the best balance between sensitivity and specificity for the presence of CI, had a moderate chance of having CI (NLR 0.17). Above 60,

there was a moderate chance of having NC (PLR 7.88). Above 65 there was a large chance (PLR >10) of having NC whereas at or below 65 the chance of having NC was small (NLR 0.23). Those at or below 50, the optimal cut-off score for detecting dementia, had moderate chance of having dementia (PLR 5.0) while above 50 there was a small chance of having dementia (NLR 0.28). Likelihood ratios also confirmed the choice of cut-off scores for each subgroup. For example, the cut-off above which younger subjects (≤75) with more formal education (≥12) had a large chance of being normal was 70. At or below 70, the chance of not being normal was also small, confirming that the optimal cut-off (≤67), lies below this.

4.5.4 Discussion of the Q*mci* Cut-off Scores

Thus, cut-off scores for the Q*mci* screen, adjusted for age and education were now available for subsequent analysis of the databases. In summary, a cut-off score of ≤60 points, provided the best balance between sensitivity and specificity for the Q*mci*. At this cut-off, it had an 89% sensitivity and 86% specificity for CI comparing well with other short cognitive tests such as the widely used MoCA which has a similar sensitivity of 90% (Nasreddine et al., 2005) but a lower specificity (Luis et al., 2009, Smith et al., 2007) at its recommended cut-off of ≤26 (Nasreddine et al., 2005). However, it must be remembered that cut-off scores, simply indicate transition points and should be interpreted with caution as cognitive performance is affected by individual variations in age and educational level (Crum et al., 1993). Placing emphasis on cut-offs rather than clinical assessment, could be misleading (Cullen et al., 2007). Obviously if 60 were a cut-off and a person scored 59 or 61, then a diagnosis is less certain than a person who scored 57 or 67. The closer a person scores to the cut-off, the less certain the diagnosis is. And clinicians know this and will rely on other factor in making a diagnosis clinically.

In summary, this section provides usable cut-off scores for the Q*mci* based upon large numbers of patients presenting with memory loss across both clinical and research settings. It shows that the Q*mci* can differentiate MCI

from NC and dementia and suggests superior sensitivity and specificity over other short cognitive screens such as the SMMSE and MoCA. This analysis also provided cut-off scores adjusted for age and education that while not used directly in subsequent analysis provide an important part of the development of any short cognitive screening test. Based upon this analysis, a cut-off score of <60 for CI (either MCI or dementia), a range of 59 to 51 for MCI, and <50 points for dementia. Thus, the Q*mci* is a useful tool in the clinic to screen for CI and to differentiate between normal cognition, MCI and dementia.

4.6 Comparison of the Q*mci* with Other Cognitive Tests

Apart from its validation against the SMMSE and its predecessor, the ABCS 135, the Q*mci* has also been compared with other cognitive and functional outcome measures. These include the MoCA (O'Caoimh et al., 2013c), the SADAS-cog, the Clinical Dementia Rating (CDR) scale and the Lawton-Brody activities of daily living scale (O'Caoimh et al., 2014). The recently developed MoCA is widely validated in the detection of early CI (Nasreddine et al., 2005), but although it has excellent sensitivity for CI, particularly for MCI and early dementia, its specificity has been questioned in older adults, especially those with lower levels of formal education. Comparison of the Q*mci* with the MoCA showed that the Q*mci* was more accurate with shorter administration times (O'Caoimh et al., 2013c). Specifically the Q*mci* was more accurate than the MoCA in differentiating MCI from those with normal cognition, area under the curve (AUC) of 0.82 versus 0.74. It also had superior accuracy in differentiating MCI from dementia, AUC of 0.96 versus 0.91. At the recommended cut-off scores for each test, the Q*mci* (<60) had greater sensitivity (88%) and specificity (88%) for cognitive impairment, compared with 96% and 41% respectively for the MoCA (<26). Median administration times are 4.52 minutes for the Q*mci* compared with 9.52 minutes for the MoCA.

We have also compared the Q*mci* with other direct and indirect cognitive screens including the SADAS-cog, a marker of ADLs, the Lawton-Brody

scale and a global test of dementia, the CDR scale. By comparing rates of change, over the one year of follow-up in a clinical trial, the DARAD, we showed that the Q*mci* had strong and significant correlation with the SADAS-cog and moderate significant correlation with ADLs and the CDR scale (O'Caoimh et al., 2014).

4.7 Conclusion and Rationale for Using the Q*mci*

Multiple short cognitive screens are in currently available to clinicians (Cullen et al., 2007), the most widely used of which is the MMSE (Folstein et al., 1975) and its standardised form, the SMMSE. There are however, several well-established difficulties with using these in clinical practice, particularly where screening for MCI and early dementia (Mitchell, 2009) and especially among older adults with high educational attainment (Crum et al., 1993). Using the cut-off scores described in section 4.5, recent research has shown that the Q*mci* has superior accuracy for identifying MCI from NC in older adults attending a memory clinic, compared with the SMMSE and the MoCA, the same population as will be assessed in this work. Although both the Q*mci* and MoCA differentiated MCI from NC and dementia, the Q*mci* was more accurate and has a shorter administration time. The MoCA had a low specificity for CI and a high rate of false positives, suggesting that it is less clinically useful among older adults.

Overall, the Q*mci* is a short screening test for cognitive impairment, developed as a rapid, valid and reliable tool for the early detection and differential diagnosis of mild cognitive impairment (MCI) and dementia (O'Caoimh et al., 2012a). The Q*mci* includes a selection of domains that while useful have different accuracy at different stages of disease progression. The Q*mci* has six domains: orientation, registration, clock drawing, delayed recall, verbal fluency (naming animals) and logical memory (LM), an immediate verbal recall of a short story. It is scored out of 100 points and has a median administration time of 4.24 minutes (O'Caoimh et al., 2013a). The Q*mci* was derived from the ABCS 135 by reweighting its subtests and adding LM (O'Caoimh et al., 2012a). It has superior sensitivity

and specificity for differentiating MCI from normal cognition and dementia compared to the SMMSE and the AB Cognitive screen 135 (O'Caoimh et al., 2012a). It also correlates with the SADAS-cog, CDR scale and the Lawton-Brody activities of daily living scale (O'Caoimh et al., 2013b). In the next chapter, Q*mci* will perform as a key cognitive measurement with SMMSE in the studies, which explore the effects of centrally acting ACE inhibitors in dementia.

CHAPTER 5 DRUG ANALYSIS

5.1 Introduction

There is growing evidence that antihypertensive agents, particularly centrally acting ACE inhibitors (CACE-Is), that cross the blood–brain barrier, are associated with a reduced rate of cognitive decline. This chapter describes how CACE-Is, one of the first anti-hypertensives to be studied, are associated with reduced rates of cognitive and functional decline in dementia, measured with Q*mci*, SMMSE and ADL tests, as the key outcome measures.

The centrally acting ACE inhibitors in this PhD research included perindopril, coversyl, aceon, ramipril, altace, tritace, lisinopril, captopril, capoten, co-zidocapt, capozide, fosinopril, monopril, zestril, prinivil, trandolapril, mavik and Tarka. Of these, perindopril, coversyl and aceon were in the perindopril group, the other centrally acting ACE inhibitors were in the "other CACE-I" group. Patients who were not currently prescribed CACE-Is were called NoCACE-I group.

This chapter discusses the association between anti-hypertensive agents, especially CACE-Is, with dementia, on cognition and function. There were three studies examined the effect of CACE-Is, on cognitive and functional rate of decline in patients with dementia. The data analyses in those studies were based on a KDD (Knowledge Discovery in Databases) process. The sections for these three studies (Section 5.3 - 5.5) rely on the data pre-processing, data analysis and data post-processing (results) procedures. The first study used the GAT (Geriatric Assessment Tool) database. We compared rates of cognitive decline in clinic patients with dementia, receiving CACE-Is (CACE-I group), to NoCACE-I group, and to those who started CACE-Is, during their first six months of treatment (NewCACE-I group). The second study used the Doxycycline and Rifampin for

Alzheimer's Disease (DARAD) database. The aim of this study was to compare rates of cognitive, functional and neuropsychological (depression and behaviour) decline in dementia patients receiving CACE-Is (CACE-I) to those not currently treated with CACE-Is (NoCACE-I). The third study pooled the GAT and DARAD databases together. We subdivided CACE-I group into perindopril and other CACE-I subgroups, and compared the rates of functional and cognitive decline in patients with established dementia between those groups. To examine the impact of CACE-Is on ADLs, we also separated ADLs into basic ADLs (BADLs) and instrumental ADLs (IADLs) to compare the rate of functional decline in subjects with dementia, who were receiving CACE-Is or not treated with CACE-Is (NoCACE-I).

5.2 Background

5.2.1 Anti-hypertensive Agents for Cognition in Dementia

As the worldwide populations aged, the incidence of dementia will increase. By 2040, approximately 81 million people worldwide will have dementia (Ferri et al., 2005). To date, no agents have been identified that prevent, modify or reverse dementia, and available treatments for dementia are predominantly symptomatic (Sloane et al., 2002). There is growing recognition of the role of cardiovascular risk factors, especially in mid-life, in the development and progression of mild cognitive impairment and dementia (Whitmer et al., 2005, Breteler et al., 1994, Rozzini et al., 2008).

Blood pressure (BP) control, in particular, is associated with both a reduced incidence of cognitive impairment and rate of cognitive decline (Duron et al., 2009, Ligthart et al., 2010, Collaborative et al., 2003, Oveisgharan and Hachinski, 2010). Varieties of anti-hypertensives improve cognition in older adults with elevated BP (Fogari et al., 2003, Fogari et al., 2004) and have potential as therapeutic agents in dementia (Kehoe and Passmore, 2012, Fournier et al., 2009, Davies et al., 2011). Results are however inconsistent (Staessen et al., 2011, Poon, 2008, Sink et al., 2009) with some observational studies even suggesting harm (Kehoe et al., 2013).

5.2.1.1 Anti-hypertensive Agents and Dementia

Several anti-hypertensive agents are associated with a reduced risk of developing dementia, including calcium channel blockers (CCBs) (Tollefson, 1990, Kennelly et al., 2012), diuretics (Collaborative et al., 2003), angiotensin receptor blockers (ARBs) (Hajjar et al., 2012b, Li et al., 2010, Lithell et al., 2003), and angiotensin converting enzyme inhibitors (ACE-Is) (Ohrui et al., 2004, Rozzini et al., 2006).

Angiotensin Converting Enzyme Inhibitors, (ACE-Is) and Angiotensin Receptor Blockers (ARBs) may lower dementia risk or slow progression, independent of their BP lowering properties (Davies et al., 2011, Li et al., 2010, Hajjar et al., 2009, Hajjar et al., 2012c). Prescription of ARBs and ACE-Is is also associated with reduced incidence of both vascular dementia (VaD) and mixed dementia subtypes (Hanes and Weir, 2007, Davies et al., 2011). Results of clinical trials investigating the potential role of anti-hypertensives are limited and conflicting (Poon, 2008). The Perindopril Protection against Recurrent Stroke Study (PROGRESS), demonstrated that a combination of Perindopril (ACE-I) and indapamide (diuretic) was associated with a significant reduction in the incidence of stroke and in cognitive decline, compared to placebo (Collaborative et al., 2003). The Systolic Hypertension in Europe (Syst-Eur) study, found that the combination of enalapril (ACE-I), nitrendipine (CCB), and/or hydrochlorothiazide (diuretic), reduced the incidence of dementia by 55%, compared to placebo (Staessen et al., 1997, Forette et al., 2002). Mono-therapy with the ARB, candesartan, in the Study on Cognition and Prognosis in the Elderly (SCOPE), also showed modest effects (Lithell et al., 2003). Not all studies have shown cognitive benefits with anti-hypertensive agents; some implicate them in the worsening of cognition (Maxwell et al., 1999). The ONTARGET and TRANSCEND trials, two parallel studies involving more than 25,000 patients, found that ACE-Is did not have any measurable effects on cognition (Teo et al., 2004). Although the evidence is limited, treatment with anti-hypertensives has been associated with reduced

rates of cognitive (Mielke et al., 2007, Bellew et al., 2004) and functional decline (Rosenberg et al., 2008a) in those with established AD.

ACE-Is were one of the first anti-hypertensives to be studied, particularly in Alzheimer's disease (AD), the most prevalent form of dementia (Brunnström et al., 2009). Patients with AD have abnormal cleavage of amyloid precursor protein (APP) resulting in a pathological accumulation of amyloid beta (Aβ), a key neuropathological hallmark of AD (Hardy, 2009). The relationship between angiotensin converting enzyme (ACE) and the accumulation of Aβ is complex and different polymorphisms have been postulated to either increase (Kehoe et al., 1999), or decrease (Lehmann et al., 2005), the risk of developing AD. ACE activity is increased in AD, proportional to the Aβ load (Miners et al., 2007).

5.2.1.2 Centrally-acting ACE–Is and Cognition

Centrally acting ACE-Is (CACE-Is), a sub-group of ACE-Is, that cross the blood-brain barrier, are associated in observational studies, with a reduced incidence of mild cognitive impairment (MCI) (Solfrizzi et al., 2011, Rozzini et al., 2006) and dementia (Sink et al., 2009), and slower rates of cognitive decline in Alzheimer's disease (AD), relative to non-centrally acting ACE-Is (Ohrui et al., 2004, Gao et al., 2013a). The CACE-I perindopril when administered to mouse models, showed a significant protective effect (Dong et al., 2011b) and reversed cognitive impairment more than the non-centrally acting imidapril and enalapril (Yamada et al., 2010). Patients receiving CACE-Is have a reduced rate of cognitive decline compared to both non-centrally acting ACE-Is and CCBs (Ohrui et al., 2004). The Cardiovascular Health Study demonstrated no reduced risk in incident dementia in those taking CACE-Is, compared to other classes of anti-hypertensives (Fried et al., 1991). Those prescribed CACE-Is, had a reduced rate of cognitive decline and less impairment in instrumental activities of daily living (IADL's), compared to those taking non-centrally acting agents (Sink et al., 2009).

The strongest pre-clinical evidence to date for the utility of ACE-Is in affecting cognitive decline is for the CACE-Is, perindopril. Perindopril reversed Aβ induced cognitive impairment (Yamada et al., 2010), inhibited brain ACE activity, elevating extra cellular acetylcholine levels in mice (Yamada et al., 2011), while two non-centrally acting ACE-Is, did not. Perindopril, but not other ACE-I's, significantly inhibited hippocampal ACE, and prevented cognitive impairment in mouse models of AD (Dong et al., 2011b, Tota et al., 2012). Clinically, the Cardiovascular Health Study reported observational data that perindopril, rather than non-centrally acting ACE-Is and calcium channel blockers, decreased the rate of decline in patients with mild to moderate AD (Sink et al., 2009). Results however are inconsistent. Secondary analyses of randomized trials have failed to detect an effect of ACE-Is (Teo et al., 2004) or ARBs on cognition (Staessen et al., 2011, Lithell et al., 2003). Furthermore, a small placebo controlled clinical trial in non-demented offspring of AD patients showed no effect on cognition (Wharton et al., 2012).

Outside of clinical trials, there is little data on the effects of CACE-Is on the rate of cognitive decline in patients with dementia. Given this, and the growing evidence for anti-hypertensive agents, particularly CACE-Is, in reducing the incidence and rate of cognitive decline, in Chapter 5.3, we compared the rates of decline in patients taking CACE-Is (CACE-I), to those not currently prescribed CACE-Is (NoCACE-I), in patients with established dementia, attending a memory clinic, based on GAT database. In that section, we also examined whether patients started on CACE-Is while attending clinic (NewCACE-I), behaved differently during their first six months of treatment, compared to the NoCACE-I group, and those already established on CACE-Is.

5.2.2 Anti-hypertensive Agents and ADL Function in Dementia

Impaired activities of daily living (ADL) affect functional independence and patient quality of life (Liu et al., 1991). Changes in ADLs represent the hallmark characteristic of progression from mild cognitive impairment

(MCI) to dementia (Patterson et al., 2007), and signal onset of progressive cognitive decline in patients with established dementia (Mortimer et al., 1992). Loss of instrumental ADLs (IADLs), such as shopping or cooking, usually occur before the loss of basic ADLs (BADLs), like dressing or toileting (Pérès et al., 2008). Hypertension is highly prevalent in older adults, including in those with cognitive impairment (CI) (Igase et al., 2011).

- **Hypertension, ACE inhibitors and Activities of Daily Living**

Hypertension may increase the risk of decline in ADLs in patients with dementia (Stuck et al., 1999). This has been found for IADLs but not BADLs (Caskie et al., 2010). Although few studies have assessed the effects of anti-hypertensive agents on rates of functional decline in patients with established dementia, data from recent observational studies suggests that beta-blockers (Rosenberg et al., 2008b) and ACE-Is may slow functional decline in patients with mild to moderate Alzheimer's disease (AD) (O'Caoimh et al., 2014). Available evidence suggests that ACE-Is are associated with improved physical function (exercise tolerance), increased muscle strength and lower falls risk (Sumukadas et al., 2007, Wong et al., 2013), in older adults with normal cognition. Furthermore, the discontinuation of ACE-Is in those with AD is associated with increased rates of functional decline (Regan et al., 2006). For example, vascular dementia has been associated with a condition called amyloid angiopathy, in which amyloid plaques accumulate in the blood-vessel walls, causing them to break down and rupture.

ACE-Is may slow functional decline by reducing inflammation, improving endothelial function and increasing muscle blood flow and glucose delivery to skeletal and cardiac muscle (Onder et al., 2002). Contradicting this, other observational studies suggest that exposure to ACE-Is is associated with increased dependency in ADLs (Sink et al., 2009), and studies investigating ACE genotypes, some of which might mimic or have comparable biological ACE activity to ACE-Is, had conflicting results on functional decline in older adults, with both increased (Seripa et al., 2011)and decreased disability (Kritchevsky et al., 2005) observed. Hence, Chapter 5.4 compared

rates of decline in patients with Alzheimer's disease (AD) receiving CACE-Is to those not currently treated with CACE-Is (NoCACE-I) in patients with mild to moderate AD, in the DARAD database.

To date, few studies have investigated whether ACE-Is affect ADLs, and to our knowledge, none if they differentially affect IADLs or BADLs. Given this, and the recent, albeit often conflicting data favoring CACE-Is in reducing the incidence and rate of cognitive decline, in Chapter 5.5, we pooled the GAT and DARAD databases together, and compared the rates of cognitive and functional decline (including IADLs and BADLs) in community dwelling older adults with established dementia taking CACE-Is (CACE-I), to those not currently prescribed CACE-Is (NoCACE-I).

5.3 Effects of CACE-Is on the Rate of Cognitive Decline in Dementia (*Study One: CACE Study in GAT Database*)

5.3.1 Introduction

The first study investigated whether patients with dementia, receiving CACE-Is, had slower rates of cognitive decline compared to others, who were not receiving CACE-Is (NoCACE-Is), irrespective of blood pressure readings or diagnosis of hypertension, based on Geriatric Assessment Tool (GAT) database. We also examined whether patients started on CACE-Is, while attending clinic (NewCACE-I), behaved differently in the first six months of treatment compared to the average change in those taking CACE-Is over a longer period of time.

This database includes two cognitive screening test score, the Standardised Mini-Mental State Examination (SMMSE) (Molloy et al., 1991a, Molloy and Standish, 1997b) and the Quick Mild Cognitive Impairment (Q*mci*) screen (O'Caoimh et al., 2012a, O'Caoimh et al., 2013a). These tests were scored by nurses in the clinic prior to the assessment, who were test-blind to the diagnosis. Cognitive assessments were performed to assist in diagnosis, treatment effects and to follow progression.

5.3.2 Data Pre-processing – Subjects Selection

A consultant geriatrician diagnosed the patients with dementia using NINCDS (McKhann et al., 1984) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (First, 1994). Patients with AD, vascular or mixed dementias (Alzheimer's/vascular) were included in the analysis. Patients with Lewy body dementia, Parkinson's disease dementia, frontotemporal dementia, alcohol-related dementia, post-trauma and post-anaesthetic dementia, were excluded, as there is little evidence that antihypertensive medications affect these dementia subtypes. Patients with normal cognition, n=181, MCI, n=235 and depression, n=397 were also excluded. Participants with depression (n= 397) were excluded: 260 with CI and comorbid depression, and 137 with normal cognition and depression, as there is little evidence that ACE-Is affect comorbid depression (Rogers and Pies, 2008), while the results of cognitive testing are negatively affected by depression (Porter et al., 2003). Patients were also excluded from the analysis if they did not have the results of either the Q*mci* or SMMSE available at both the baseline and end point (last visit). In total, 456 (56%) dementia patients with only one cognitive test record were excluded. In order to facilitate comparisons, changes between the baseline and end-point scores were standardised at six months, between all groups. There was no significant difference in baseline SMMSE (p=0.06) or Q*mci* scores (p=0.51), using regression analysis, adjusting for baseline characteristics (age, gender, education and BP) between participants without follow-up and those included. Figure 5.1 graphically presents the process of patient selection.

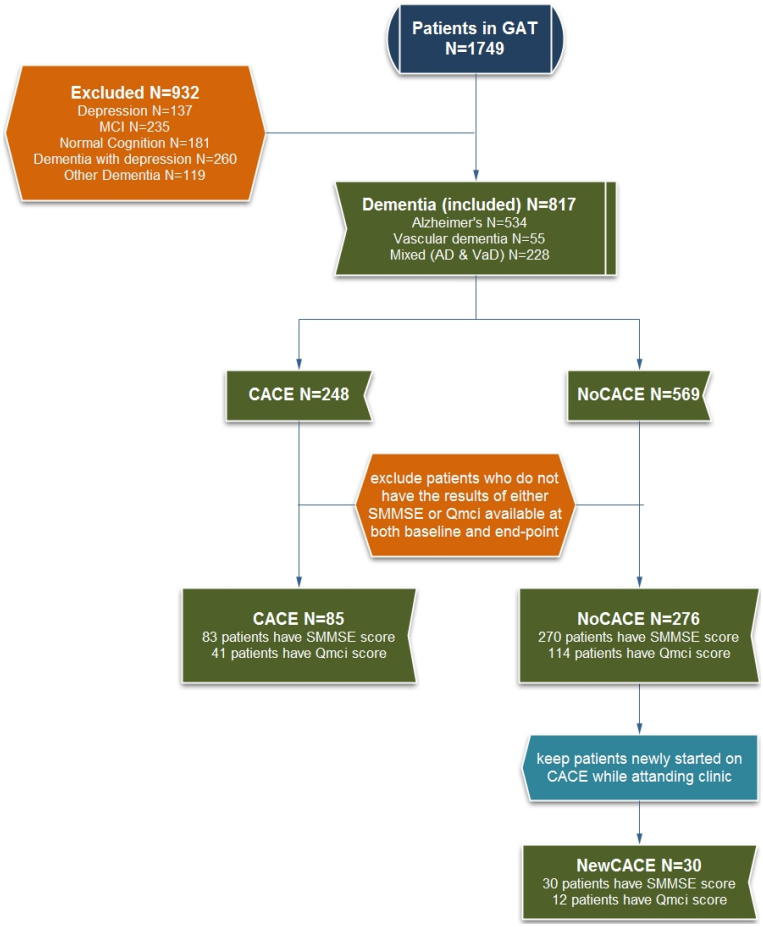


Figure 5. 1 Flow Chart Demonstrates the Breakdown of the Patients Who were Included in the GAT Database

The CACE-I group included patients currently prescribed the centrally acting ACE inhibitors. NoCACE-I included patients who were not currently receiving centrally acting ACE inhibitors, irrespective of the BP readings, diagnosis of hypertension or whether they were receiving other antihypertensive medications.

5.3.3 Data Analysis

Baseline Q*mci* and SMMSE scores (the time-point when cognitive scores were first available for each subject) were compared to end-point scores (the time-point when cognitive scores were last available), between subjects taking CACE-Is and NoCACE-Is, and between those newly started on CACE-Is during a clinic visit (NewCACE-Is) and all other CACE-Is

subjects. The goal was to determine whether there were differences in their rates of cognitive decline. Average rates of decline in cognitive scores were initially calculated for each subject, per month. Given that regulatory authorities, including the Food and Drug Authority, require evidence of change in cognitive tests over six months, to confirm the benefit of new medications, longitudinal outcomes were changes measured from baseline, expressed on a six monthly basis (Matthews et al., 2000), according to the formula: Rate of decline = (Baseline score – End-point score)/ Duration in months.

Data were analysed using SPSS V.18.0. Normality was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Mann-Whitney U test was used to compare the non-normally distributed data. Categorical data were analysed with χ^2 tests. Multivariate regression was used to compare rate of change between the three groups (CACE-I, NoCACE-I and NewCACE-I), adjusted for the baseline cognitive scores and characteristics (age, years of education, duration of follow-up and BP). Data were presented as median and interquartile range (IQR), as most of them were non-parametric.

5.3.4 Results

5.3.4.1 Baseline Characteristics

Table 5.1 and 5.2 present demographics, medication use, baseline and end-point Q*mci* and SMMSE scores for subjects taking CACE-Is, NoCACE-Is or NewCACE-Is. There were 817 subjects, in total, with dementia, who were divided into CACE-Is, (n=248) and NoCACE-Is (n=569). The mean age of the total sample was 77.9, with a SD of $\pm$ 8.1 years. The mean age of subjects taking CACE-Is, was 77.2, compared to 77 for the NoCACE-Is group. There were no significant differences in age profiles between the two, p=0.57. The total sample was 50.3% male. Subjects receiving CACE-Is were 51.8% male, compared to 49.6% of NoCACE-Is subjects, and again there was no significant difference between both groups, p=0.12. There were no differences in use of cholinesterase

inhibitors or mean-time between subjects taking CACE-Is, NoCACE-Is or NewCACE-Is.

Table 5. 1 Baseline Characteristics of CACE-I, NoCACE-I and NewCACE-I Patients

Groups	CACE-I	NoCACE-I	NewCACE-I
Number	85	276	30
Age (mean ± SD)	77.2 ± 6.4	77.0 ± 7.6	77.3 ± 8.2
Male (%)	44 (51.8 %)	137 (49.6%)	15 (50%)
Education (mean ± SD)	10.6 ± 3.8	11.4 ± 4.0	12.1 ± 3.9
Systolic BP in mmHg (mean ± SD)	133.4 ± 21.2	135.5 ± 16.9	141.1 ± 16.2
Diastolic BP in mmHg (mean ± SD)	70.1 ± 12.6	72.5 ± 11.5	78.1 ± 17.0
Cholinesterase Inhibitor use (%)	75 (88.2%)	228 (82.6 %)	24 (80%)
Memantine use (%)	23 (27.1 %)	72 (26.1 %)	8 (26.7%)

There were 147 participants who had both SMMSE and Q*mci* scores at baseline and end point; 206 participants had SMMSE scores only, and 8 had Q*mci* scores alone. The median duration of follow up between baseline and end-point are presented in Table 5.2. The mean SMMSE score at baseline was 21.6 (± 5.6); the mean score at end-point was 18.1 (± 8.0). The mean Q*mci* scores were 36.8 (± 13.6) and 31.3 (± 18.3) at baseline and end-point, respectively. There were 83 subjects taking CACE-Is and 270 NoCACE-I who had SMMSE scores available at both baseline and end-point. For CACE-I subjects, the median baseline SMMSE was 22 (6), similar to NoCACE-I 23 (7), p=0.943. Q*mci* scores were available for 41 subjects taking CACE-Is and 114 NoCACE-I and again, there was no significant difference between Q*mci* median scores, at baseline between CACE-I, 36 (11) and NoCACE-I, 38 (20), p=0.39. There were no significant differences in the baseline SMMSE and Q*mci* scores between the three groups (CACE-I, NoCACE-I and NewCACE-I), adjusted by the baseline characteristics (age, education, duration of follow-up and BP).

Table 5. 2 Baseline and End-Point (Last Visit) SMMSE and Q*mci* Scores

		N	Baseline Mean(±SD) Age	Gender (male,%)	Median Duration of follow-up in months	Baseline Median (Q3-Q1) Score	End-point Median (Q3-Q1) Score
SMMSE	CACE-I	83	77.3 (± 6.6)	53.0%	17 (34-7)	22 (25-19)	20 (25-14)
	NoCACE-I	270	77.1(± 7.6)	49.3%	18 (31-9)	23 (26-19)	20 (25-13)
	NewCACE-I	30	77.3 (± 8.2)	50%	6 (7-4)	23 (27-18)	24 (27-19)
Q*mci*	CACE-I	41	78.9 (± 6.1)	56.1%	16 (31-7)	36 (44-23)	29 (49-15)
	NoCACE-I	114	78.0 (±7.6)	49.1%	11 (24-6)	38 (47-27)	32 (45-17)

Within the CACE-I group, 30 subjects had recently (median six months) been started on CACE-Is (NewCACE-I) while attending clinic. The median SMMSE score for NewCACE-I was 23 (9), mean Q*mci* score 35.6 (+/-18.0). There was no significant difference between the baseline scores for NewCACE-I with the other two subgroups.

There were no differences in use of cholinesterase inhibitors (CholEI) or memantine between patients taking CACE-Is, NoCACE-Is or NewCACE-Is. Eight subjects taking NewCACE-Is were co-administered other medications that are associated with improvement in cognitive scores: CholEI (n=5), a diuretic (n=1), CCB (n=1) and L-thyroxine (n=1), while three had such medications discontinued: CholEI (n=1) and diuretic (n=2).

5.3.4.2 Rate of Decline

For the total sample, the median rate of cognitive decline, between baseline and end-point, measured by the SMMSE, was 0.69 points per six months (IQR of 2). The median changes in SMMSE scores were 0.8, 1.0 and −1.2, respectively, for the CACE-I, NoCACE-I and NewCACE-I groups, per six months. The median change for Q*mci* was two points per six months, while the median Q*mci* score differences for the CACE-I and NoCACE-I groups were 1.8 and 2.1, respectively, per six months.

The differences were examined using both one tail and two tail tests, the results were the same. Using the two tail test as an example, the difference in the SMMSE median rate of decline over six months for CACE-I patients, was small but non-significant, compared to NoCACE-I patients. The median rates of decline between CACE-I and NoCACE-I in Q*mci* scores, reached borderline significance, p=0.049. The median decline on SMMSE score was −1.2 points for the NewCACE-I group, per six months, significantly less than for the CACE-I group (median 0.8); p=0.003 and NoCACE-I group (median 1.0), p=0.001. The numbers on Q*mci* score for the NewCACE-I group were too small to compare. These results are presented in Table 5.3. After adjusting for baseline cognitive scores, (SMMSE and Q*mci*) and patient characteristics (age, education, duration of follow-up and BP), multivariate regression analysis was used to compare the end-point SMMMSE and Q*mci* scores. Significant differences were seen in end-point scores on the SMMSE (p=0.002) scores between CACE-I, NoCACE-I and NewCACE-I groups. There was no significant difference between the CACE-I and NoCACE-I groups, (p=0.172), for the Q*mci*.

Table 5. 3 Comparison of Differences in Q*mci* and SMMSE Scores between Baseline and End-Point

<table>
<tr><th></th><th colspan="2">Groups</th><th>Mann-Whitney U test (two tail)</th><th>Mann-Whitney U test (one tail)</th><th>MANOVA test</th></tr>
<tr><td rowspan="2">Changes in Qmci</td><td colspan="2">CACE-I (53) vs NoCACE-I (102)</td><td rowspan="2">p = 0.049</td><td rowspan="2">P=0.02</td><td rowspan="2">P=0.172</td></tr>
<tr><td>median*=1.8</td><td>median*=2.1</td></tr>
<tr><td rowspan="8">Changes in SMMSE</td><td colspan="2">CACE-I (113) vs NoCACE-I (240)</td><td rowspan="2">p = 0.77</td><td rowspan="2">P=0.06</td><td rowspan="8">P=0.002</td></tr>
<tr><td>median*=0.8</td><td>median*=1.0</td></tr>
<tr><td colspan="2">NewCACE-I (30) vs NoCACE-I (240)</td><td rowspan="2">p = 0.001</td><td rowspan="2">P<0.001</td></tr>
<tr><td>median*= - 1.2</td><td>median*= 1.0</td></tr>
<tr><td colspan="2">NewCACE-I (30) vs CACE-I** (83)</td><td rowspan="2">p = 0.003</td><td rowspan="2">P=0.002</td></tr>
<tr><td>median*= - 1.2</td><td>median*= 0.8</td></tr>
<tr><td colspan="6">*Median score is for the change in six months for CACE-I, NoCACE-I and NewCACE-I
** CACE-I group excluding NewCACE-I subjects.</td></tr>
</table>

5.3.5 Conclusion

A small reduction was demonstrated in this study in the rate of cognitive decline, in patients receiving CACE-Is compared to the NoCACE-I group, measured with the Q*mci* and SMMSE There was a small but statistically significant difference in the changes in Q*mci* scores over six months. The changes in SMMSE scores were not significant, but it suggested a possible slower progression in the CACE-I group. A median improvement was showed in NewCACE-I patients, rather than a decline in SMMSE scores, compared to the CACE-Is and NoCACE-Is groups, over the first six months of treatment. The findings of an association between a reduced rate of cognitive decline and the initiation of treatment were confirmed between the use of CACE-Is, during the first six months of treatment.

Compared to those already established on maintenance treatment, this is the first study to demonstrate that cognitive scores improve in patients starting on CACE-Is. Better medication compliance, increased cerebrovascular perfusion after initial treatment or the effects of improved BP control.[54] [55] may relate to this.

There are several strengths to this study. It includes different (AD, vascular and mixed) dementia subtypes in large numbers. The effects of CACE-Is were investigated in an unselected clinic sample of older adults, whose mean age approached 80 years. It also has a number of limitations. This study is an analysis of observational study. The data were collected in a 'real world' setting, where based on clinical judgment treatments were administrated, including antihypertensive agents. Observational studies like this are subject to bias in that those who receive treatment may be systematically different from those who do not. It means that the baseline demographic characteristics of the groups were similar, and few NewCACE-I subjects received other medications that could have accounted for the differences observed. Compliance with antihypertensive treatment, which has been shown to reduce with time (Chapman et al., 2005, Conlin et al., 2001), may have accounted for the improvement in the NewCACE-I

group, and could also have been a confounding factor. Similarly, for the CACE-I and NoCACE-I groups, in this retrospective analysis, it was not possible to establish the duration of treatment with antihypertensive medications, prior to attending clinic.

Most patients' Q*mci* or SMMSE records were in the database. However, a large proportion lacked results at the baseline or end point, limiting the numbers included in the analysis. The results would possible have differed with more complete data on all patients. However, the baseline cognitive scores were similar between those included and excluded, because of missing data. As this is the accepted time scale to show evidence of benefit in clinical drug trials, changes over the first six months of treatment were analysed, and used to compare the subgroup scores (Matthews et al., 2000). Although a shorter interval with a small percentage (9%) between the baseline and end-point scores exists, the duration of follow-up was standardised at six months to facilitate comparisons. ADAS-cog is the accepted standard for measuring cognitive change (Rosen et al., 1984). In this observational study, in a clinic setting, only the Q*mci* and the commonly used SMMSE were available. Of these, the Q*mci* has been shown to be as sensitive to change as the SADAS-cog (O'Caoimh et al., 2013b). Significant differences on SMMSE, could not be replicated with the Q*mci*, between NewCACE-I and the other groups' scores, as the numbers were too small to analyse.

To sum up, an association between the use of CACE-Is and reduced rates of cognitive decline was demonstrated in this study, in the first six months of treatment, in an unselected sample of clinic patients with dementia. This supports the increasing evidence for the use of ACE-Is and other antihypertensive agents in dementia management (Poon, 2008). Even though there are small and uncertain clinical significant differences, if sustained over years, the compounding effects may well have significant clinical benefits. This is supported by recent evidence suggesting that ACE-Is, could contribute to increased amyloid burden (Hu et al., 2001, Kehoe and Passmore, 2012, Fournier et al., 2009), by interfering with

degradation of Aβ, which potentially increases rates of cognitive decline and dementia severity (Sink et al., 2009). Indeed, mortality in patients with CI may be raised by ACE-Is, suggesting that if ACE-Is are proven to be beneficial in dementia, not all patients will benefit (Kehoe et al., 2013). The next study is going to use the similar process to compare the rate of functional and neuropsychological decline in CACE-I and NoCACE-I patients with dementia, in DARAD database. We explored if these findings could be replicated in a different dementia database.

5.4 Effects of CACE-Is on Functional Decline in Patients with Alzheimer's Disease (*Study Two: CACE Study in DARAD Database*)

5.4.1 Introduction

The aim of the second study, was to compare rates of cognitive, functional and neuropsychological decline, in patients with AD receiving CACE-Is (called CACE-Is) to those not currently treated with CACE-Is (NoCACE-I). This study conducted a secondary analysis of data from the Doxycycline and Rifampin for Alzheimer's Disease (DARAD) trial (Molloy et al., 2012). DARAD was a multi-centre, blinded, randomized 2x2 factorial controlled trial. Patients were recruited from 2006 to 2010, comparing doxycycline and rifampicin to placebo, to investigate if these can slow down the progression of AD (Molloy et al., 2012). There were eight outcome measures: the Standardised Alzheimer's Disease Assessment Scale – Cognitive Subscale (SADAS-cog) (Standish et al., 1996), the Clinical Dementia Rating scale-Sum of the Boxes (CDR-SB) (Schafer et al., 2004), the Standardised Mini-Mental State Examination (SMMSE) (Molloy et al., 1991a, Molloy and Standish, 1997b), Quick Mild Cognitive Impairment screen (Q*mci*) (O'Caoimh et al., 2012a), the Geriatric Depression Scale (GDS) (Yesavage, 1988), Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988), Lawton-Brody ADL Scale (Self-maintenance, 1969), and the Dysfunctional Behaviour Rating Instrument (DBRI), frequency (DBRIF) and reaction (DBRIR), subscales (Molloy et al., 1991b, Molloy et al., 1997).

5.4.2 Data Pre-processing – Subjects Selection

In total, there were 406 mild to moderate AD (SMMSE scores between 14 and 26) patients included from 14 geriatric outpatient clinics in Canada. It included patients aged 50 or over, and who met the National Institute of Neurological Disorders and Stroke (NINCDS) criteria for AD (McKhann et al., 1984). In this study, patients were separated into two groups: CACE-I group, which included patients currently taking centrally acting ACE-Is: ramipril (n=57), perindopril (n=21), lisinopril (n=9), trandolapril (n=3), and fosinopril (n=1) (Sink et al., 2009, Solfrizzi et al., 2011), and NoCACE-I group, who were not currently receiving CACE-Is, irrespective of BP readings, diagnosis of hypertension or receipt of other anti-hypertensives.

5.4.3 Data Analysis

The difference between baseline and 12-month scores were compared between CACE-I and the NoCACE-I group, for the average 12-month rate of change. Those changes were calculated as the baseline minus the 12-month score, for the Q*mci*, CSDD, GDS, Lawton-Brody ADLs scales. The changes for SADAS-cog, CDR-SB, DBRIF and DBRIR scales were calculated as month 12 score minus the baseline score. In this way, positive change represented improvement, irrespective of the scoring instructions. Data were analysed in SPSS 20.0. Non-normally distributed numerical data were presented as medians with interquartile range. Chi-square tests were used for categorical data. Multivariate regression was used to compare rates of change between the three groups (CACE-I, NoCACE-I and NewCACE-I), adjusted for the baseline cognitive scores and characteristics (age, years of education, and blood pressure). Multivariate regression was also used to compare the rate of decline between the subgroups, for each measure.

5.4.4 Results

5.4.4.1 Baseline Demographics

There were in total 365 patients available for all outcome measures at 12 months. Overall, 41 patients were excluded because of refusal (n=14), death (n=13), withdrawal from the trial (n=5), adverse events (n=6) and for other reasons (n=3). Patients' baseline characteristics are presented in Table 5.4. In the 365 patients, 91 were receiving CACE-Is: 21 were taking perindopril and 70 other CACE-Is (see Figure 5.2). There was no difference in baseline scores between the CACE-I and NoCACE-I groups. However, there was a marginal statistically significant difference in baseline characteristics for gender (p=0.05), cholinesterase inhibitor use (p=0.03) and SADAS-cog scores (p=0.04), between the CACE-I subgroups (perindopril and other CACE-Is) and the NoCACE-I group.

Table 5. 4 Differences in Baseline Demographic Characteristics and Outcome Measures between CACE-I Group to NoCACE-I Group

	CACE-I (n = 91) Median (IQR)	**NoCACE-I** (n = 274) Median (IQR)	**Perindopril** (n = 21) Median (IQR)	**Other CACE-I** (n = 70) Median (IQR)	**P-value**[1]	**P-value**[2]
Age	79 (8)	78 (10)	78 (9)	79 (10)	P=0.90	P=0.72
Gender (male %)	45.1%	51.1%	23.8%	51.4%	P=0.46	P=0.05
Education (years)	12 (4)	12 (5)	12 (5)	12 (3.5)	P=0.06	P=0.15
BP systolic	138 (19)	134 (22.5)	140 (19)	135.5 (17.25)	P=0.41	P=0.45
BP diastolic	70 (14)	72 (14)	70 (11)	70 (12.5)	P=0.41	P=0.66
Cholinesterase Inhibitor use (%)	89.0%	92.3%	76.2%	92.9%	P=0.32	P=0.03
Memantine use (%)	15.4%	15.3%	14.2%	15.7%	P=0.64	P=0.99
SMMSE	23 (4.5)	22.5 (5)	24 (2)	23 (5)	P=0.14	P=0.22
Q*mci*	39.5 (18)	39 (19)	40 (12)	39 (20)	P=0.74	P=0.90
SADAS-cog	18 (12)	21 (11)	16 (9)	19 (12)	P=0.05	P=0.04
Lawton-Brody ADL	51 (10)	52 (10)	52 (9)	51 (11)	P=0.34	P=0.57
CDR-SB	5 (4)	5 (4)	4.5 (4)	6 (4)	P=0.74	P=0.23
CSDD	3 (5)	3 (4)	4 (8)	3 (5)	P=0.09	P=0.23
GDS	1 (2)	1 (3)	2 (2)	1 (2)	P=0.74	P=0.82
DBRIF	4 (13)	5 (10)	3 (11)	4 (13)	P=0.61	P=0.88
DBRIR	11 (12)	13(11)	12 (16)	11 (12)	P=0.45	P=0.75

[1] P-values are provided for independent samples median test (numerical data) or Chi-square test (categorical data) for comparison between CACE-I and NoCACE-I groups.

[2] P-values are provided for independent samples median test (numerical data) or Chi-square test (categorical data) for comparison between perindopril, Other CACE-Is and NoCACE-I groups.

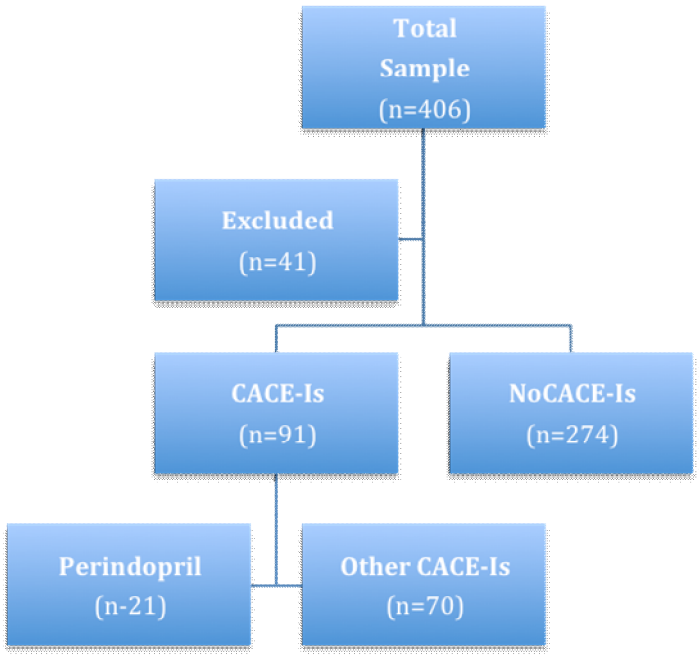


Figure 5. 2 Flow Diagram for CACE-I and NoCACE-I Patients in DARAD Database

5.4.4.2 Rate of Decline

The rates of decline were examined using both one tail and two tail tests, the results were the same. Using the two tail test as an example, a median decline of three points (IQR six) in ADL scores was seen in CACE-I patients, between baseline and 12 months, compared to a median decline of four points (IQR seven) in the NoCACE-I group (p=0.024). There was no statistically significant difference in decline for the other outcome measures in the analysis. In particular, CACE-I patients demonstrated a median decline in Q*mci* scores, four (IQR 12) versus five (IQR 13) points, in the NoCACE-I group (p = 0.15). The rate of decline in CDR-SB and CCSD scores was also smaller in the CACE-I group than the NoCACE-I group, even though the differences were not statistically significant (see Table 5.5). A significant difference in ADL scores was confirmed after adjusting for age, education, gender and BP (p=0.034). Another significant one point difference was seen in the rate of decline in the CSDD scores, between CACE-I and NoCACE-I groups, using the same adjusted analysis (p=0.001, see Table 5.5).

Table 5. 5 Comparison of the Rate of Decline, from Baseline to One Year, between CACE-I and NoCACE-I Patients

Variable	CACE-I Median (IQR)	NoCACE-I Median (IQR)	P-value[1]	P-value[2]	P-value[3]
BP (systolic)	0(30)	1.5(24)	P=0.38	P=0.13	P=0.69*
BP (diastolic)	0(20)	0(18)	P=0.69	P=0.25	P=0.71*
SADAS-cog	2(9)	4(8)	P=0.41	P=0.19	P=0.86
CDR-SB	2(4)	1.5(3.5)	P=0.83	P=0.40	P=0.84
Q*mci*	4(12)	5(13)	P=0.15	P=0.20	P=0.49
Lawton-Brody (ADL)	3(6)	4(7)	P=0.024	P=0.01	P=0.034
CSDD	0(3)	1(4)	P=0.13	P=0.03	P=0.001
GDS	0(2)	0(2)	P=0.95	P=0.37	P=0.94
DBRIF	0(9)	0(8)	P=0.50	P=0.26	P=0.24
DBRIR	4(13)	2(11)	P=0.50	P=0.32	P=0.44

[1] P-values are provided for unadjusted comparison between CACE-I and NoCACE-I groups, using two tail Mann-Whitney U test.

[2] P-values are provided for unadjusted comparison between CACE-I and NoCACE-I groups, using one tail Mann-Whitney U test.

[3] P-values are provided for multivariate regression (adjusted for age, gender, education and blood pressure, BP) for comparison between the CACE-I and NoCACE-I groups.

* Adjusted for age, gender and education.

There was a significant median reduction in the rate of decline in ADLs (p=0.01), comparing perindopril to NoCACE-I group, one point compared to four points. The CDR-SB had a borderline significant reduction for the perindopril compared to the NoCACE-I group (p=0.04), and perindopril compare to other CACE-I group (p=0.05). There was a median decline shown in patients receiving other CACE-Is in ADL scores, of three points (IQR seven), compared to one point (IQR six) for perindopril (p=0.09).

5.4.5 Conclusion

In this study, a small (25%, three versus four points) reduction was found in the rate of decline in ADL scores, over a 12-month period, in patients taking CACE-Is compared to those not currently receiving CACE-Is, measured with the Lawton-Brody ADL Scale. Although only changes in ADL and

CSSD scores were statistically significant, other outcomes measures generally demonstrated a decreased progression for the CACE-I, compared to the NoCACE-I group. In particular, the Q*mci* screen scores declined 20% less (four versus five points respectively), in the CACE-I group over one year. These data are consistent with the other studies demonstrating a slower rate of cognitive decline in patients with dementia receiving CACE-Is (Ohrui et al., 2004, Gao et al., 2013a, Hanes and Weir, 2007).

To our knowledge, a reduced rate of decline in ADLs has not been demonstrated previously, for subjects with established dementia, receiving CACE-Is, although the effect has been shown with beta-blockers (Rosenberg et al., 2008b). Given the non-significant changes in blood pressure, over the 12-month follow-up period, it is unlikely to be an anti-hypertensive effect. There are a number of other plausible mechanisms by which CACE-Is could preferentially impact upon ADLs. Perindopril improves exercise tolerance in older adults, with normal cognition, with (Henriksen and Jacob, 2003) and without heart failure (Sumukadas et al., 2007). Potential explanations for this include the ability of ACE-Is to improve endothelial function and to reduce inflammation, increasing muscle blood flow and glucose delivery (Onder et al., 2002), to skeletal as well as cardiac muscle, thereby improving exercise tolerance and capacity. Benefits have been demonstrated in the previous trials, equivalent to six months of training, with four weeks exposure to ACE-Is (Sumukadas et al., 2007). These effects appear to be unique to ACE-Is, when compared to other anti-hypertensive agents (Montgomery et al., 1999), again suggesting that they are independent of the drugs' BP lowering properties. In addition, individuals with polymorphisms resulting in low ACE activity, have a better response to training (Montgomery et al., 1999). The association between treatments with either ARBs and/or ACE-Is, and with a lower incidence of falls, also supports the theory that these medications may produce effects on physical functional activities (Wong et al., 2013). Thus, one year of ACE-I treatment could result in improvements in function and muscle strength, sufficient to alter the rate of decline in ADLs, theoretically.

In this study, perindopril was associated with a slower rate of decline in measures of ADLs, global function (CDR-SB) and cognition (SADAS-cog and Q*mci*), compared to other CACE-Is, although only the CDR-SB reached statistical significance. The potential benefits of perindopril on exercise tolerance, has been reported previously (Hutcheon et al., 2002), over other ACE-Is, with most studies reporting positive findings using perindopril (Henriksen and Jacob, 2003, Sumukadas et al., 2007) and negative findings using other classes such as quinapril (Zi et al., 2003) or fosinopril (Hutcheon et al., 2002).

There were minimal or no effects of CACE-Is, on mood or the BPSD, in this study. Both the CACE-I and NoCACE-I groups appeared to demonstrate little difference in rates of decline in their GDS, CSDD and DBRI scores over the year of follow-up. Although more subjects in the CACE-I group, compared to the NoCACE-I group, showed improvement in CSDD scores (57% versus 47%) over one year, baseline CSDD scores were significantly higher in the CACE-I group at baseline. This is reflective of the current evidence base, which suggests the ACE-Is, in general, have little effect on mood and depression (Deary et al., 1991, Rogers and Pies, 2008).

The strength of the study lies in the fact that these data came from a clinical trial, with rigorous interviewer training and quality checks. Moreover, the DARAD trial had good compliance with measurements throughout and relatively low loss to follow-up (Molloy et al., 2012). Other strengths include measurement of a wide variety of outcomes over one year, the large numbers and regular assessments (Molloy et al., 2012).

There are a number of limitations to this study. The subjects who had established dementia, median SMMSE of 23, and may have been taking CACE-Is for many years. As this was a secondary analysis of data from a randomised control trial (RCT), it was not possible to identify duration or previous history of anti-hypertensive treatment. Overall 41% of patients in the NoCACE-I group were not taking any anti-hypertensive treatment. Lower blood pressure is associated with slower progression of functional

and cognitive impairment (Rosenberg et al., 2008b). These medications may have caused bias from confounding by indication, favouring those currently receiving them. However, baseline characteristics, including BP were similar between the CACE-I and NoCACE-I groups, and did not affect rates of decline. Hence, most anti-hypertensive drugs may have associated with reduced rates of cognitive and or functional decline (Davies et al., 2011, Li et al., 2010, Sink et al., 2009). There were borderline significant differences between the three groups (CACE-I, NoCACE-I and perindopril) in gender, SADAS-cog scores and cholinesterase inhibitor use. However, after adjustment for these variables, the difference in deterioration in ADL remained. In addition, even though the Lawton-Brody ADL Scale score is not a gold standard outcome measure, it is still a widely used instrument to score both basic and instrumental activities of daily living (Lawton, 1970, Sheehan, 2012). Like most instruments measuring ADLs, limitations include potential bias arising from self or informant reporting rather than a demonstration of ability, and insensitivity to small changes in function. Compliance with anti-hypertensive treatment, which has been shown to reduce with time, may also have been a confounder. Small effects may reflect that this analysis was conducted in patients with more advanced disease. Therefore greater effects might be gained from longer treatment periods in patients with early stages of cognitive impairment (e.g. MCI) or with less advanced pathology (Solfrizzi et al., 2011, Rozzini et al., 2006).

In summary, this study demonstrates the benefit of CACE-Is compared to a group not currently treated with CACE-Is, in dementia patients, across a range of outcome measures, particularly ADLs. The most notable finding is the reduced rate of progression in ADL disability. The progress reduction in ADLs is small, and if real, of uncertain significance and with an unclear mechanism. If such an effect were sustained over years, patient may benefit greatly by these effects. These findings provide positive support for CACE-Is, and perhaps perindopril in particular, in that it slows functional reduction in patients with dementia. At present there have been no anti-hypertensive agents licensed for the treatment of dementia. These data support the need for further study. The next study combined the GAT and

DARAD databases together, and expands ADLs into basic and instrumental ADLs, to explore the effect on CACE-I. It incorporated previous studies to determine if greater numbers would allow for more detailed analysis on the outcome measures.

5.5 CACE-Is and Functional Decline in Dementia: Do They Affect Instrumental or Basic ADLs (*Study Three: CACE Study in GAT and DARAD Databases Combined*)

5.5.1 Introduction

The third study expanded on the results of the previous two studies. This analysis was conducted on the data from two databases: the GAT (Geriatric Assessment Tool), a geriatric medicine outpatient clinic database and the DARAD (Doxycycline and Rifampacin for Alzheimers Disease) study, a clinical trial (Molloy et al., 2012). All patients had been diagnosed with Alzheimer's disease, vascular or mixed dementias. Patients were included if baseline and end-point scores were available on the three outcome measures: Standardised Mini-Mental State Examination (SMMSE), Quick Mild Cognitive Impairment screen (Q*mci*), and a modified Lawton-Brody ADL Scale (ADLs). The ADL score was divided into basic and instrumental ADLs. The aim of this study was to confirm if centrally acting angiotensin converting enzyme inhibitors (CACE-Is) are associated with reduced rates of cognitive and possibly functional decline in dementia.

In this study, the outcome measures were the SMMSE, Q*mci* and a shortened version of the Lawton-Brody ADL scale. The original Lawton-Brody ADL scale (Self-maintenance, 1969), scored out of 64 points, includes 14 categories; higher scores denote greater independence. It was used as an outcome measure in the DARAD trial. However, due to time limitations in busy clinics, not all subtests of the Lawton-Brody ADL scale were recorded in the GAT. Therefore, this study included a modified Lawton-Brody ADL scale. Of these available subtests, bathing, walking, grooming, feeding, and toileting are BADLs; using the phone, finances,

medication administration, and food preparation are IADLs. This modified ADL scale was scored from 9 to 39 points, with higher scores denoting greater independence.

5.5.2 Data Pre-processing – Subjects Selection

The National Institute of Neurological Disorders and Stroke (McKhann et al., 1984) criteria were used to diagnose patients with dementia. Only patients with AD, vascular or mixed dementias (Alzheimer's-vascular), aged 50 years or more, were included. There were in total 1223 patients with dementia available, 406 from the DARAD database and 817 from the GAT database. Of the GAT patients, 439 patients were excluded, as they did not have either Q*mci*, SMMSE or ADL scores, available at both baseline and end-point. Of the DARAD patients, 41 were excluded because of missing data. Figure 5.3 graphically presents the patient selection. In this study, patients were subdivided into CACE-I group, those currently receiving Centrally Acting ACE-Is, and NoCACE-I group, who were not currently receiving CACE-Is, irrespective of diagnosis of hypertension, BP readings or receipt of other anti-hypertensives. The CACE-I group were then separated into two sub-groups: Perindopril and an 'other CACE-I' group.

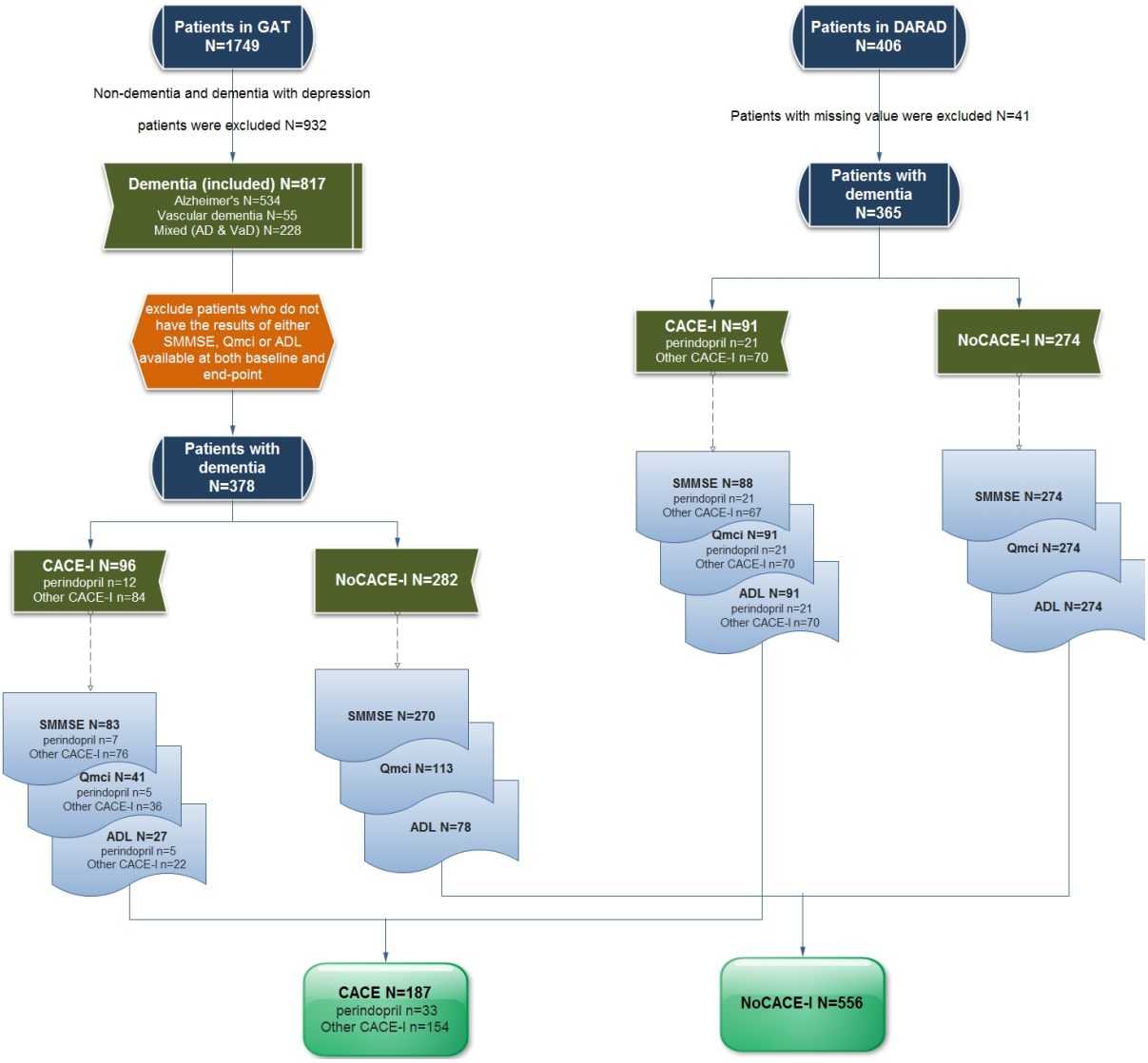


Figure 5. 3 Flow Chart for Patients in GAT and DARAD Databases

5.5.3 Data Analysis

We examined differences in the rate of change in Q*mci*, SMMSE and ADL scores, from baseline to end-point, between those in the CACE-I, perindopril, other CACE-I and NoCACE-I groups. Given that regulatory authorities, like the United States Food and Drug Administration, require evidence of change in cognitive tests over six months, to confirm benefit from new medications, the change scores were calculated from baseline, on a six monthly basis, using the formula: Rate of decline = (Baseline score – End-point score) x 6/ Duration in months. We also used multivariate regression to compare end-point cognitive (SMMSE and Q*mci*) and ADL

scores, adjusted for baseline cognitive scores and characteristics (age, years of education, duration of follow-up and BP), between the three groups (perindopril, other CACE-I and NoCACE-I). Data were analysed using SPSS 18.0. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality. Non-normally distributed data were compared with the Mann-Whitney U test. Categorical data were analysed with Chi-squared tests.

5.5.4 Results

5.5.4.1 Baseline Characteristics

There were totally 743 dementia patients, with either a Q*mci*, SMMSE or ADL score available at both baseline and end point included in the analyses, including 378 from the GAT databases, and 365 from the DARAD. Of these, 187 were receiving CACE-Is and 556 were not. Within the CACE-I group, 33 were taking perindopril (excluding seven patients who started on CACE-Is while attending clinic), and 154 patients were taking other CACE-Is. The mean age of those included (n=743) was 77.4 years. Half (49.6%) were men, and the mean time spent in education was 11.7 years. There were no significant differences in gender between the CACE-I and NoCACE-I groups (p=0.83), nor between the perindopril, other CACE-I and NoCACE-I groups (p=0.06). The perindopril group had more females (75%) compared to other CACE-I group, p<0.001. The mean systolic and diastolic BP for the total sample was 134.1mmHg and 72.5mmHg, respectively. Most of the population were receiving cholinesterase inhibitors (ChEI), a smaller percentage were taking memantine. No significant differences were seen in the distribution of ChEI (p=0.73) or memantine (p=0.79) use between the CACE-I and NoCACE-I groups. Table 5.6 demonstrates the baseline characteristics, including baseline and end-point SMMSE, Q*mci* and ADL scores, for the CACE-I, perindopril, other CACE-I and NoCACE-I groups. In total, the mean SMMSE, Q*mci* and ADL scores at baseline and end-point were 21.9 (SD ± 4.5) and 19.5 (SD ± 6.6), 38.2 (SD ± 13.1) and 32.7 (SD ± 16.2), and 32.7 (SD ± 4.6) and 29.8 (SD ± 5.9), respectively. There were no

significant differences in baseline SMMSE, Q*mci* and ADL scores between the perindopril, other CACE-I and NoCACE-I groups, after adjusting for baseline characteristics (age, gender, education, duration of follow-up and BP).

Table 5. 6 Baseline Characteristics for CACE-I, Perindopril, Other CACE-I and NoCACE-I Patients (BP=blood pressure)

		CACE-I	NoCACE-I	Perindopril	Other CACE-I
Number		187	556	33	154
Age (mean ± SD)		78.0 ± 6.5	77.2 ± 7.4	75.6 ± 7.5	78.5 ± 6.2
Gender (male %)		49.0%	49.8%	30.3%	52.9%
Education (mean ± SD)		11.0 ± 3.5	11.9 ± 3.8	12.0 ± 4.1	10.8 ± 3.4
BP systolic (mean ± SD)		135.2 ± 16.4	133.8 ± 16.4	136.6 ± 14.3	134.8 ± 16.9
BP diastolic (mean ± SD)		71.2 ± 9.9	72.9 ± 10.8	70.7 ± 10.4	71.4 ± 9.8
Cholinesterase Inhibitor use (%)		90.9%	91.7%	78.8%	93.5%
Memantine use (%)		20.3%	21.2%	15.2%	21.4%
Mean Duration of Follow-up (months)		16.2 (13.5)	16.7 (13.5)	12.9 (9.9)	16.9 (14.0)
SMMSE	**N=**	171	544	28	143
	Baseline age (mean ± SD)	77.9 ± 6.5	77.1 ± 7.4	75.8 ± 7.3	78.4 ± 6.2
	Gender (male, %)	48.8%	50.2%	25%	53.6%
	Median baseline score (IQR)	23 (5)	23 (6)	23 (3)	23 (5)
	Median end-point score (IQR)	21 (10)	21 (8)	22.5 (8)	20 (10)
Q*mci*	**N=**	132	387	26	106
	Baseline age (mean ± SD)	78.7 ± 6.2	77.4 ± 7.4	76.1 ± 7.1	79.3 ± 5.8
	Gender (male, %)	48.9%	50.5%	23%	55.4%
	Median baseline score (IQR)	39 (17)	39 (19)	39.5 (15)	38 (20)
	Median end-point score (IQR)	34 (26)	32 (24)	38.5 (23)	33 (25)
ADLs	**N=**	118	352	26	92
	Baseline age (mean ± SD)	78.3 ± 6.2	76.8 ± 7.1	75.5 ± 7.9	79.1 ± 5.5
	Gender (male, %)	47%	48.9%	31.1%	51.6%
	Median baseline score (IQR)	33.5 (7)	34 (5)	34 (9)	33 (6)
	Median end-point score (IQR)	31 (7)	31 (7)	33 (7)	31 (7)
Basic ADLs (score 5-24)	**Median baseline score (IQR)**	23 (2)	23 (2)	23 (4)	23 (2)
	Median end-point score (IQR)	23 (4)	23 (4)	23 (4)	23 (4)
Instrumental ADLs (score 4-15)	**Median baseline score (IQR)**	10 (5)	10.5 (5)	11 (4)	10 (6)
	Median end-point score (IQR)	9 (4)	8 (5)	10 (7)	9 (4)

5.5.4.2 Rate of Decline

For the total sample, the median change in SMMSE scores was 0.5 points per six months interquartile range (IQR of two), between baseline and end-point. The median change over six months in Q*mci* score was 2.25 points (IQR of seven). The median change in ADLs was one point per six months (IQR of three), with median differences for the perindopril, other CACE-I, CACE-I and NoCACE-I groups of 0.5, 1.0, 0.95 and 1.4, respectively.

The differences were examined using both one tail and two tail tests, the results were the same, except for the changes between other CACE-I and NoCACE-I groups in Q*mci* score (the p value of the two tail test is 0.06, but the p value of the one tail test is 0.03). Using the two tail test as an example, there was a significant reduction in the median rate of decline in total ADL scores in the CACE-I group compared to the NoCACE-I group, 0.95 compared to 1.4 points respectively, p=0.002. The difference in median rates of decline in Qmci scores was on borderline significance, p=0.05. There was a small but non-significant difference (p=0.19) in the SMMSE median six-month rate of decline for CACE-I patients, compared to NoCACE-I, 0.5 versus 0.6. Significant differences were observed on both the perindopril and other CACE-I groups, in rate of decline in ADL scores, compared with the NoCACE-I group, 0.5 versus 1.4, p=0.004 and 1.0 versus 1.4, p=0.037, respectively. There were no significant differences in SMMSE, Qmci or ADL scores, between the perindopril and other CACE-I groups. See Table 5.7.

Table 5. 7 Comparison of Six-Month Cognitive and Functional Rate of Decline in CACE-I, NoCACE-I, Perindopril and Other CACE-I Patients

	Groups		Mann-Whitney U test (two tail)	Mann-Whitney U test (one tail)	MANOVA test
Changes in SMMSE	CACE-I (201) vs NoCACE-I (514)		p = 0.19	p=0.10	P=0.46
	median*=0.5	median*=0.6			
	Perindopril (40) vs NoCACE-I (514)		p = 0.14	p=0.08	
	median*=0	median*=0.6			
	Other CACE-I (161) vs NoCACE-I (514)		p = 0.40	p=0.20	
	median*=0.5	median*=0.6			
	Perindopril (40) vs Other CACE-I (161)		p = 0.32	p=0.16	
	median*=0	median*=0.5			
Changes in Q*mci*	CACE-I (143) vs NoCACE-I (376)		p = 0.046 #	p=0.02 #	P=0.28
	median*=2.0	median*=2.5			
	Perindopril (31) vs NoCACE-I (376)		p = 0.32	p=0.10	
	median*=2.0	median*=2.5			
	Other CACE-I (112) vs NoCACE-I (376)		p = 0.06	p=0.03 #	
	median*=2.0	median*=2.5			
	Perindopril (31) vs Other CACE-I (112)		p = 0.83	p=0.47	
	median*=2.0	median*=2.0			
Changes in ADLs	CACE-I (128) vs NoCACE-I (342)		p = 0.002 #	P<0.001 #	P=0.012
	median*=0.95	median*=1.4			
	Perindopril (32) vs NoCACE-I (342)		p = 0.004 #	p=0.002 #	
	median*=0.5	median*=1.4			
	Other CACE-I (96) vs NoCACE-I (342)		p = 0.037 #	p=0.02 #	
	median*=1.0	median*=1.4			
	Perindopril (32) vs Other CACE-I (96)		p = 0.17	p=0.10	
	median*=0.5	median*=1.0			

* Median score is for the change in six months for CACE-I, NoCACE-I and NewCACE-I
# statistically significant *p* values

After adjusting the baseline scores (SMMSE, Q*mci* and ADLs) for patient characteristics (age, gender, education, duration of follow-up and BP), multivariate regression analysis was used to compare end-point SMMSE, Q*mci* and total ADL scores. This confirmed the significant differences in ADL scores between all three groups (perindopril, other CACE-I and NoCACE-I), (p=0.012), but no significant differences in cognitive scores between them; SMMSE (p=0.46) and Q*mci* (p=0.28).

- **Effect on Basic and Instrumental ADLs**

By examining basic and instrumental ADL scores using both one tail and two tail tests, there was no median reduction and no significant difference in

BADL scores over six months between the CACE-I and NoCACE-I groups. Using two tail test as an example, there was a median 0.83 point decline in IADLs in NoCACE-I patients, compared to a median 0.5 point reduction for the CACE-I group (p=0.001). For BADL scores, there was a significant difference between perindopril and the NoCACE-I (p=0.002) and other CACE-I (p=0.006) groups. Subjects taking perindopril had a significant rate of decline in IADL scores compared to the NoCACE-I group, median 0.28 points compared to 0.83, p=0.026. These results were presented in Table 5.8. When multivariate regression analysis was used to compare the differences in rates of decline in BADLs and IADLs, adjusted for baseline ADLs and patient characteristics (age, gender, education, duration of follow-up and BP), there were significant differences in IADLs (p=0.017), between the three groups (perindopril, other CACE-I and NoCACE-I), but no significant differences in BADL scores (p=0.06).

Table 5. 8 Comparison of differences in rates of change in basic and instrumental activities of daily living (ADL) between CACE-I, NoCACE-I, perindopril and Other CACE-I groups

	Groups		Mann-Whitney U test (two tail)	Mann-Whitney U test (one tail)	MANOVA test
Changes in Basic ADLs	CACE-I (128) vs NoCACE-I (342)		p = 0.19	p = 0.10	P=0.06
	median*=0	median*=0			
	Perindopril (32) vs NoCACE-I (342)		p = 0.002#	p = 0.001#	
	median*=0	median*=0			
	Other CACE-I (96) vs NoCACE-I (342)		p = 0.94	p = 0.46	
	median*=0.23	median*=0			
	Perindopril (32) vs Other CACE-I (96)		p = 0.006#	p = 0.002#	
	median*=0	median*=0.23			
Changes in Instrumental ADLs	CACE-I (128) vs NoCACE-I (342)		p = 0.001#	p < 0.001#	P=0.017
	median*=0.5	median*=0.83			
	Perindopril (32) vs NoCACE-I (342)		p = 0.026#	p = 0.01#	
	median*=0.28	median*=0.83			
	Other CACE-I (96) vs NoCACE-I (342)		p = 0.005#	p = 0.002#	
	median*=0.5	median*=0.83			
	Perindopril (32) vs Other CACE-I (96)		p = 0.80	p = 0.39	
	median*=0.28	median*=0.5			
*Median score is for the change in six months for CACE-I, NoCACE-I and NewCACE-I # statistically significant *p* values					

5.5.5 Conclusion

Data from secondary analyses were presented in this observational study presents for older adults with CI, derived from pooling data from two clinical databases. A small (32%, 0.95 versus 1.4 points) reduction were found in the rate of decline in ADL scores, measured using a modified version of the Lawton-Brody ADL scale, between those currently prescribed CACE-Is and patients not currently receiving CACE-Is, over 6 months period. These data are consistent with our previous studies, demonstrating a slower rate of cognitive and functional decline in persons with dementia receiving CACE-Is (Gao et al., 2013a, O'Caoimh et al., 2014). In this study, the difference in median rates of decline in ADLs for those in the CACE-I compared to the NoCACE-I group, was most apparent for IADLs (0.5

versus 0.83 points). This may reflect that the patients with mild to moderate dementia (median SMMSE score of 23) had relatively well preserved BADLs at baseline. A feature of mild dementia is that there is loss of IADLs prior to BADLs (Pérès et al., 2008). Patients with mild dementia, by definition are independent in BADL activities, and are likely to score very high in this. There was no significant difference in baseline BP readings between those in the CACE-I and NoCACE-I groups, after adjusting for age, gender and education. This means that the effects observed on cognition and ADL were independent of BP lowering.

The results also suggest that use of perindopril was associated with a slower rate of decline in total ADL scores, BADL scores, and IADL scores, compared to other CACE-Is. The changes between patients taking perindopril (CACE-P) with NoCACE-I group, in basic and instrumental ADL scores, BADLs and IADLs, over six months, were small but statistically significant, p=0.002 and p=0.026, respectively. These results suggest that perindopril is superior to other CACE-Is, and associated with a statistically significant reduction in the rate of decline in total ADL, BADLs and IADLs scores, compared to NoCACE-Is. Perindopril was associated with a significant reduction in the rate of decline in BADLs scores, compared to other CACE-Is (CACE-O) (p=0.006). Patients taking CACE-Is, and its subgroup (CACE-O), compared to NoCACE-I group, had a significant reductions in the rate of decline in instrumental ADL scores, IADL, p=0.001 and p=0.005, respectively. Perindopril reduces the rate of functional decline in both basic and instrumental ADLs (BADLs and IADLs), while CACE-O only showed significant effects on IADLs. With respect to ADLs, perindopril was also associated with improved exercise tolerance in older adults, with normal cognition (Hutcheon et al., 2002, Sumukadas et al., 2007). Of note, similar differences in median rates of decline were seen between those treated with other CACE-Is, predominantly ramipril, suggesting a class effect characteristic of all CACE-Is.

The strengths of this study are that the data came from large numbers and included different (AD, vascular and mixed) dementia subtypes, collected

from different databases. The study also investigates the effects of CACE-Is in an unselected clinic sample of older adults, whose mean age approached 80 years. The paper has a number of limitations. This study is an analysis of observational data of treatments, with anti-hypertensive agents. These medications may have caused bias from confounding by indication favouring those currently receiving them. Another limitation is that, the marker of ADLs used, the standardised Lawton-Brody ADL Scale score, is not a gold standard outcome measure. This said, it is a widely used instrument that incorporates both instrumental and basic activities of daily living (Self-maintenance, 1969, Sheehan, 2012, Sink et al., 2009). Like most instruments measuring ADLs, limitations include potential bias arising from self or informant reporting rather than a demonstration of ability, and insensitivity to small changes in function.

Overall, this study suggests that there is a possible benefit of CACE-Is compared to a group not currently treated with CACE-Is, in patients with established dementia, across a range of outcome measures, particularly ADLs. CACE-Is may have more beneficial effects on IADLs than BADLs. Potentially, perindopril may offer even more benefit. As similar effects were seen in those receiving other CACE-Is, the effect of ACE-Is may be important, and cannot be excluded. The mechanism by which CACE-Is exerting these effects is still unclear. While observed differences were small and of uncertain clinical significance, if sustained over years, the compounding effects could have significant clinical benefits. This paper adds to the growing evidence supporting the potential beneficial effects of CACE-Is in dementia, and highlights the need for further investigation with an adequately powered randomized controlled trial.

5.6 Conclusion

This chapter presents evidence that centrally acting angiotensin-converting enzyme (ACE) inhibitors (CACE-Is), which cross the blood-brain barrier, are associated with reduced rate of cognitive and functional decline. The changes in cognition and function, over six months, were small but statistical

significant. Many statistical methods were applied to analyse the data and prove the results. Q*mci*, SMMSE and Lawton-Brody ADLs were used as the outcome measures. The data analyses in these studies of this chapter were based on the Knowledge Discovery in Databases (KDD) process.

Three studies were presented in this chapter that showed an association between CACE-Is and a reduction in rate of cognitive and ADL decline in dementia:

The first study demonstrated that dementia patients taking CACE inhibitors declined slower than those not taking them. This study followed the rates of cognitive decline in three groups of patients: dementia patients being treated with centrally acting ACE inhibitors (CACE-I), dementia patients being treated with non-centrally acting ACE inhibitors (NoCACE-I), and dementia patients newly treated with centrally acting ACE inhibitors (newCACE-I). After six months, there was a significant reduction in the rate of cognitive decline between the CACE-I group and the NoCACE-I group, assessed by the Quick Mild Cognitive Impairment (Q*mci*) score, and a similar but not significant reduction in the Standardised Mini-Mental State Examination (SMMSE), irrespective of the blood pressure readings or diagnosis of hypertension.

A novel finding, however, was that the NewCACE-I patients, started on CACE-Is while attending clinic, showed CACE-Is may have cognitive enhancing effects, over the first 6 months of treatment, compared to those already taking CACE-Is, and those not currently treated with CACE-Is. This is the first study to show cognitive scores improved for patients starting, rather than those already on maintenance treatment, with CACE-Is, in dementia. This may have been related to better medication compliance or the effects of improved BP control and cerebrovascular perfusion after initial treatment. The findings indicate that ACE inhibitors hold promise as an inexpensive way to ease the burden of dementia, which may have very important treatment benefit in dementia.

The second study reported that centrally acting ACE inhibitors were associated with rate of the functional decline of 25%. The benefits were statistically significant, over a 12-month period, in patients taking CACE-Is compared to those not currently receiving CACE-Is. Although only changes in ADL and CSDD scores were statistically significant, the other outcomes measures generally demonstrated decreased progression for the CACE-I, compared to the NoCACE-I group. In particular, the Q*mci* screen scores, declined 32% less (1.9 points), for the CACE-I group over one year. These data are consistent with the first study demonstrating a slower rate of cognitive decline in persons with dementia.

The results presented in this study also suggest that perindopril was superior to other CACE-Is. Use of perindopril resulted in a slower rate of decline in measures of cognition (SADAS-cog and Q*mci*), global function (CDR-SB) and ADLs, compared to CACE-Is. Although no statistically significant differences were seen when perindopril was compared directly to other CACE-Is, the subgroup taking perindopril had slower rates of decline in these outcome measures, many of which approached significance.

The third study polled the data together from two clinical databases from the two previous studies. Pooling data increased the number of patients receiving CACE-Is available for analysis. This study found a significant reduction in the rate of decline in total ADL scores, over six months, in patients taking CACE-Is, compared to those who were not. This reflects other studies suggesting similar reduced rates of decline in those prescribed beta-blockers (Rosenberg et al., 2008b) or CACE-Is (O'Caoimh et al., 2014). In this study, total ADLs were divided into basic ADLs (BADLs) and instrumental ADLs (IADLs). The difference in median rates of decline in ADLs for those in the CACE-I, compared to the NoCACE-I group, was most apparent for IADLs ($p=0.001$). This may reflect the population studied, patients with mild to moderate dementia (median SMMSE score of 23) who had relatively preserved BADLs at baseline, and as a result were unlikely to show any significant change over the period of time. Loss of IADLs characteristically

occurs prior to BADLs, and usually in those with mild dementia (Pérès et al., 2008).

The results of this study also suggest that perindopril may be superior to other CACE-Is, with a relatively larger difference in median rates of functional decline in six months (64%, 0.5 versus 1.4 points) compared to those not currently receiving CACE-Is. This effect was again evident for IADLs but not for BADLs. It has been consistently associated with reduced cognitive decline (Gao et al., 2013a).

ACE activity is increased in Alzheimer's disease, proportional to the Aβ load. Centrally acting ACE-Is (CACE-Is) that cross the blood-brain barrier may have a greater impact than those that do not. The effects could be due to these drugs reducing swelling in brain tissue or improving blood flow to the brain. Anther possibility, is that these drugs reduce inflammation in the brain. People who already need treatment for cardiovascular disease such as high blood pressure and who are at risk of dementia may benefit if they take a centrally-acting ACE inhibitor.

There are a number of other plausible mechanisms by which CACE-Is could preferentially impact upon ADLs. Perindopril improves exercise tolerance in older adults, with normal cognition, with (Henriksen and Jacob, 2003) and without heart failure (Sumukadas et al., 2007). This might be explained by the reported ability of ACE-Is to reduce inflammation and to improve endothelial function, increasing muscle blood flow and glucose delivery (Onder et al., 2002), to both skeletal and cardiac muscle, thereby improving exercise tolerance and capacity.

In general, the current drugs (donepezil, galantamine and rivastigmine) used in the treatment of Alzheimer’s, work for a year and then stop working. However, many of these patients were on ACE inhibitors for years. The importance of these findings is that these data suggested that they continue to extract beneficial effects. While differences were small and of uncertain clinical significance, if sustained over years, the compounding effects could

have significant clinical benefits. Thus, there is a strong scientific rationale for recommending CACE-Is therapy to slow cognitive decline. It is too early for doctors to prescribe ACE inhibitors to everyone at risk of dementia. Large randomized trials are needed to gain additional insight and to confirm these findings.

CHAPTER 6 CONCLUSIONS

6.1 Introduction

This chapter presents the overall conclusions of the research study. It begins with the background of cognitive impairment, and reviews the research aims and conclusions from the research study. The next two sections briefly introduce the databases and outcome measures used in the study. In the following section, contributions and potential benefits from the research work are presented. The last section finishes with the conclusions, and discusses the potential benefits and future direction of research based on these findings.

6.2 Research Background: Databases and Outcome Measures

One of the major challenges facing societies in the world today, is population ageing. Population ageing will result in an increase in disability and a very significant increase in the incidence of age-related health problems, especially Alzheimer's disease (AD) and other dementias. Dementia is a collective term that describes a wide range of symptoms associated with a decline in memory or other skills, that are severe enough to reduce a person's ability to perform everyday activities. The prevalence of dementia doubles roughly every five years after the age of 65 years (Prince and Jackson, 2009). Alzheimer Disease International (ADI) predicts that approximately 115.4 million people worldwide will be affected by dementia in 2050 (Dartigues, 2009).

Alzheimer's Disease and other dementias are one of the most challenging illnesses confronting countries with ageing populations. There is as yet no treatment to prevent, halt or reverse the progressive decline of brain functions (Luengo-Fernandez et al., 2011). It is an expensive condition, with

a considerable cost to both public and private finances. In 2009, the total worldwide societal cost of dementia was estimated at $422 billion, based on 34.4 million people with dementia (Wimo et al., 2010). Dementia care costs more than cancer and heart disease care combined[20]. As the prevalence of dementia is linked to increasing age, and the number of the ageing people is rising, the costs of dementia care will increase considerably in the coming decades (Wimo et al., 1997). Currently, for most dementias, including Alzheimer's disease (AD), only symptomatic treatment options exist. Although there is currently no cure for dementia, multiple drugs can slow disease progression and treat symptoms.

Data analysis is a cost effective way to look at the effects of potential drugs. There is a need, to discover efficient ways to obtain useful information, to improve decision making from large databases containing clinical data (Lemke and Mueller, 2003). This interactive and iterative process involves various subtasks and decisions and is called Knowledge Discovery in Databases (KDD). The engine of KDD, where data is transformed into knowledge for decision-making, is data analysis. The aim of this research was to investigate the effects of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive and functional decline in dementia, using a three phased Knowledge Discovery in Databases (KDD) process. This research also validated the Quick mild cognitive impairment (Q*mci*) test, a new and more effective screen tool, as one of the key measures for cognition, against the other popular screening and assessment tools.

KDD was used to analyse existing databases, to investigate the effects of different drugs, and assess whether certain treatments could slow down the rate of cognitive or functional decline in patients with dementia. It was also used to compare the abilities of different assessment instruments, e.g. the Quick Mild Cognitive Impairment (Q*mci*) screen, the SMMSE (Standardised Mini-Mental State Examination) and ADL (Activities of Daily

[20] http://www.express.co.uk/news/retirement/155986/Dementia-costs-more-than-cancer-and-heart-disease-combined-but-given-less-funding

Living) tests, to measure and track changes with treatments over time. The principles of KDD were applied throughout the analytical components of this research. Three clinical databases, containing information from patients with different types and degrees of cognitive impairment, were used in this research, and provided a rich data resource. These included the Geriatric Assessment Tool (GAT), the Doxycycline and Rifampin for Alzheimer's Disease (DARAD), and the Q*mci* validation databases. All databases were derived from several different geriatric clinics in Canada.

6.2.1 The Databases

While each of the three databases analysed were similar, each had unique properties. In summary, the GAT is a customised software application that automates clinicians' outpatient reviews (Gao et al., 2013a). GAT data were collected in outpatient geriatric medicine clinics in two university hospitals in Ontario, Canada between 1999 and 2010. The GAT records demographic data (age, gender, educational level, medical conditions, diagnoses and laboratory findings) and two cognitive screening tests, the Standardised Mini-Mental State Examination (SMMSE) and the Q*mci*. The Q*mci* was administered to each subject by trained raters (clinic nurses), prior to each clinic assessment and blind to the eventual diagnosis. The DARAD was a multi-centre, blinded, randomised trial conducted between 2006 and 2010, comparing the effect of rifampacin and doxycycline to placebo, on the progression of AD (Molloy et al., 2012). The DARAD database included subjects with mild to moderate AD, recruited from 14 Canadian centers. These subjects had detailed cognitive assessments including the SMMSE and Q*mci*, performed every three months, for one year. The Q*mci* database, included subjects recruited from four memory clinics in Ontario Canada (O'Caoimh et al., 2012a). It included only subjects aged ≥ 55 years, referred for assessment of cognition, and excluded those with LBD, PDD and depression.

6.2.2 The Outcome Measures

The outcome measures used in the analyses were an ADL scale, called the Lawton-Brody ADL score, SMMSE, and Q*mci*. The Lawton-Brody scale (Self-maintenance, 1969) is an instrument used to assess independence in instrumental and basic ADL. It contains 14 subtests, and can be separated into basic ADLs (BADLs) and instrumental ADLs (IADLs). The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) is an widely used screening instrument, developed to assess cognitive function in the elderly. It evaluates orientation, memory loss, language problems and visuo-constructive abilities. The Standardised Mini-Mental State Examination (SMMSE) improved inter-rater reliability by the inclusion of explicit administration and scoring guidelines (Molloy et al., 1991a, Molloy and Standish, 1997a). The Q*mci* is a new short assessment test. It has potential to replace SMMSE as a screening test for cognition in the clinic and in clinical trials. It has improved sensitivity and specificity for differentiating MCI from normal cognition, and dementia, compared to the SMMSE and the AB Cognitive screen 135 (O'Caoimh et al., 2012a). It correlates with the Standardised Alzheimer`s Disease Assessment Scale-cognitive section (SADAS-cog), Clinical Dementia Rating (CDR) scale and the Lawton-Brody ADL scale (O'Caoimh et al., 2014). It is also being validated against the Montreal Cognitive Assessment (MoCA), another short cognitive screen with high accuracy in the assessment of early cognitive impairment (O'Caoimh et al., 2013c). As an adjunct to this work, we used data analysis methods to assess the accuracy of the Q*mci* and its subtests to identify different stages of cognition from normal to MCI, to dementia. The Q*mci* is used as a key cognitive measurement for determining the effects of drug therapy on the rate of decline of patients with dementia in this research.

6.3 Research Objective and Research Questions

The aim of this research is to investigate the effects of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive and functional decline in

dementia, using a three phased Knowledge Discovery in Databases (KDD) process. There are three research questions in Table 6.1 addressed the research objective.

Table 6. 1 Three Research Questions

Research Objective	*To investigate the effects of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive and functional decline in dementia, using a three phased Knowledge Discovery in Databases (KDD) process.*		
Research Questions	**RQ1: key outcome instruments for cognition in dementia**	**RQ2: effect of CACE-Is on cognitive decline in dementia**	**RQ3: effect of CACE-Is on functional decline in dementia**
Purpose	To define the key outcome instruments for measuring the rate of cognitive decline in dementia.	To prove that centrally acting ACE-Is may reduce the rate of cognitive decline in dementia.	To prove that centrally acting ACE-Is may reduce the rate of functional decline in dementia.
Motivation	1. To distinguish the memory loss types. 2. Reliable and more sensitive instruments are required. 3. Short instruments are required.	1. BP control is associated with rate of cognitive decline. 2. There is little data on the effects of CACE-Is on the rate of cognitive decline in dementia.	1. Hypertension may affect the risk of decline in ADL score in dementia. 2. Few studies have investigated whether ACE-Is affect ADLs
Results	1. Develop a short and simple instrument. 2. Enhance the properties of the test to differentiate NC from MCI. 3. Prove that Q*mci* strongly correlates with SADAS-cog. 4. Prove that Q*mci* has superior sensitivity and specificity for differentiating MCI from NC and dementia compared to the SMMSE, the ABCS 135, and MoCA.	1. Prove that the use of CACE-Is is associated with a reduced rate of cognitive decline in dementia. 2. Prove that cognitive scores may improve in the first six months after CACE-I treatment.	1. Prove that CACE-Is are associated with a reduced rate of functional decline in dementia. 2. Prove that CACE-Is may have more beneficial effects on instrumental ADLs. 3. Prove that patients taking perindopril had a significant reduction in rate of functional decline.

RQ1 (Research Question 1) proves that Q*mci*, a new screening test for cognitive impairment, has better sensitivity and specificity for differentiating MCI from normal cognition and dementia compared to the SMMSE, the ABCS 135, and MoCA. It also correlates with the SADAS-cog, CDR scale and the Lawton-Brody ADL scale. RQ2 finds that, there is a statistically significance difference, in the median, six-month, rate of decline in cognitive scores between CACE-I and NoCACE-I patients. The findings in RQ3 show that, there is a significant reduction in the rate of decline in total ADL scores in patients taking CACE-Is, compared to those who were not (NoCACE-I group).

6.4 Contributions and Results

This research makes a number of contributions as follows. The *primary contributions* of the study are to explain: (1) the effect of the centrally acting ACE inhibitors on the rate of cognitive and functional decline in dementia; and (2) the validation of a new and quick cognitive screening tool, Q*mci*, which can potentially replace the cognitive screening tools currently in use today. The *secondary contribution* of the study is its development of a prototype of a clinical data process that can be used by clinicians and researchers in designing data analysis systems for their studies. The objective of this section is, to briefly re-examine this study to ascertain the contributions it makes in the following areas: cognitive screening test, and the effect of CACE-Is in dementia. Table 6.2 demonstrates the relationships between research questions, studies and contributions in this research.

Table 6. 2 The Map on Research Questions, Studies and Primary Contributions

Research Objective	*To investigate the effects of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive and functional decline in dementia, using a three phased Knowledge Discovery in Databases (KDD) process.*		
Research Questions	**RQ1: key outcome instruments for cognition in dementia**	**RQ2: effect of CACE-Is on cognitive decline in dementia**	**RQ3: effect of CACE-Is on functional decline in dementia**
Studies (chapter number)	(Chapter 4)	Study One (Chapter 5)	Study Two & Three (Chapter 5)
Research Contributions	*Contribution Two*: • Cut-off scores were developed for the Q*mci* in patients presenting with memory loss. • Q*mci* can differentiate MCI from NC, and dementia, and suggests superior sensitivity and specificity over other short cognitive screening tools. • Q*mci* incorporates several important cognitive domains making it useful across the spectrum of CI. LM is the best performing subtest for differentiating MCI from NC.	*Contribution One*: • Patients currently taking CACE-Is, declined slower than those not currently treated with them in dementia. • The NewCACE-I group improved slightly over the first six months of treatment, compared to CACE-I and NoCACE-I groups. • CACE-Is are associated with a reduced rate of functional decline in dementia. • Perindopril may be superior to other CACE-Is in ADLs. • CACE-Is are associated with a significant reduction in the rate of decline in instrumental ADLs in dementia.	

The following sections provide the details of the two research contributions.

6.4.1 Research Contribution One

- *This research presents the evidence that centrally acting angiotensin-converting enzyme (ACE) inhibitors (CACE-Is), are associated with a reduced rate of cognitive and functional decline in dementia.*

Three studies were used in this research to investigate an association between anti-hypertensive drugs, which lower high blood pressure or hypertension, called centrally acting ACE inhibitors (CACE-Is) and the reduction in the rates of decline in dementia. As there is little evidence that anti-hypertensive medications affect other dementia subtypes (Hardy, 2009, Kehoe et al., 1999, Lehmann et al., 2005), only patients with AD, vascular, or mixed AD-vascular dementia, were included in this research.

6.4.1.1 Study One: CACE Study in GAT Database

The first study found that patients with dementia, currently taking CACE-Is, declined slower than those not currently treated with them. This study investigated rates of cognitive decline in three groups of patients: dementia patients being treated with centrally acting ACE inhibitors (the CACE-I group), dementia patients being treated with non-centrally acting ACE inhibitors (NoCACE-I), and dementia patients who started and were newly treated with centrally acting ACE inhibitors (NewCACE-I). After six months, there was a significantly greater reduction in the rate of cognitive decline between the CACE-I group and the NoCACE-I group, assessed by the Q*mci* score. There was a similar, but not significant reduction, in the SMMSE, irrespective of the blood pressure readings or diagnosis of

hypertension.

A novel finding, however, was that the NewCACE-I group, started on CACE-Is while attending clinic, declined at a significantly slower rate, improving slightly over the first six months of treatment, compared to those already taking CACE-Is and those not currently treated with CACE-Is. This suggests that CACE-Is may have cognitive enhancing effects, particularly when patients are initially started on treatment. This is the first study to show improvement in cognitive scores in patients starting, rather than those already on maintenance treatment, with CACE-Is, in dementia. Although this may have been related to better medication compliance, or the effects of improved BP control, and cerebrovascular perfusion after initial treatment, it is an important and potentially interesting finding. Overall, the results of this first study suggest that ACE inhibitors hold promise as an inexpensive way to modify the rate of progression of dementia and indicated that further study is required.

6.4.1.2 Study Two: CACE Study in DARAD Database

The second study found that centrally acting ACE inhibitors also affected clinically meaningful patient outcomes such as ADLs and mood, as well as supporting the findings of the first study (investigating the effects on cognition). In this second study CACE-Is slowed functional decline (decline in ADLs) by 25%. This reduction in the rate of decline in ADLs, was statistically significant over a 12-month period, between patients taking CACE-Is to those not currently receiving CACE-Is. Although only changes in ADLs and certain depression scores (CSDD) were statistically significant, the other outcomes measures generally demonstrated decreased progression for the CACE-I, compared to the NoCACE-I group. In particular, the Q*mci* screen scores declined 32% less (1.9 points), in the CACE-I group, over one

year. These data were consistent with the first study demonstrating a slower rate of cognitive decline in persons with dementia.

The results presented in this study also suggest that perindopril may be superior to other CACE-Is. Perindopril was associated with a slower rate of decline in measures of cognition (SADAS-cog and Q*mci*), global function (CDR-SB) and ADLs, compared to other CACE-Is. Although no statistically significant differences were seen in the subgroup taking perindopril, they had slower rates of decline in these outcome measures, many of which approached significance. The subgroup taking perindopril was small and not robust enough to show statistical differences.

6.4.1.3 Study Three: CACE Study in GAT and DARAD Databases Combined

The third study pooled the data from the two clinical databases together from the two previous studies. Data were pooled to increase the power of the analyses by increasing the number of patients currently receiving CACE-Is, available for analysis. This study found a significant reduction in the rate of decline in total ADL scores, over six months, in patients taking CACE-Is, compared to those who were not. Another question addressed in this analysis was whether the apparent effects on ADLs were attributable to changes in basic ADLs (BADLs) and/or instrumental ADLs (IADLs). In this study, total ADLs were divided into BADLs and IADLs. The difference in median rates of decline in ADLs, for those in the CACE-I compared to the NoCACE-I group, was greater than IADLs ($p=0.001$). We hypothesise that this may reflect the population studied. Patients with mild to moderate dementia (median SMMSE score of 23), have relatively impaired IADL and well preserved BADL scores. So given that BADL scores were very high, it was not possible to show differences in these scores between groups. So this

population had improvement in IADL scores and BADL scores for the most part remained constant.

The results of this study again suggested that perindopril may be superior to other CACE-Is, with a relatively larger reduction in median rates of functional decline over six months (64%, 0.5 versus 1.4 points), compared to those not currently receiving CACE-Is. This effect was again evident for IADLs but not for BADLs. The study also confirmed a consistent association between use of CACE-Is and reduced rates of cognitive decline (Gao et al., 2013a).

In summary, the findings from the three studies may help to provide further research in the area to improve the treatment of dementia patients. The observed effects (differences) were small and of uncertain clinical significance for the treatment periods explored. Yet the compounding effects of these benefits, if sustained over years, could have significant clinical benefits. In the MCI and early stage dementia patients, it could effectively prevent or delay progress from MCI to dementia. CACE-Is improve ADLs, and help dementia patients maintain independence. Potentially, perindopril may offer even more benefit than the other CACE-Is.

6.4.2 Research Contribution Two

- *This research validated that the Quick Mild Cognitive Impairment (Qmci) test is an efficient, quick, and accurate screening tool for screening patients with cognitive impairment.*

Adults with memory loss present a challenge to clinicians, who must determine if the memory changes represent normal aging, mild cognitive impairment or early dementia. Screening for the presence of cognitive

impairment (CI) is important to facilitate early diagnosis, plan for the future, identify reversible causes and initiate treatment (Boise et al., 1999). While screening programmes for detecting CI are advocated (Boustani et al., 2003) (Cordell et al., 2013), there is limited evidence supporting routine screening in clinical practice (Boustani et al., 2005), primarily because there are no sensitive and specific cognitive screening tests that can differentiate normal cognition (NC) and MCI from dementia (Winblad et al., 2004, Boustani et al., 2005), but particularly because of the effects of age and education compound interpretation of these tests, and must be taken into account. Few tests have sufficient sensitivity and specific in people with low education (Cordell et al., 2013).

A number of cognitive screening instruments have been used in an attempt to differentiate normal cognition (NC), and MCI from dementia (Molloy et al., 2005, Lonie et al., 2009). To standardise assessments and allow comparison between settings, there is a need for short instruments that are reliable, valid, and responsive to change, across a wide range of cognitive function. They need multiple standardised scoring formats that measure changes early (high ceiling) and continue to measure changes effectively into the late stages of dementia (low floor). Table 6.3 lists the key characters of several existing well-known cognitive screening instruments, comparing with Q*mci*.

Table 6. 3 Key Characteristics for Cognitive Screening Instruments

Test Name / Characters	SMMSE	SADAS-cog	MoCA	ABCS 135	Q*mci*
Examining Time	10 minutes	45 minutes, and requires training	At least 10 minutes	3 - 5 minutes	4 minutes
Total scores	30 points	70 points	30 points	135 points	100 points
Has total cut off scores for NC, MCI and dementia?	Yes.	Yes.	Yes, but with poor specificity.	No.	Yes. Age and education specific cut-offs are available as well.
Differentiation of MCI from NC and dementia	Only 1 - 2 points range for MCI.	It is comprehensive and useful at different stages of dementia.	Highly sensitive and specific at differentiating MCI from NC and dementia.	Some subtests, such as orientation, registration and clock drawing did not enhance the discriminatory properties of the test in differentiating NC from MCI.	It has 10 points range for MCI. It has superior accuracy for detecting MCI compared to the SMMSE and similar accuracy as MoCA.

However, no single existing cognitive screening instrument is ideal, and to date, none are established as the standard (Gifford and Cummings, 1999). They are limited by their inability to detect significant variations between patients with respect to age and/or educational status (Crum et al., 1993). Hence, new instruments are required that have a higher ceiling and are not as dependent on education. The Quick Mild Cognitive Impairment screen (Q*mci*) was developed to address this problem. It is the improved version of ABCS 135, and developed to enhance the sensitivity of the ABCS 135.

The Q*mci* is a short screening test for CI, that was developed as a rapid, valid and reliable tool for the early detection and differential diagnosis of MCI and dementia (O'Caoimh et al., 2012a). It is scored out of 100 points and has a median administration time of 4 minutes (O'Caoimh et al., 2013a). Throughout the analysis, Q*mci* has better sensitivity and specificity for differentiating MCI from normal cognition and dementia, compared to the SMMSE and the ABCS 135 (O'Caoimh et al., 2012a). It correlates with the standardised Alzheimer`s Disease Assessment Scale-cognitive section (SADAS-cog), Clinical Dementia Rating (CDR) scale and the Lawton-Brody activities of daily living scale (O'Caoimh et al., 2014). It was also being validated against MoCA, with more accuracy, and a shorter administration time.

This research provides usable cut-off scores for the Q*mci* based upon large numbers of patients presenting with memory loss across both clinical and research settings. It shows that the Q*mci* can differentiate MCI from NC, and dementia, and suggests superior sensitivity and specificity over other short cognitive screens such as the SMMSE (Molloy et al., 1991a) and MoCA (Nasreddine et al., 2005). This analysis also provided cut-off scores, adjusted for age and education, which not used directly in subsequent analysis, provide an important part of the development of any short

cognitive screening test. Based upon this analysis, a cut-off score of <60 for CI (either MCI or dementia), a range of 59 to 51 for MCI, and <50 points for dementia is suggested. Thus, the Q*mci* is a useful tool in the clinic, to screen for CI, and to differentiate between normal cognition, MCI and dementia.

6.4.3 Research Contribution Three

- *This is a secondary contribution. By using the KDD process in these studies, this research introduced a new data process prototype, CDAF (Clinical Data Analysis Framework), for data analysis especially in clinical research.*

Healthcare systems around the world are struggling to keep up with patient needs, and improve quality of care, while reducing costs at the same time. Meanwhile, more and more data is being captured around healthcare processes. As data get collected, they are not only required to store in an electronic format but also to use them in meaningful ways. As we know KDD is a generic term for processing data, and there is a need to standardise the data processing procedure in clinical research. To formalize the KDD process in clinical research, we introduce the concept of the Clinical Data Analysis Framework (CDAF). It helps clinicians and researchers to better understand the data analysis procedure in clinical research, and provide a roadmap to follow while planning and executing the analysis in the project. The results can provide support to healthcare providers on issues such as preventive care, diagnosis, treatment, monitoring and follow ups, using artificial intelligence reasoning to synthesize clinical information, as a precursor to a Randomized Control Trial. The CDAF is not developed to replace a clinicians' assessment but, instead, to facilitate correct assessment and reasoning. The processes of CDAF are shown as Figure 6.1.

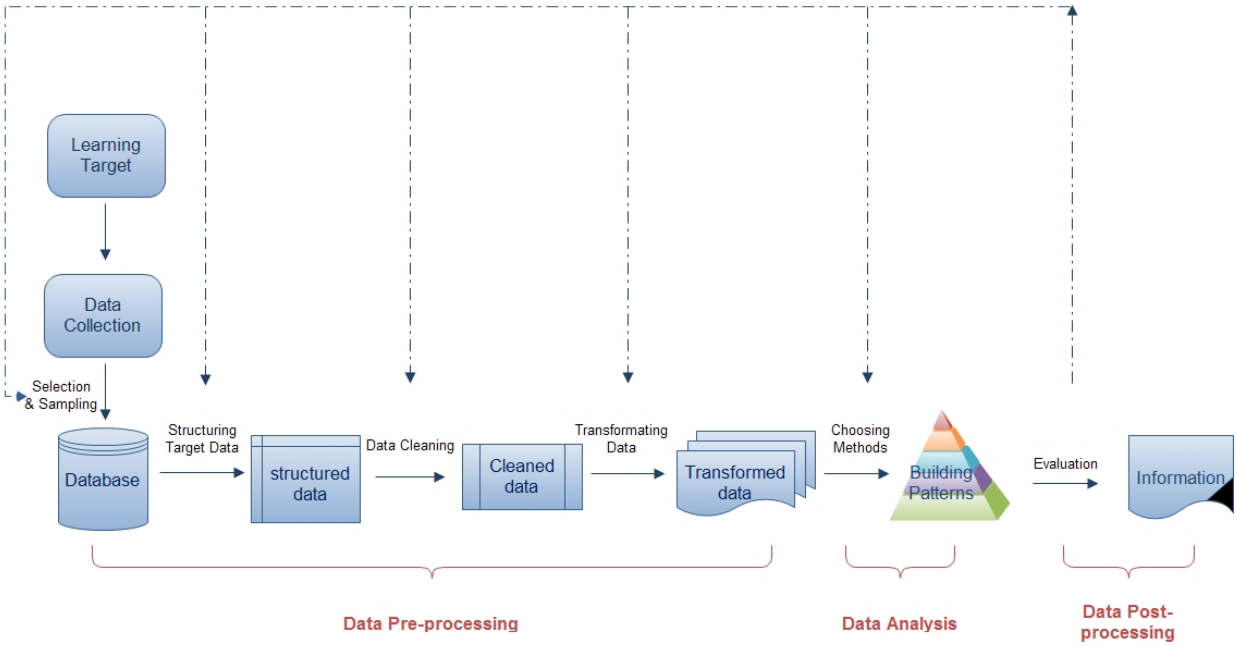


Figure 6. 1. Data Process Steps in CDAF

In the CDAF, the Data Pre-processing phase includes a number of steps to prepare data: learning target, data collection, data warehousing into database, structuring target data, data cleaning, and data transforming. And then data analysis methods are applied to build patterns/extract findings in the Data Analysis phase. Finally, in the Data Post-processing phase, discovered information is evaluated, visualised and applied to support clinical decision or enhance the understanding of diseases. These phases can be summarised as follows:

1. Data Pre-processing. This is the phase for preparing the clinical data. At the beginning, researchers need to determinate medical and data analysis goals, learn the terminology and relevant prior knowledge. Then understand the mechanisms of data collection, initial data exploration and verification. Selection of row data samples on which the discovery process is to be performed. Decisions on algorithm inputs (features) and structuring and cleaning the database need to be considered. This includes decisions on

strategies for handling missing data fields or evidently inadmissible instances. The processed data will then be transformed into an appropriate format for the analysis tools.

2. Data Analysis. This phase includes the decisions on algorithms, training and testing procedures; generation of diagnostic rules in a particular representational form or set of such representations. It is concerned with applying computational techniques to the actual extraction of the information from the data.

3. Data Post-processing. This phase describes and discusses the results, including interpreting the discovered patterns as well as a possible visualization of the extracted patterns. The discovered information may be incorporated into an up-and-running system, taking an action based on the knowledge or simply documenting it for management or later use.

The CDAF phases provide a platform for traceability, allowing for 'stepping back' in the data analysis process. Therefore, the CDAF can save time during clinical data analysis. Potentially, a computerized intelligent CDAF system could reduce healthcare costs through avoiding delays in treatment, redundant tests or referrals due to misdiagnosis. Furthermore, the efficiency and ease of extracting the data from the CDAF system and use them for reporting are very important for clinicians. Depending on the nature of data, denormalised data structure is better suited for some data sets such as Vital Signs, where as normalised data structure is better suited for some data sets such as labs. Thus, there are benefits of a CDAF for the clinician, researchers and those in charge of financial budgets.

6.5 Research Limitations

This research had a number of limitations including:

- The GAT was not a randomized control trial study.
- Neither the GAT nor the DARAD were designed to examine the effects of CACE-Is. Both were secondary analyses of existing databases and thus were observational studies, limiting the strength of conclusions which could be drawn.
- Another limiting factor is the potential for confounding by indication for drugs (CACE-Is), such that other reasons for using CACE-Is could have created bias.
- Pooling patients from different sources may also create bias. The GAT data sampled outpatients (unselected patients referred to a geriatric medicine memory clinic), while the DARAD included a highly selected sample of patients, selected to meet the inclusion criteria for a multi-centre randomized control trial. That said, common inclusion and exclusion criteria were used in this pooled analysis, and patients were assessed and managing by the same supervising consultant geriatrician.
- The patients included in these studies all had established dementia and therefore may have been taking CACE-Is for many years. It was not possible to identify duration of treatment, or previous history of anti-hypertensive treatment, retrospectively, from the databases. The duration of hypertension or the presence of end organ damage related to hypertension was likewise not taken into account. Furthermore, although it was possible to adjust findings for some commonly prescribed treatments for dementia, such as the use of Cholinesterase Inhibitors and Memantine, it was not possible to comment on other treatments.
- The NoCACE-I group is a large heterogeneous group of patients, including those treated for hypertension, those without hypertension, and those with hypertension, but not on treatment. For example, a large

percentage of patients in the NoCACE-I group (i.e. in DARAD, 41%) were not receiving any anti-hypertensive treatments. This limits the conclusions that can be drawn about comparisons of the rates of decline between the CACE-I and NoCACE-I groups.

- Several of the outcome measures used in this study, while widely used in clinical practice, are not recognized standards. The marker of ADLs used, the Lawton-Brody ADL Scale score, is not a gold standard outcome measure, but it is a widely used instrument that incorporates both instrumental and basic activities of daily living. Likewise the *Qmci* is not a gold standard and is not widely used in clinical practice. This necessitated the need to validate the instrument, work that was done in the department as a side issue to this thesis. In this work, we showed that the *Qmci* compares to gold standards including the Standardised ADAS-cog and the CDR.
- Finally, the data included in these databases were collected in a single country, Canada. This may reduce the generalizability of the findings. However, Canada is a large multi-cultural country, and the data were collected over many years across the whole country with 14 clinical research centers contributing data.

6.6 Summaries, Suggestions and Future Work

In summary, these three studies suggest that CACE-Is are associated with a reduced rate of cognitive and functional decline, as assessed with Q*mci*, SMMSE and ADLs, in patients with AD, vascular or mixed AD-vascular dementias. Potentially, of all the CACE-Is, perindopril may offer the most benefit. This supports the growing body of evidence for the use of ACE-Is and other anti-hypertensive agents in the management of dementia (Poon, 2008). The finding of a reduced rate of progression in cognition and function was small. However, if such differences were sustained over years,

the compounding effects may well have significant clinical benefits. Future study with an appropriately powered randomised trial is needed to confirm these findings and determine if, and for how long, these effects are sustained (Todd et al., 2010). In a randomised trial of sufficient length, if these data can be reproduced, incorporating appropriate outcome measures, such as an amyloid positron emission tomography, then these agents are likely to have significant benefits in delaying or even preventing dementia (Gao et al., 2013a). This study is important and these findings showed lead to new research to investigate if commonly used anti-hypertensive medications can modify AD and other dementing illnesses.

Although much of the early work looking at anti-hypertensives in dementia focused on ACE-Is, more recently other anti-hypertensives have been implicated. These include drugs that also act on the renin-angiotensin aldosterone system, such as ARBs and direct renin inhibitors and other classes of anti-hypertenives, including beta-blockers and calcium channel blockers (CCB).

ARBs, including valsartan (Wang et al., 2007) and telmisartan (Mogi et al., 2008), can reduce Aβ levels in animal studies. Some observational studies show that Angiotensin receptor blockers are associated with a significant reduction in the incidence and progression of dementia (Li et al., 2010). Those currently treated with ARBs have lower incident rates of dementia, compared to those taking some CACE-Is, or other cardiovascular comparator drugs (Li et al., 2010).

Direct renin inhibitor (DRI) aliskiren, acting as an active inhibitor of renin (Brown, 2008), can reduce the formation of angiotensin I from angiotensinogen. It also may provide neuronal protection in subcortical vascular dementia (Dong et al., 2011b). Aliskiren reduces brain damage and

working memory deficits related to acute cerebral ischaemia, possibly through a reduction in oxidative stress in mouse models (Dong et al., 2011b). The effects of DRIs on Aβ and ischaemia may be an important factor that induces neuronal damage in mixed dementia (Brunnström et al., 2009).

A recent study suggests beta blockers might reduce the risk of dementia (White et al., 2013). By lowering the heart rate, beta blockers may reduce wear and tear on small blood vessels throughout the body, including those that carry oxygen and fuel to every corner of the brain. Fed by healthier vessels, the aging brain would be less likely to suffer microinfarcts. Further prospective randomized studies comparing different antihypertensive classes are needed to provide more evidence regarding the effects of antihypertensive drugs on dementia risk and to determine whether certain antihypertensive classes provide greater benefits than others.

Furthermore, the findings in this research were based on the data-driven analytical methods, following with Clinical Data Analysis Framework (CDAF) based on Knowledge Discovery Databases (KDD) process, including three phases of data processing (data pre-processing, data analysis, and data post-processing). CDAF provides scientific ways to structure and select useful data, extract implicit and useful information from raw data, and visualise the outcomes. Data analysis is the core phase in CDAF, which consists of applying different methods (i.e. statistics or data mining) that, under acceptable computational efficiency limitations, produce a particular enumeration of patterns (or models) over the data. This research successfully applied a number of statistical methods to find useful information from a verity of clinical databases.

The use of appropriate data analytical processes and methods could effectively lead to finding new and useful knowledge in the medical area.

By using CDAF, the data process steps are traceable, and the results are more believable. On the other hand, unlike the traditional knowledge discovery process in clinical trials, CDAF can be very advantageous, as it allows quicker and less expensive approaches to store, prepare, demonstrate and analyse data. It focuses on the implementation of discovery results in databases, and novel techniques can be used to find unknown patterns or relationships in clinical data. This approach in clinical databases can be used into future work, to examine different diseases from different data sources. We could choose the best drug candidates, to see which are the most effective in modifying various diseases. Similar methodology can be applied in different clinical trials and databases, as it is very low-cost and quick. In this way, researchers can build the case to examine the data from clinical trials and studies for the future.

REFERENCES

ABBOTT, P. 2000. Knowledge discovery in large data sets: A primer for data mining applications in health care. *Nursing Informatics: Where caring and technology meet*, 139-148.

ADAMS, W. J. 1974. *The life and times of the central limit theorem*, American Mathematical Soc.

AISEN, P. S., SCHAFER, K. A., GRUNDMAN, M., PFEIFFER, E., SANO, M., DAVIS, K. L., FARLOW, M. R., JIN, S., THOMAS, R. G. & THAL, L. J. 2003. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *Jama,* 289**,** 2819-2826.

ALEXOPOULOS, G. S., ABRAMS, R. C., YOUNG, R. C. & SHAMOIAN, C. A. 1988. Cornell Scale for Depression in Dementia. *Biol Psychiatry,* 23**,** 271-84.

ALLEN, J., OYEBODE, J. R. & ALLEN, J. 2009. Having a father with young onset dementia The impact on well-being of young people. *Dementia,* 8**,** 455-480.

ALTMAN, D. G. & BLAND, J. M. 1994a. Diagnostic tests. 1: Sensitivity and specificity. *BMJ: British Medical Journal,* 308**,** 1552.

ALTMAN, D. G. & BLAND, J. M. 1994b. Statistics Notes: Diagnostic tests 2: predictive values. *Bmj,* 309**,** 102.

ALTMAN, D. G. & BLAND, J. M. 2009. Parametric v non-parametric methods for data analysis. *Bmj,* 338.

ANDERSON, T. W. 1996. *The new statistical analysis of data*, Springer.

ASSOCIATION, A. P. & DSM-IV., A. P. A. T. F. O. 1994. *Diagnostic and statistical manual of mental disorders: DSM-IV*, Amer Psychiatric Pub Inc.

ASSOCIATION, A. S. 2010. 2010 Alzheimer's disease facts and figures. *Alzheimer's & dementia: the journal of the Alzheimer's Association,* 6**,** 158.

AUFFRAY, C., CHEN, Z. & HOOD, L. 2009. Systems medicine: the future of medical genomics and healthcare. *Genome Med,* 1**,** 2.

BARKAN, N. 2001. Statistical inference on r* specificity+ sensitivity. *Unpublished Doctoral dissertation, University of Haifa***,** 69-74.

BARTLETT, M. S. A note on tests of significance in multivariate analysis. Proceedings of the Cambridge Philosophical Society, 1939. Cambridge Univ Press, 180-185.

BELLAZZI, R. & ZUPAN, B. 2008. Predictive data mining in clinical medicine: current issues and guidelines. *International journal of medical informatics,* 77**,** 81-97.

BELLEW, K. M., PIGEON, J. G., STANG, P. E., FLEISCHMAN, W., GARDNER, R. M. &

BAKER, W. W. 2004. Hypertension and the rate of cognitive decline in patients with dementia of the Alzheimer type. *Alzheimer Disease & Associated Disorders,* 18**,** 208-213.

BERGMANS, B. A. & DE STROOPER, B. 2010. γ-secretases: from cell biology to therapeutic strategies. *The Lancet Neurology,* 9**,** 215-226.

BOISE, L., CAMICIOLI, R., MORGAN, D. L., ROSE, J. H. & CONGLETON, L. 1999. Diagnosing dementia: perspectives of primary care physicians. *The Gerontologist,* 39**,** 457-464.

BOUSTANI, M., CALLAHAN, C. M., UNVERZAGT, F. W., AUSTROM, M. G., PERKINS, A. J., FULTZ, B. A., HUI, S. L. & HENDRIE, H. C. 2005. Implementing a screening and diagnosis program for dementia in primary care. *Journal of general internal medicine,* 20**,** 572-577.

BOUSTANI, M., PETERSON, B., HANSON, L., HARRIS, R. & LOHR, K. N. 2003. Screening for dementia in primary care: a summary of the evidence for the US Preventive Services Task Force. *Annals of Internal Medicine,* 138**,** 927-937.

BOWEN, J., TERI, L., KUKULL, W., MCCORMICK, W., MCCURRY, S. M. & LARSON, E. B. 1997. Progression to dementia in patients with isolated memory loss. *The Lancet,* 349**,** 763-765.

BRETELER, M. M. B., CLAUS, J. J., GROBBEE, D. E. & HOFMAN, A. 1994. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. *Bmj,* 308**,** 1604-1608.

BRINK, T. L., YESAVAGE, J. A., LUM, O., HEERSEMA, P. H., ADEY, M. & ROSE, T. L. 1982. Screening tests for geriatric depression. *Clinical gerontologist,* 1**,** 37-43.

BRODATY, H., SEEHER, K. & GIBSON, L. 2012. Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. *International psychogeriatrics,* 24**,** 1034.

BRUNNSTRÖM, H., GUSTAFSON, L., PASSANT, U. & ENGLUND, E. 2009. Prevalence of dementia subtypes: a 30-year retrospective survey of neuropathological reports. *Archives of gerontology and geriatrics,* 49**,** 146-149.

CAOIMH, R. O., TRAWLEY, S. & MOLLOY, D. The Quick Activities of Daily Living Screen, Qadl: Presenting a New, Combined Basic and Instrumental ADL Tool to Predict Cognitive Impairment. IRISH JOURNAL OF MEDICAL SCIENCE, 2012. SPRINGER LONDON LTD 236 GRAYS INN RD, 6TH FLOOR, LONDON WC1X 8HL, ENGLAND, S294-S295.

CASKIE, G. I., SUTTON, M. C. & MARGRETT, J. A. 2010. The relation of hypertension to changes in ADL/IADL limitations of mexican american older adults. *The*

Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 65**,** 296-305.

CHAKRABARTI, S., ESTER, M., FAYYAD, U., GEHRKE, J., HAN, J., MORISHITA, S., PIATETSKY-SHAPIRO, G. & WANG, W. 2004. Data mining curriculum: A proposal (Version 0.91).

CHAPMAN, R. H., BENNER, J. S., PETRILLA, A. A., TIERCE, J. C., COLLINS, S. R., BATTLEMAN, D. S. & SCHWARTZ, J. S. 2005. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Archives of Internal Medicine,* 165**,** 1147.

CHEN, R. & HERSKOVITS, E. H. 2010. Machine-learning techniques for building a diagnostic model for very mild dementia. *Neuroimage,* 52**,** 234-244.

CHENG, S.-T., CHOW, P. K., SONG, Y.-Q., YU, E., CHAN, A., LEE, T. & LAM, J. H. 2013. Mental and Physical Activities Delay Cognitive Decline in Older Persons With Dementia. *The American Journal of Geriatric Psychiatry*.

CHERTKOW, H. 2002. Mild cognitive impairment. *Current opinion in neurology,* 15**,** 401-407.

CHRISTENSEN, H. 2001. What cognitive changes can be expected with normal ageing? *Australian and New Zealand Journal of Psychiatry,* 35**,** 768-775.

CHU, C. C. 1997. Age-distribution dynamics and aging indexes. *Demography,* 34**,** 551-563.

CIOS, K. J., PEDRYCZ, W. & SWINIARSKI, R. W. 1998. *Data Mining and Knowledge Discovery*, Springer.

CIOS, K. J., SWINIARSKI, R. W., PEDRYCZ, W. & KURGAN, L. A. The knowledge discovery process. Data Mining, 2007. Springer, 9-24.

COLLABORATIVE, P., NEAL, B. & MACMAHON, S. 2003. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med,* 163**,** 1069-1075.

CONLIN, P. R., GERTH, W. C., FOX, J., ROEHM, J. B. & BOCCUZZI, S. J. 2001. Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. *Clinical therapeutics,* 23**,** 1999-2010.

CONNOR, D. J. & SABBAGH, M. N. 2008. Administration and scoring variance on the ADAS-Cog. *Journal of Alzheimer's Disease,* 15**,** 461-464.

CORDELL, C. B., BORSON, S., BOUSTANI, M., CHODOSH, J., REUBEN, D., VERGHESE, J., THIES, W. & FRIED, L. B. 2013. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. *Alzheimer's*

& Dementia, 9**,** 141-150.

COREN, S. 2003. *Sensation and perception*, Wiley Online Library.

CROOK, T., BARTUS, R. T., FERRIS, S. H., WHITEHOUSE, P., COHEN, G. D. & GERSHON, S. 1986. Age‐associated memory impairment: Proposed diagnostic criteria and measures of clinical change—report of a national institute of mental health work group.

CRUM, R. M., ANTHONY, J. C., BASSETT, S. S. & FOLSTEIN, M. F. 1993. Population-based norms for the Mini-Mental State Examination by age and educational level. *Jama,* 269**,** 2386-2391.

CULLEN, B., O'NEILL, B., EVANS, J. J., COEN, R. F. & LAWLOR, B. A. 2007. A review of screening tests for cognitive impairment. *Journal of Neurology, Neurosurgery & Psychiatry,* 78**,** 790-799.

DA COSTA, A. L., VARELA, J. S., MAZETTI, O., RESTELATTO, L., COSTA, A. F., GODINHO, C., CAMOZZATO, A. L., PICON, P. D. & CHAVES, M. L. 2008. Comparison of the Mini Mental State Examination and depressive symptoms between high cardiovascular risk and healthy community elderly groups. *Dement Neuropsychol,* 2**,** 294-299.

DARTIGUES, J. F. 2009. Alzheimer's disease: a global challenge for the 21st century. *The Lancet Neurology,* 8**,** 1082-1083.

DAVIES, N. M., KEHOE, P. G., BEN-SHLOMO, Y. & MARTIN, R. M. 2011. Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *Journal of Alzheimer's Disease,* 26**,** 699-708.

DAVIS, P. B., MORRIS, J. C. & GRANT, E. 1990. Brief screening tests versus clinical staging in senile dementia of the Alzheimer type. *Journal of the American Geriatrics Society*.

DEARY, I., CAPEWELL, S., HAJDUCKA, C. & MUIR, A. 1991. The effects of captopril vs atenolol on memory, information processing and mood: a double‐blind crossover study. *British journal of clinical pharmacology,* 32**,** 347-353.

DEEKS, J. J. & ALTMAN, D. G. 2004. Statistics Notes: Diagnostic tests 4: likelihood ratios. *BMJ: British Medical Journal,* 329**,** 168.

DONG, Y.-F., KATAOKA, K., TOKUTOMI, Y., NAKO, H., NAKAMURA, T., TOYAMA, K., SUETA, D., KOIBUCHI, N., YAMAMOTO, E. & OGAWA, H. 2011a. Perindopril, a centrally active angiotensin-converting enzyme inhibitor, prevents cognitive impairment in mouse models of Alzheimer's disease. *The FASEB Journal,* 25**,** 2911-2920.

DONG, Y. F., KATAOKA, K., TOKUTOMI, Y., NAKO, H., NAKAMURA, T., TOYAMA,

K., SUETA, D., KOIBUCHI, N., YAMAMOTO, E. & OGAWA, H. 2011b. Perindopril, a centrally active angiotensin-converting enzyme inhibitor, prevents cognitive impairment in mouse models of Alzheimer's disease. *The FASEB Journal,* 25**,** 2911-2920.

DOUGLAS, I. J. & SMEETH, L. 2008. Exposure to antipsychotics and risk of stroke: self controlled case series study. *BMJ: British Medical Journal,* 337.

DURON, E., RIGAUD, A. S., DUBAIL, D., MEHRABIAN, S., LATOUR, F., SEUX, M. L. & HANON, O. 2009. Effects of antihypertensive therapy on cognitive decline in Alzheimer's disease. *American journal of hypertension,* 22**,** 1020-1024.

EDELSTEIN, H. A. 1999. Introduction to data mining and knowledge discovery. *Two Crows Corporation,* 2.

ELLIOTT, A. C. & WOODWARD, W. A. 2007. *Statistical analysis quick reference guidebook: With SPSS examples*, Sage.

ELLIS, D. 1993. Modeling the information-seeking patterns of academic researchers: A grounded theory approach. *The Library Quarterly***,** 469-486.

ELO, S. & KYNGÄS, H. 2008. The qualitative content analysis process. *Journal of advanced nursing,* 62**,** 107-115.

EPSTEIN, I. 2010. *Clinical data-mining: Integrating practice and research*, Oxford University Press New York, NY.

FARLOW, M. 2002. A clinical overview of cholinesterase inhibitors in Alzheimer's disease. *International psychogeriatrics,* 14**,** 93.

FAYYAD, U., PIATETSKY-SHAPIRO, G. & SMYTH, P. 1996a. From data mining to knowledge discovery in databases. *AI magazine,* 17**,** 37.

FAYYAD, U., PIATETSKY-SHAPIRO, G. & SMYTH, P. 1996b. The KDD process for extracting useful knowledge from volumes of data. *Communications of the ACM,* 39**,** 27-34.

FAYYAD, U. M., PIATETSKY-SHAPIRO, G. & SMYTH, P. Knowledge Discovery and Data Mining: Towards a Unifying Framework. KDD, 1996c. 82-88.

FAYYAD, U. M., PIATETSKY-SHAPIRO, G., SMYTH, P. & UTHURUSAMY, R. 1996d. Advances in knowledge discovery and data mining.

FERREIRA, D., OLIVEIRA, A. & FREITAS, A. 2012. Applying data mining techniques to improve diagnosis in neonatal jaundice. *BMC medical informatics and decision making,* 12**,** 143.

FERRI, C. P., PRINCE, M., BRAYNE, C., BRODATY, H., FRATIGLIONI, L., GANGULI, M., HALL, K., HASEGAWA, K., HENDRIE, H., HUANG, Y., JORM, A., MATHERS, C., MENEZES, P. R., RIMMER, E. & SCAZUFCA, M. 2005. Global

prevalence of dementia: a Delphi consensus study. *Lancet,* 366**,** 2112-7.

FERRIS, S. H., MACKELL, J. A., MOHS, R., SCHNEIDER, L. S., GALASKO, D., WHITEHOUSE, P. J., SCHMITT, F. A., SANO, M., THOMAS, R. G. & ERNESTO, C. 1997. A multicenter evaluation of new treatment efficacy instruments for Alzheimer's disease clinical trials: overview and general results. *Alzheimer Disease & Associated Disorders,* 11**,** 1-12.

FINCKH, U., MÜLLER-THOMSEN, T., MANN, U., EGGERS, C., MARKSTEINER, J., MEINS, W., BINETTI, G., ALBERICI, A., HOCK, C. & NITSCH, R. M. 2000. High prevalence of pathogenic mutations in patients with early-onset dementia detected by sequence analyses of four different genes. *The American Journal of Human Genetics,* 66**,** 110-117.

FIRST, M. B. 1994. Diagnostic and statistical manual of mental disorders. *DSM IV-4th edition. APA. p***,** 97-327.

FISHER, R. A. 1922. On the mathematical foundations of theoretical statistics. *Philosophical Transactions of the Royal Society of London. Series A, Containing Papers of a Mathematical or Physical Character,* 222**,** 309-368.

FISHER, R. A. On a distribution yielding the error functions of several well known statistics. Proceedings of the international congress of mathematics, 1924. 805-813.

FISHER, R. A. 1925. *Statistical methods for research workers*, Genesis Publishing.

FISHER, R. A. 1935. The design of experiments.

FISK, J. D., MERRY, H. R. & ROCKWOOD, K. 2003. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology,* 61**,** 1179-1184.

FOGARI, R., MUGELLINI, A., ZOPPI, A., DEROSA, G., PASOTTI, C., FOGARI, E. & PRETI, P. 2003. Influence of losartan and atenolol on memory function in very elderly hypertensive patients. *Journal of human hypertension,* 17**,** 781-785.

FOGARI, R., MUGELLINI, A., ZOPPI, A., MARASI, G., PASOTTI, C., POLETTI, L., RINALDI, A. & PRETI, P. 2004. Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension. *European journal of clinical pharmacology,* 59**,** 863-868.

FOLSTEIN, M. F., FOLSTEIN, S. E. & MCHUGH, P. R. 1975. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research,* 12**,** 189-198.

FORETTE, F., SEUX, M. L., STAESSEN, J. A., THIJS, L., BABARSKIENE, M. R., BABEANU, S., BOSSINI, A., FAGARD, R., GIL-EXTREMERA, B. & LAKS, T.

2002. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Archives of Internal Medicine,* 162**,** 2046.

FOURNIER, A., OPRISIU-FOURNIER, R., SEROT, J.-M., GODEFROY, O., ACHARD, J.-M., FAURE, S., MAZOUZ, H., TEMMAR, M., ALBU, A. & BORDET, R. 2009. Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. *Expert review of neurotherapeutics,* 9**,** 1413-1431.

FRIED, L. P., BORHANI, N. O., ENRIGHT, P., FURBERG, C. D., GARDIN, J. M., KRONMAL, R. A., KULLER, L. H., MANOLIO, T. A., MITTELMARK, M. B. & NEWMAN, A. 1991. The cardiovascular health study: design and rationale. *Annals of epidemiology,* 1**,** 263-276.

GADDUM, J. 1945. Lognormal distributions. *Nature,* 156**,** 463-466.

GAGLIARDI, F. 2011. Instance-based classifiers applied to medical databases: Diagnosis and knowledge extraction. *Artificial Intelligence in Medicine,* 52**,** 123-139.

GALIMBERTI, D. & SCARPINI, E. 2011. Disease-modifying treatments for Alzheimer's disease. *Therapeutic advances in neurological disorders,* 4**,** 203-216.

GANZERT, S., GUTTMANN, J., KERSTING, K., KUHLEN, R., PUTENSEN, C., SYDOW, M. & KRAMER, S. 2002. Analysis of respiratory pressure–volume curves in intensive care medicine using inductive machine learning. *Artificial Intelligence in Medicine,* 26**,** 69-86.

GAO, Y., O'CAOIMH, R., HEALY, L., KERINS, D. M., EUSTACE, J., GUYATT, G., SAMMON, D. & MOLLOY, D. W. 2013a. Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia. *BMJ open,* 3.

GAO, Y., O'CAOIMH, R., HEALY, L., KERINS, D. M., EUSTACE, J., GUYATT, G., SAMMON, D. & MOLLOY, D. W. 2013b. Effects of Centrally Acting Angiotensin Converting EnzymeInhibitors on the Rate of Cognitive Decline and Activities of Daily Living in Dementia. *Irish Gerontological Society meeting 2013*. Dublin, Ireland.

GAO, Y., O'CAOIMH, R., KEHOE, P. G., SAMMON, D. & MOLLOY, D. W. Centrally Acting Angiotensin Converting Enzyme Inhibitors and Functional Decline in Dementia: Do they Affect Instrumental or Basic ADLs? In press.

GAUSS, C. F. 1809. *Theoria motus corporum coelestium in sectionibus conicis solem ambientium*.

GAUTHIER, S., REISBERG, B., ZAUDIG, M., PETERSEN, R. C., RITCHIE, K.,

BROICH, K., BELLEVILLE, S., BRODATY, H., BENNETT, D. & CHERTKOW, H. 2006. Mild cognitive impairment. *Lancet,* 367**,** 1262-1270.

GESLANI, D. M., TIERNEY, M. C., HERRMANN, N. & SZALAI, J. P. 2005. Mild cognitive impairment: an operational definition and its conversion rate to Alzheimer's disease. *Dementia and geriatric cognitive disorders,* 19**,** 383-389.

GIFFORD, D. R. & CUMMINGS, J. L. 1999. Evaluating dementia screening tests Methodologic standards to rate their performance. *Neurology,* 52**,** 224-224.

GILL, D. J., FRESHMAN, A., BLENDER, J. A. & RAVINA, B. 2008. The Montreal cognitive assessment as a screening tool for cognitive impairment in Parkinson's disease. *Movement disorders,* 23**,** 1043-1046.

GONG, C.-X., GRUNDKE-IQBAL, I. & IQBAL, K. 2010. Targeting tau protein in Alzheimer's disease. *Drugs & aging,* 27**,** 351-365.

GOODWIN, L., VANDYNE, M., LIN, S. & TALBERT, S. 2003. Data mining issues and opportunities for building nursing knowledge. *Journal of Biomedical Informatics,* 36**,** 379-388.

GREEN, D. M. & SWETS, J. A. 1966. *Signal detection theory and psychophysics*, Wiley New York.

GRIFFIN, W. S. T. 2006. Inflammation and neurodegenerative diseases. *The American journal of clinical nutrition,* 83**,** 470S-474S.

HAJJAR, I., BROWN, L., MACK, W. J. & CHUI, H. 2012a. Impact of angiotensin receptor blockers on Alzheimer's disease neuropathology in a large brain autopsy series. *Archives of neurology,* 69**,** 1632.

HAJJAR, I., BROWN, L., MACK, W. J. & CHUI, H. 2012b. Impact of Angiotensin Receptor Blockers on Alzheimer Disease Neuropathology in a Large Brain Autopsy Series. *Archives of neurology***,** 1.

HAJJAR, I., HART, M., CHEN, Y.-L., MACK, W., MILBERG, W., CHUI, H. & LIPSITZ, L. 2012c. Effect of antihypertensive therapy on cognitive function in early executive cognitive impairment: a double-blind randomized clinical trial. *Archives of Internal Medicine,* 172**,** 442.

HAJJAR, I., HART, M., MILBERG, W., NOVAK, V. & LIPSITZ, L. 2009. The rationale and design of the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial in elderly hypertensives with early cognitive impairment: Role of the renin angiotensin system inhibition. *BMC geriatrics,* 9**,** 48.

HAN, J. & KAMBER, M. 2001. Data mining: concepts and techniques. *San Francisco, CA, itd: Morgan Kaufmann,* 5.

HAN, J., KAMBER, M. & PEI, J. 2006. *Data mining: concepts and techniques*, Morgan

kaufmann.

HANES, D. S. & WEIR, M. R. 2007. Usefulness of ARBs and ACE inhibitors in the prevention of vascular dementia in the elderly. *The American journal of geriatric cardiology,* 16**,** 175-182.

HARDY, J. 2009. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. *Journal of neurochemistry,* 110**,** 1129-1134.

HARTWIG, F. 1979. *Exploratory data analysis*, Sage.

HEBERT, L. E., WEUVE, J., SCHERR, P. A. & EVANS, D. A. 2013a. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*.

HEBERT, L. E., WEUVE, J., SCHERR, P. A. & EVANS, D. A. 2013b. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology,* 80**,** 1778-1783.

HENLEY, D. B., MAY, P. C., DEAN, R. A. & SIEMERS, E. R. 2009. Development of semagacestat (LY450139), a functional γ-secretase inhibitor, for the treatment of Alzheimer's disease.

HENRIKSEN, E. J. & JACOB, S. 2003. Modulation of metabolic control by angiotensin converting enzyme (ACE) inhibition. *Journal of cellular physiology,* 196**,** 171-179.

HILDEN, J. & GLASZIOU, P. 1996. Regret graphs, diagnostic uncertainty and Youden's Index. *Statistics in medicine,* 15**,** 969-986.

HILL, T. & LEWICKI, P. 2006. *Statistics: methods and applications: a comprehensive reference for science, industry, and data mining*, StatSoft, Inc.

HOLMES, J. H. 2014. Chapter 7 - Knowledge Discovery in Biomedical Data: Theory and Methods. *In:* NEIL, S. (ed.) *Methods in Biomedical Informatics.* Oxford: Academic Press.

HOWE, D., COSTANZO, M., FEY, P., GOJOBORI, T., HANNICK, L., HIDE, W., HILL, D. P., KANIA, R., SCHAEFFER, M. & ST PIERRE, S. 2008. Big data: The future of biocuration. *Nature,* 455**,** 47-50.

HU, J., IGARASHI, A., KAMATA, M. & NAKAGAWA, H. 2001. Angiotensin-converting enzyme degrades Alzheimer amyloid β-peptide (Aβ); retards Aβ aggregation, deposition, fibril formation; and inhibits cytotoxicity. *Journal of Biological Chemistry,* 276**,** 47863-47868.

HUGHES, C. P., BERG, L., DANZIGER, W. L., COBEN, L. A. & MARTIN, R. L. 1982. A new clinical scale for the staging of dementia. *The British Journal of Psychiatry,* 140**,** 566-572.

HURD, M. D., MARTORELL, P., DELAVANDE, A., MULLEN, K. J. & LANGA, K. M.

2013. Monetary costs of dementia in the United States. *New England Journal of Medicine,* 368**,** 1326-1334.

HUTCHEON, S., GILLESPIE, N., CROMBIE, I., STRUTHERS, A. & MCMURDO, M. 2002. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomised double blind placebo controlled trial. *Heart,* 88**,** 373-377.

IGASE, M., KOHARA, K. & MIKI, T. 2011. The association between hypertension and dementia in the elderly. *International journal of hypertension,* 2012.

INZA, I., LARRAÑAGA, P., BLANCO, R. & CERROLAZA, A. J. 2004. Filter versus wrapper gene selection approaches in DNA microarray domains. *Artificial Intelligence in Medicine,* 31**,** 91-103.

IQBAL, K., SISODIA, S. S. & WINBLAD, B. 2003. *Alzheimer's disease: advances in etiology, pathogenesis and therapeutics*, John Wiley & Sons.

IVNIK, R. J., MALEC, J. F., SMITH, G. E., TANGALOS, E. G., PETERSEN, R. C., KOKMEN, E. & KURLAND, L. T. 1992. Mayo's Older Americans Normative Studies: WAIS-R norms for ages 56 to 97. *The Clinical Neuropsychologist,* 6**,** 1-30.

KANE, R. L., KANE, R. A. & EELLS, M. 2000. *Assessing older persons: Measures, meaning, and practical applications*, Oxford University Press New York.

KARP, A., PAILLARD-BORG, S., WANG, H.-X., SILVERSTEIN, M., WINBLAD, B. & FRATIGLIONI, L. 2006. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and geriatric cognitive disorders,* 21**,** 65-73.

KEHOE, P. G., DAVIES, N. M., MARTIN, R. M. & BEN-SHLOMO, Y. 2013. Associations of Angiotensin Targeting Antihypertensive Drugs with Mortality and Hospitalization in Primary Care Patients with Dementia. *Journal of Alzheimer's Disease,* 33**,** 999-1008.

KEHOE, P. G. & PASSMORE, P. A. 2012. The Renin-Angiotensin System and Antihypertensive Drugs in Alzheimer's Disease: Current Standing of the Angiotensin Hypothesis? *Journal of Alzheimer's Disease,* 30**,** S251-S268.

KEHOE, P. G., RUSS, C., MCILORY, S., WILLIAMS, H., HOLMANS, P., HOLMES, C., LIOLITSA, D., VAHIDASSR, D., POWELL, J. & MCGLEENON, B. 1999. Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. *Nature genetics,* 21**,** 71.

KENNELLY, S., ABDULLAH, L., KENNY, R. A., MATHURA, V., LUIS, C. A., MOUZON, B., CRAWFORD, F., MULLAN, M. & LAWLOR, B. 2012.

Apolipoprotein E genotype‐specific short‐term cognitive benefits of treatment with the antihypertensive nilvadipine in Alzheimer's patients—an open‐label trial. *International journal of geriatric psychiatry,* 27**,** 415-422.

KHAN, F. S., ANWER, R. M., TORGERSSON, O. & FALKMAN, G. 2008. Data mining in oral medicine using decision trees. *World Academy of Science, Engineering and Technology,* 37**,** 225-230.

KLÖSGEN, W. & ZYTKOW, J. M. The knowledge discovery process. Handbook of data mining and knowledge discovery, 2002. Oxford University Press, Inc., 10-21.

KORCZYN, A. D., VAKHAPOVA, V. & GRINBERG, L. T. 2012. Vascular dementia. *Journal of the neurological sciences*.

KRITCHEVSKY, S. B., NICKLAS, B. J., VISSER, M., SIMONSICK, E. M., NEWMAN, A. B., HARRIS, T. B., LANGE, E. M., PENNINX, B. W., GOODPASTER, B. H. & SATTERFIELD, S. 2005. Angiotensin-converting enzyme insertion/deletion genotype, exercise, and physical decline. *JAMA: the journal of the American Medical Association,* 294**,** 691-698.

KRUSKAL, W. H. 1957. Historical notes on the Wilcoxon unpaired two-sample test. *Journal of the American Statistical Association,* 52**,** 356-360.

KURZ, A. 2013. Psychosoziale Interventionen bei Demenz. *Der Nervenarzt,* 84**,** 93-105.

LANG, T. A., SECIC, M. & POLLOCK, A. 1998. How to report statistics in medicine. *European Journal of Surgery-Acta Chirurgica,* 164**,** 638-638.

LANGA, K. M., FOSTER, N. L. & LARSON, E. B. 2004. Mixed dementia. *JAMA: the journal of the American Medical Association,* 292**,** 2901-2908.

LAROSE, D. T. 2006. *Data mining methods & models*, John Wiley & Sons.

LAUNER, L., ANDERSEN, K., DEWEY, M., LETENNEUR, L., OTT, A., AMADUCCI, L., BRAYNE, C., COPELAND, J., DARTIGUES, J.-F. & KRAGH-SORENSEN, P. 1999. Rates and risk factors for dementia and Alzheimer's disease Results from EURODEM pooled analyses. *Neurology,* 52**,** 78-78.

LAVRAC, N., KERAVNOU, E. & ZUPAN, B. 2000. Intelligent data analysis in medicine. *Encyclopedia of computer science and technology,* 42**,** 113-157.

LAWTON, M. P. 1970. Assessment, integration, and environments for older people. *The Gerontologist,* 10**,** 38-46.

LEE, S.-M. & ABBOTT, P. A. 2003. Bayesian networks for knowledge discovery in large datasets: basics for nurse researchers. *Journal of Biomedical Informatics,* 36**,** 389-399.

LEGENDRE, A. M. 1805. *Nouvelles méthodes pour la détermination des orbites des cometes*, F. Didot.

LEHMANN, D. J., CORTINA-BORJA, M., WARDEN, D. R., SMITH, A. D., SLEEGERS, K., PRINCE, J. A., VAN DUIJN, C. M. & KEHOE, P. G. 2005. Large meta-analysis establishes the ACE insertion-deletion polymorphism as a marker of Alzheimer's disease. *American journal of epidemiology,* 162**,** 305-317.

LEMKE, F. & MUELLER, J.-A. 2003. Medical data analysis using self-organizing data mining technologies. *Systems Analysis Modelling Simulation,* 43**,** 1399-1408.

LI, N. C., LEE, A., WHITMER, R. A., KIVIPELTO, M., LAWLER, E., KAZIS, L. E. & WOLOZIN, B. 2010. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ: British Medical Journal,* 340.

LICHTENBERG, P. A. & CHRISTENSEN, B. 1992. EXTENDED NORMATIVE DATA FOR THE LOGICAL MEMORY SUBTESTS OF THE WECHSLER MEMORY SCALE-REVISED: RESPONSES FROM A SAMPLE OF COGNITIVELY INTACTELDERLY MEDICAL PATIENTS. *Psychological reports,* 71**,** 745-746.

LIGTHART, S. A., VAN CHARANTE, E. P. M., VAN GOOL, W. A. & RICHARD, E. 2010. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. *Vascular health and risk management,* 6**,** 775.

LITHELL, H., HANSSON, L., SKOOG, I., ELMFELDT, D., HOFMAN, A., OLOFSSON, B., TRENKWALDER, P. & ZANCHETTI, A. 2003. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *Journal of hypertension,* 21**,** 875-886.

LIU, K., COUGHLIN, T. & MCBRIDE, T. 1991. Predicting nursing-home admission and length of stay: A duration analysis. *Medical care***,** 125-141.

LONIE, J. A., TIERNEY, K. M. & EBMEIER, K. P. 2009. Screening for mild cognitive impairment: a systematic review. *International journal of geriatric psychiatry,* 24**,** 902-915.

LUENGO-FERNANDEZ, R., LEAL, J. & GRAY, A. M. 2011. Cost of dementia in the pre-enlargement countries of the European Union. *Journal of Alzheimer's Disease,* 27**,** 187-196.

LUIS, C. A., KEEGAN, A. P. & MULLAN, M. 2009. Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. *International journal of geriatric psychiatry,* 24**,** 197-201.

MALLACH, E. G. 2000. *Decision support and data warehouse systems*, McGraw-Hill Higher Education.

MANN, H. B. & WHITNEY, D. R. 1947. On a test of whether one of two random variables is stochastically larger than the other. *The annals of mathematical statistics,* 18**,**

50-60.

MARC, L. G., RAUE, P. J. & BRUCE, M. L. 2008. Screening performance of the geriatric depression scale (GDS-15) in a diverse elderly home care population. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry,* 16**,** 914.

MATHEUS, C. J., CHAN, P. K. & PIATETSKY-SHAPIRO, G. 1993. Systems for knowledge discovery in databases. *Knowledge and Data Engineering, IEEE Transactions on,* 5**,** 903-913.

MATTHEWS, H. P., KORBEY, J., WILKINSON, D. G. & ROWDEN, J. 2000. Donepezil in Alzheimer's disease: eighteen month results from Southampton Memory Clinic. *International journal of geriatric psychiatry,* 15**,** 713-720.

MAXWELL, C. J., HOGAN, D. B. & EBLY, E. M. 1999. Calcium-channel blockers and cognitive function in elderly people: results from the Canadian Study of Health and Aging. *Canadian Medical Association Journal,* 161**,** 501-506.

MCGEE, S. 2002. Simplifying likelihood ratios. *Journal of general internal medicine,* 17**,** 647-650.

MCKHANN, G., DRACHMAN, D., FOLSTEIN, M., KATZMAN, R., PRICE, D. & STADLAN, E. M. 1984. Clinical diagnosis of Alzheimer's disease Report of the NINCDS‐ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology,* 34**,** 939-939.

MIELKE, M., ROSENBERG, P., TSCHANZ, J., COOK, L., CORCORAN, C., HAYDEN, K., NORTON, M., RABINS, P., GREEN, R. & WELSH-BOHMER, K. 2007. Vascular factors predict rate of progression in Alzheimer disease. *Neurology,* 69**,** 1850-1858.

MINERS, J., ASHBY, E., VAN HELMOND, Z., CHALMERS, K., PALMER, L., LOVE, S. & KEHOE, P. 2007. Angiotensin‐converting enzyme (ACE) levels and activity in Alzheimer's disease, and relationship of perivascular ACE‐1 to cerebral amyloid angiopathy. *Neuropathology and applied neurobiology,* 34**,** 181-193.

MITCHELL, A. J. 2009. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *Journal of psychiatric research,* 43**,** 411-431.

MITCHELL, T. M. 1997. Machine learning. 1997. *Burr Ridge, IL: McGraw Hill,* 45.

MITNITSKI, A. B., MOGILNER, A. J., GRAHAM, J. E. & ROCKWOOD, K. 2003. Techniques for knowledge discovery in existing biomedical databases: estimation of individual aging effects in cognition in relation to dementia. *Journal of Clinical Epidemiology,* 56**,** 116-123.

MLADENIC, D. 2003. *Data mining and decision support: Integration and collaboration*, Kluwer Academic Pub.

MOHS, R. C., KNOPMAN, D., PETERSEN, R. C., FERRIS, S. H., ERNESTO, C., GRUNDMAN, M., SANO, M., BIELIAUSKAS, L., GELDMACHER, D. & CLARK, C. 1997. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. *Alzheimer Disease & Associated Disorders,* 11**,** 13-21.

MOLLOY, D. W., ALEMAYEHU, E. & ROBERTS, R. 1991a. Reliability of a standardized mini-mental state examination compared with the traditional mini-mental state examination. *Am J Psychiatry,* 148**,** 102-105.

MOLLOY, D. W., BÉDARD, M., GUYATT, G. H. & LEVER, J. 1997. Dysfunctional behavior rating instrument. *International psychogeriatrics,* 8**,** 333-341.

MOLLOY, D. W., MCLLROY, W., GUYATT, G. H. & LEVER, J. 1991b. Validity and reliability of the dysfunctional behaviour rating instrument. *Acta Psychiatrica Scandinavica,* 84**,** 103-106.

MOLLOY, D. W., STANDISH, T. & LEWIS, D. L. 2005. Screening for mild cognitive impairment: comparing the SMMSE and the ABCS. *Can J Psychiatry,* 50**,** 52-58.

MOLLOY, D. W., STANDISH, T., ZHOU, Q. & GUYATT, G. 2012. A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. *International journal of geriatric psychiatry*.

MOLLOY, D. W. & STANDISH, T. I. 1997a. A guide to the standardized Mini-Mental State Examination. *International psychogeriatrics,* 9**,** 87-94.

MOLLOY, D. W. & STANDISH, T. I. M. 1997b. A guide to the standardized Mini-Mental State Examination. *International psychogeriatrics,* 9**,** 87-94.

MONTGOMERY, H., CLARKSON, P., BARNARD, M., BELL, J., BRYNES, A., DOLLERY, C., HAJNAL, J., HEMINGWAY, H., MERCER, D. & JARMAN, P. 1999. Angiotensin-converting-enzyme gene insertion/deletion polymorphism and response to physical training. *The Lancet,* 353**,** 541-545.

MOODY, H. R. 2006. *Aging: Concepts and controversies*, Pine Forge Press.

MORRIS, J. C. 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*.

MORRIS, J. C., STORANDT, M., MILLER, J. P., MCKEEL, D. W., PRICE, J. L., RUBIN, E. H. & BERG, L. 2001. Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of neurology,* 58**,** 397.

MORTIMER, J. A., EBBITT, B., JUN, S.-P. & FINCH, M. D. 1992. Predictors of cognitive

and functional progression in patients with probable Alzheimer's disease. *Neurology,* 42**,** 1689-1689.

MOUNT, C. & DOWNTON, C. 2006. Alzheimer disease: progress or profit? *Nature medicine,* 12**,** 780-784.

MULLINS, I. M., SIADATY, M. S., LYMAN, J., SCULLY, K., GARRETT, C. T., GREG MILLER, W., MULLER, R., ROBSON, B., APTE, C. & WEISS, S. 2006. Data mining and clinical data repositories: Insights from a 667,000 patient data set. *Computers in biology and medicine,* 36**,** 1351-1377.

NASREDDINE, Z. S., PHILLIPS, N. A., BÉDIRIAN, V., CHARBONNEAU, S., WHITEHEAD, V., COLLIN, I., CUMMINGS, J. L. & CHERTKOW, H. 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society,* 53**,** 695-699.

NEYMAN, J. & PEARSON, E. S. 1931. *On the problem of k samples*, Imprimerie de l'Université.

NOETHER, G. E. 1967. *Elements of nonparametric statistics*, Wiley New York.

O'BRIEN, J. & LEVY, R. 1992. Age associated memory impairment. *BMJ: British Medical Journal,* 304**,** 913.

O'CAOIMH, R., GAO, Y., GALLAGHER, P. F., EUSTACE, J., MCGLADE, C. & MOLLOY, D. W. 2013a. Which part of the Quick mild cognitive impairment screen (Qmci) discriminates between normal cognition, mild cognitive impairment and dementia? *Age and ageing,* 42**,** 324-330.

O'CAOIMH, R., GAO, Y., GALLAGHER, P. F., EUSTACE, J. & MOLLOY, D. W. Adjusting cut-off scores for age and education in patients presenting with symptomatic memory loss. In press.

O'CAOIMH, R., GAO, Y., MCGLADE, C., HEALY, L., GALLAGHER, P., TIMMONS, S. & MOLLOY, D. W. 2012a. Comparison of the quick mild cognitive impairment (Qmci) screen and the SMMSE in screening for mild cognitive impairment. *Age and ageing,* 41**,** 624-629.

O'CAOIMH, R., GAO, Y., MCGLADE, C., HEALY, L., GALLAGHER, P., TIMMONS, S. & MOLLOY, D. W. The Quick Mild Cognitive Impairment (Qmci) Screen: A New Screening Tool for Mild Cognitive Impairment. IRISH JOURNAL OF MEDICAL SCIENCE, 2012b. SPRINGER LONDON LTD 236 GRAYS INN RD, 6TH FLOOR, LONDON WC1X 8HL, ENGLAND, S228-S229.

O'CAOIMH, R., HEALY, L., GAO, Y., SVENDROVSKI, A., KERINS, D. M., EUSTACE, J., KEHOE, P. G., GUYATT, G. & MOLLOY, D. W. 2014. Effects of Centrally acting Angiotensin Converting Enzyme Inhibitors on Functional Decline in

Patients with Alzheimer's Disease. *Journal of Alzheimer's Disease*.

O'CAOIMH, R., SVENDROVSKI, A., JOHNSTON, B. C., GAO, Y., MCGLADE, C., EUSTACE, J., TIMMONS, S., GUYATT, G. & MOLLOY, D. W. 2013b. The Quick Mild Cognitive Impairment screen correlated with the Standardized Alzheimer's Disease Assessment Scale–cognitive section in clinical trials. *Journal of Clinical Epidemiology*.

O'CAOIMH, R., TIMMONS, S. & MOLLOY, D. Comparison of the Quick Mild Cognitive Impairment Screen (Qmci) to the Montreal Cognitive Assessment. IRISH JOURNAL OF MEDICAL SCIENCE, 2013c. SPRINGER LONDON LTD 236 GRAYS INN RD, 6TH FLOOR, LONDON WC1X 8HL, ENGLAND, S286-S286.

O'NEIL, M. E., FREEMAN, M. & PORTLAND, V. 2011. *A systematic evidence review of non-pharmacological interventions for behavioral symptoms of dementia*, Department of Veterans Affairs.

OHRUI, T., TOMITA, N., SATO-NAKAGAWA, T., MATSUI, T., MARUYAMA, M., NIWA, K., ARAI, H. & SASAKI, H. 2004. Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression. *Neurology,* 63**,** 1324-1325.

ONDER, G., PENNINX, B. W., BALKRISHNAN, R., FRIED, L. P., CHAVES, P. H., WILLIAMSON, J., CARTER, C., BARI, M. D., GURALNIK, J. M. & PAHOR, M. 2002. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. *The Lancet,* 359**,** 926-930.

OVEISGHARAN, S. & HACHINSKI, V. 2010. Hypertension, executive dysfunction, and progression to dementia: the Canadian Study of Health and Aging. *Archives of neurology,* 67**,** 187.

OWNBY, R. L., HARWOOD, D. G., ACEVEDO, A., BARKER, W. & DUARA, R. 2001. Factor structure of the Cornell Scale for Depression in Dementia for Anglo and Hispanic patients with dementia. *The American Journal of Geriatric Psychiatry,* 9**,** 217-224.

OXMAN, A. D., COOK, D. J., GUYATT, G. H. & GROUP, E.-B. M. W. 1994. Users' guides to the medical literature. *Jama,* 272**,** 1367-1371.

PATTERSON, C., FEIGHTNER, J., GARCIA, A. & MACKNIGHT, C. 2007. General risk factors for dementia: A systematic evidence review. *Alzheimer's & Dementia,* 3**,** 341-347.

PEACOCK, J. & PEACOCK, P. 2010. *Oxford handbook of medical statistics*, Oxford University Press.

PEARSON, E. & HARTLEY, H. 1972. 0.(1972). Biometrika tables for statisticians, Vol. 2.

Cambridge University Press.

PEARSON, K. 1900. X. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science,* 50**,** 157-175.

PEARSON, K. 1907. XXVII. On the influence of past experience on future expectation. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science,* 13**,** 365-378.

PENG, Y., KOU, G., SHI, Y. & CHEN, Z. 2008. A descriptive framework for the field of data mining and knowledge discovery. *International Journal of Information Technology & Decision Making,* 7**,** 639-682.

PEPE, M. S., JANES, H., LONGTON, G., LEISENRING, W. & NEWCOMB, P. 2004. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *American journal of epidemiology,* 159**,** 882-890.

PÉRÈS, K., HELMER, C., AMIEVA, H., ORGOGOZO, J. M., ROUCH, I., DARTIGUES, J. F. & BARBERGER‐GATEAU, P. 2008. Natural History of Decline in Instrumental Activities of Daily Living Performance over the 10 Years Preceding the Clinical Diagnosis of Dementia: A Prospective Population‐Based Study. *Journal of the American Geriatrics Society,* 56**,** 37-44.

PETERSEN, R. C. 2001. Mild cognitive impairment: Transition from aging to Alzheimer's disease. *Alzheimer's Disease: Advances in Etiology, Pathogenesis and Therapeutics***,** 141-151.

PETERSEN, R. C. 2004. Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine,* 256**,** 183-194.

PETERSEN, R. C., DOODY, R., KURZ, A., MOHS, R. C., MORRIS, J. C., RABINS, P. V., RITCHIE, K., ROSSOR, M., THAL, L. & WINBLAD, B. 2001. Current concepts in mild cognitive impairment. *Archives of neurology,* 58**,** 1985-1992.

PETERSEN, R. C., SMITH, G. E., WARING, S. C., IVNIK, R. J., TANGALOS, E. G. & KOKMEN, E. 1999. Mild cognitive impairment: clinical characterization and outcome. *Archives of neurology,* 56**,** 303-308.

PHILLIPS, J. 1999. *How to think about statistics*, Macmillan.

PIATETSKY-SHAPIRO, G. 1991. Discovery, analysis, and presentation of strong rules. *Knowledge discovery in databases***,** 229-238.

PIATETSKY-SHAPIRO, G., BRACHMAN, R. J., KHABAZA, T., KLOESGEN, W. & SIMOUDIS, E. An Overview of Issues in Developing Industrial Data Mining and

Knowledge Discovery Applications. KDD, 1996. 89-95.

POON, I. O. 2008. Effects of antihypertensive drug treatment on the risk of dementia and cognitive impairment. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy,* 28**,** 366-375.

PORTER, R. J., GALLAGHER, P., THOMPSON, J. M. & YOUNG, A. H. 2003. Neurocognitive impairment in drug-free patients with major depressive disorder. *The British Journal of Psychiatry,* 182**,** 214-220.

PRATHER, J. C., LOBACH, D. F., GOODWIN, L. K., HALES, J. W., HAGE, M. L. & HAMMOND, W. E. Medical data mining: knowledge discovery in a clinical data warehouse. Proceedings of the AMIA annual fall symposium, 1997. American Medical Informatics Association, 101.

PRINCE, M., BRYCE, R., ALBANESE, E., WIMO, A., RIBEIRO, W. & FERRI, C. P. 2013. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's & Dementia,* 9**,** 63-75. e2.

PRINCE, M. & JACKSON, J. 2009. *World Alzheimer Report 2009*, Alzheimer's Disease International.

QASEEM, A., SNOW, V., CROSS, J. T., FORCIEA, M. A., HOPKINS, R., SHEKELLE, P., ADELMAN, A., MEHR, D., SCHELLHASE, K. & CAMPOS-OUTCALT, D. 2008. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Annals of Internal Medicine,* 148**,** 370-378.

RAJAK, A. & GUPTA, M. K. Association rule mining-applications in various areas. Proceedings of International Conference on Data Management, Ghaziabad, India, 2008. 3-7.

REGAN, C., KATONA, C., WALKER, Z., HOOPER, J., DONOVAN, J. & LIVINGSTON, G. 2006. Relationship of vascular risk to the progression of Alzheimer disease. *Neurology,* 67**,** 1357-1362.

REISBERG, B. 1987. Functional assessment staging (FAST). *Psychopharmacology bulletin,* 24**,** 653-659.

REISBERG, B., DOODY, R., STÖFFLER, A., SCHMITT, F., FERRIS, S. & MÖBIUS, H. J. 2003. Memantine in moderate-to-severe Alzheimer's disease. *New England Journal of Medicine,* 348**,** 1333-1341.

RENCHER, A. C. & CHRISTENSEN, W. F. 2012. *Methods of multivariate analysis*, John Wiley & Sons.

RENU, R. S., MOCKO, G. & KONERU, A. 2013. Use of Big Data and Knowledge Discovery to Create Data Backbones for Decision Support Systems. *Procedia*

Computer Science, 20**,** 446-453.

RITCHIE, K. 2004. Mild cognitive impairment: an epidemiological perspective. *Dialogues in clinical neuroscience,* 6**,** 401.

ROBLES, V. C., LARRANAGA, P., PENA, J. M., MENASALVAS, E., PÉREZ, M. A. S., HERVES, V. & WASILEWSKA, A. 2004. Bayesian network multi-classifiers for protein secondary structure prediction. *Artificial Intelligence in Medicine,* 31**,** 117-136.

ROGERS, D. & PIES, R. 2008. General medical drugs associated with depression. *Psychiatry (Edgmont),* 5**,** 28.

ROSEN, W. G., MOHS, R. C. & DAVIS, K. L. 1984. A new rating scale for Alzheimer's disease. *The American Journal of Psychiatry; The American Journal of Psychiatry*.

ROSENBERG, P., MIELKE, M., TSCHANZ, J., COOK, L., STAT, M., CORCORAN, C., HAYDEN, K., NORTON, M., RABINS, P. & GREEN, R. 2008a. Effects of cardiovascular medications on rate of functional decline in Alzheimer disease. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry,* 16**,** 883.

ROSENBERG, P. B., MIELKE, M., TSCHANZ, J., COOK, L., CORCORAN, C., HAYDEN, K., NORTON, M., RABINS, P., GREEN, R. & WELSH-BOHMER, K. 2008b. Effects of cardiovascular medications on rate of functional decline in Alzheimer disease. *The American Journal of Geriatric Psychiatry,* 16**,** 883-892.

ROY WALKER, P., SMITH, B., LIU, Q. Y., FAZEL FAMILI, A., VALDÉS, J. J., LIU, Z. & LACH, B. 2004. Data mining of gene expression changes in Alzheimer brain. *Artificial Intelligence in Medicine,* 31**,** 137-154.

ROZZINI, L., CHILOVI, B. V., BERTOLETTI, E., CONTI, M., RIO, I. D., TRABUCCHI, M. & PADOVANI, A. 2006. Angiotensin converting enzyme (ACE) inhibitors modulate the rate of progression of amnestic mild cognitive impairment. *International journal of geriatric psychiatry,* 21**,** 550-555.

ROZZINI, L., VICINI CHILOVI, B., TRABUCCHI, M. & PADOVANI, A. 2008. Antihypertensive medications influence the rate of conversion from mild cognitive impairment to Alzheimer disease. *Archives of neurology,* 65**,** 993.

SALLOWAY, S., MINTZER, J., WEINER, M. F. & CUMMINGS, J. L. 2008. Disease-modifying therapies in Alzheimer's disease. *Alzheimer's & Dementia,* 4**,** 65-79.

SCHAFER, K. A., TRACTENBERG, R. E., SANO, M., MACKELL, J. A., THOMAS, R. G., GAMST, A., THAL, L. J. & MORRIS, J. C. 2004. Reliability of monitoring the

clinical dementia rating in multicenter clinical trials. *Alzheimer Disease & Associated Disorders,* 18**,** 219-222.

SEIZE, T. K. 1977. Student's t-test. *Southern Medical Journal,* 70**,** 1299.

SELF-MAINTENANCE, P. 1969. Assessment of older people: self-maintaining and instrumental activities of daily living.

SERIPA, D., PARONI, G., MATERA, M. G., GRAVINA, C., SCARCELLI, C., CORRITORE, M., D'AMBROSIO, L. P., URBANO, M., D'ONOFRIO, G. & COPETTI, M. 2011. Angiotensin-converting enzyme (ACE) genotypes and disability in hospitalized older patients. *AGE,* 33**,** 409-419.

SHAPIRO, S. S. & WILK, M. B. 1965. An analysis of variance test for normality (complete samples). *Biometrika,* 52**,** 591-611.

SHEEHAN, B. 2012. Assessment scales in dementia. *Therapeutic advances in neurological disorders,* 5**,** 349-358.

SHIEKH, J. & YESAVAGE, J. 1986. Geriatric Depression Scale: recent findings and development of a short version. *Clinical Gerontology: A Guide to Assessment and Intervention, BrinkT (ed.). Howarth Press: New York*.

SINK, K. M., LENG, X., WILLIAMSON, J., KRITCHEVSKY, S. B., YAFFE, K., KULLER, L., YASAR, S., ATKINSON, H., ROBBINS, M. & PSATY, B. 2009. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Archives of Internal Medicine,* 169**,** 1195.

SLOANE, P. D., ZIMMERMAN, S., SUCHINDRAN, C., REED, P., WANG, L., BOUSTANI, M. & SUDHA, S. 2002. The public health impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances. *Annual Review of Public Health,* 23**,** 213-231.

SMITH, G. E., PETERSEN, R. C., PARISI, J. E., IVNIK, R. J., KOKMEN, E., TANGALOS, E. G. & WARING, S. 1996. Definition, course, and outcome of mild cognitive impairment. *Aging, Neuropsychology, and Cognition,* 3**,** 141-147.

SMITH, M., WANG, X. & RANGAYYAN, R. 2009. Evaluation of the sensitivity of a medical data-mining application to the number of elements in small databases. *Biomedical signal processing and control,* 4**,** 262-268.

SMITH, T., GILDEH, N. & HOLMES, C. 2007. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *Canadian Journal of Psychiatry,* 52**,** 329.

SOCIETY, R. 1894. *Philosophical Transactions of the Royal Society of London*, The Society.

SOLFRIZZI, V., SCAFATO, E., FRISARDI, V., SERIPA, D., LOGROSCINO, G., KEHOE, P. G., IMBIMBO, B. P., BALDERESCHI, M., CREPALDI, G. & DI CARLO, A. 2011. Angiotensin-converting enzyme inhibitors and incidence of mild cognitive impairment. The Italian Longitudinal Study on Aging. *AGE*, 1-13.

SPEARMAN, C. 1904. The proof and measurement of association between two things. *The American journal of psychology,* 15, 72-101.

SPILKER, B. 1990. *Quality of life assessments in clinical trials*, Raven Press New York.

SRIVATHSA, P. Knowledge Discovery in Medical Mining by using Genetic Algorithms and Artificial Neural Networks. AIP Conference Proceedings, 2011. 67.

STAESSEN, J. A., FAGARD, R., THIJS, L., CELIS, H., ARABIDZE, G. G., BIRKENHÄGER, W. H., BULPITT, C. J., DE LEEUW, P. W., DOLLERY, C. T. & FLETCHER, A. E. 1997. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *The Lancet,* 350, 757-764.

STAESSEN, J. A., THIJS, L., RICHART, T., ODILI, A. N. & BIRKENHÄGER, W. H. 2011. Placebo-Controlled Trials of Blood Pressure–Lowering Therapies for Primary Prevention of Dementia. *Hypertension,* 57, e6-e7.

STANDISH, T., MOLLOY, D. W., BÉDARD, M., LAYNE, E. C., MURRAY, E. A. & STRANG, D. 1996. Improved reliability of the Standardized Alzheimer's Disease Assessment Scale (SADAS) compared with the Alzheimer's Disease Assessment Scale (ADAS). *Journal of the American Geriatrics Society,* 44, 712.

STANDISH, T. I., MOLLOY, D. W., CUNJE, A. & LEWIS, D. L. 2007. Do the ABCS 135 short cognitive screen and its subtests discriminate between normal cognition, mild cognitive impairment and dementia? *International journal of geriatric psychiatry,* 22, 189-194.

STUCK, A. E., WALTHERT, J. M., NIKOLAUS, T., BÜLA, C. J., HOHMANN, C. & BECK, J. C. 1999. Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Social science & medicine,* 48, 445-469.

SULLIVAN, M. G. 2007. Tramiprosate Falls Short in Phase III Alzheimer's Trial. *Clin Psychiatry News,* 35, 27.

SUMUKADAS, D., WITHAM, M. D., STRUTHERS, A. D. & MCMURDO, M. E. 2007. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. *Canadian Medical Association Journal,* 177, 867-874.

TAN, K. C., YU, Q., HENG, C. & LEE, T. H. 2003. Evolutionary computing for knowledge

discovery in medical diagnosis. *Artificial Intelligence in Medicine,* 27**,** 129-154.

TAN, P.-N. 2007. *Introduction to data mining*, Pearson Education India.

TEO, K., YUSUF, S., SLEIGHT, P., ANDERSON, C., MOOKADAM, F., RAMOS, B., HILBRICH, L., POGUE, J. & SCHUMACHER, H. 2004. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *American heart journal,* 148**,** 52.

TIERNEY, M., SZALAI, J., SNOW, W., FISHER, R., NORES, A., NADON, G., DUNN, E. & GEORGE-HYSLOP, P. S. 1996a. Prediction of probable Alzheimer's disease in memory-impaired patients A prospective longitudinal study. *Neurology,* 46**,** 661-665.

TIERNEY, M., SZALAI, J., SNOW, W., FISHER, R., TSUDA, T., CHI, H., MCLACHLAN, D. & GEORGE-HYSLOP, P. S. 1996b. A prospective study of the clinical utility of ApoE genotype in the prediction of outcome in patients with memory impairment. *Neurology,* 46**,** 149-154.

TIERNEY, W. M., MURRAY, M. D., GASKINS, D. L. & ZHOU, X.-H. 1997. Using computer-based medical records to predict mortality risk for inner-city patients with reactive airways disease. *Journal of the American Medical Informatics Association,* 4**,** 313-321.

TODD, S., MCGUINNESS, B. & PASSMORE, A. P. 2010. Designing Appropriate Clinical Trials to Assess ACEI Use and Cognitive Decline in Older Adults With Hypertension. *Archives of Internal Medicine,* 170**,** 107.

TODHUNTER, I. 1865. *A History of the Mathematical Theory of Probability from the Time of Pascal to that of Laplace*, Macmillan.

TOLLEFSON, G. D. 1990. Short-term effects of the calcium channel blocker nimodipine (Bay-e-9736) in the management of primary degenerative dementia. *Biological psychiatry,* 27**,** 1133-1142.

TOTA, S., NATH, C., NAJMI, A. K., SHUKLA, R. & HANIF, K. 2012. Inhibition of central angiotensin converting enzyme ameliorates scopolamine induced memory impairment in mice: role of cholinergic neurotransmission, cerebral blood flow and brain energy metabolism. *Behavioural brain research,* 232**,** 66-76.

TSUMOTO, S. 2000. Knowledge discovery in clinical databases and evaluation of discovered knowledge in outpatient clinic. *Information Sciences,* 124**,** 125-137.

TSUMOTO, S., IWATA, H., HIRANO, S. & TSUMOTO, Y. 2013. Similarity-based

behavior and process mining of medical practices. *Future Generation Computer Systems*.

UHLENBERG, P. 2013. Demography Is Not Destiny: The Challenges and Opportunities of Global Population Aging. *Generations,* 37**,** 12-18.

VAN DAM, D. & DE DEYN, P. P. 2006. Drug discovery in dementia: the role of rodent models. *Nature Reviews Drug Discovery,* 5**,** 956-970.

VERTESI, A., LEVER, J. A., MOLLOY, D. W., SANDERSON, B., TUTTLE, I., POKORADI, L. & PRINCIPI, E. 2001. Standardized Mini-Mental State Examination. Use and interpretation. *Canadian Family Physician,* 47**,** 2018-2023.

VIDA, S., DES ROSIERS, P., CARRIER, L. & GAUTHIER, S. 1994. Depression in Alzheimer's disease: receiver operating characteristic analysis of the Cornell Scale for Depression in Dementia and the Hamilton Depression Scale. *Journal of Geriatric Psychiatry and Neurology,* 7**,** 159-162.

VIDENOVIC, A., BERNARD, B., FAN, W., JAGLIN, J., LEURGANS, S. & SHANNON, K. M. 2010. The Montreal Cognitive Assessment as a screening tool for cognitive dysfunction in Huntington's disease. *Movement disorders,* 25**,** 401-404.

WANG, L., CHIANG, H.-C., WU, W., LIANG, B., XIE, Z., YAO, X., MA, W., DU, S. & ZHONG, Y. 2012. Epidermal growth factor receptor is a preferred target for treating Amyloid-β–induced memory loss. *Proceedings of the National Academy of Sciences,* 109**,** 16743-16748.

WEBER, G., VINTERBO, S. & OHNO-MACHADO, L. 2004. Multivariate selection of genetic markers in diagnostic classification. *Artificial Intelligence in Medicine,* 31**,** 155-167.

WECHSLER, D. 2008. Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). *San Antonio, TX: NCS Pearson*.

WHARTON, W., STEIN, J. H., KORCARZ, C., SACHS, J., OLSON, S. R., ZETTERBERG, H., DOWLING, M., YE, S., GLEASON, C. E. & UNDERBAKKE, G. 2012. The effects of ramipril in individuals at risk for Alzheimer's disease: results of a pilot clinical trial. *Journal of Alzheimer's Disease,* 32**,** 147-156.

WHITLEY, E. & BALL, J. 2002. Statistics review 6: Nonparametric methods. *CRITICAL CARE-LONDON-,* 6**,** 509-513.

WHITMER, R., SIDNEY, S., SELBY, J., JOHNSTON, S. C. & YAFFE, K. 2005. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology,* 64**,** 277-281.

WILCOX, R. R. 1996. *Statistics for the social sciences*, Academic Press.

WILCOXON, F. 1945. Individual comparisons by ranking methods. *Biometrics bulletin,* 1**,** 80-83.

WIMO, A., LJUNGGREN, G. & WINBLAD, B. 1997. Costs of dementia and dementia care: a review. *International journal of geriatric psychiatry,* 12**,** 841-856.

WIMO, A., WINBLAD, B. & JÖNSSON, L. 2010. The worldwide societal costs of dementia: Estimates for 2009. *Alzheimer's & Dementia,* 6**,** 98-103.

WINBLAD, B., PALMER, K., KIVIPELTO, M., JELIC, V., FRATIGLIONI, L., WAHLUND, L. O., NORDBERG, A., BÄCKMAN, L., ALBERT, M. & ALMKVIST, O. 2004. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of internal medicine,* 256**,** 240-246.

WISCHIK, C., EDWARDS, P., LAI, R., ROTH, M. & HARRINGTON, C. 1996. Selective inhibition of Alzheimer disease-like tau aggregation by phenothiazines. *Proceedings of the National Academy of Sciences,* 93**,** 11213-11218.

WITTEN, I. H. & FRANK, E. 2005. *Data Mining: Practical machine learning tools and techniques*, Morgan Kaufmann.

WONG, A., XIONG, Y. Y., KWAN, P. W., CHAN, A. Y., LAM, W. W., WANG, K., CHU, W. C., NYENHUIS, D. L., NASREDDINE, Z. & WONG, L. K. 2009. The validity, reliability and clinical utility of the Hong Kong Montreal Cognitive Assessment (HK-MoCA) in patients with cerebral small vessel disease. *Dementia and geriatric cognitive disorders,* 28**,** 81-87.

WONG, A. K., LORD, S. R., STURNIEKS, D. L., DELBAERE, K., TROLLOR, J. N. & CLOSE, J. C. 2013. Angiotensin System–Blocking Medications Are Associated with Fewer Falls over 12 Months in Community‐Dwelling Older People. *Journal of the American Geriatrics Society*.

WOODWARD, M. C. 2012. Drug Treatments in Development for Alzheimer's Disease. *Journal of Pharmacy Practice & Research,* 42.

WORSTER, A., FAN, J. & UPADHYE, S. 2006. Understanding receiver operating characteristic (ROC) curves. *Cjem,* 8**,** 19-20.

WRIGHT, T. M. 2006. Tramiprosate. *Drugs of today (Barcelona, Spain: 1998),* 42**,** 291-298.

XIAO, Z. 1998. Statistics and Data Mining. *National University of Singapore*.

YAMADA, K., HORITA, T., TAKAYAMA, M., TAKAHASHI, S., TAKABA, K., NAGATA, Y., SUZUKI, N. & KANDA, T. 2011. Effect of a centrally active angiotensin converting enzyme inhibitor, perindopril, on cognitive performance in chronic cerebral hypo-perfusion rats. *Brain research,* 1421**,** 110-120.

YAMADA, K., UCHIDA, S., TAKAHASHI, S., TAKAYAMA, M., NAGATA, Y., SUZUKI, N., SHIRAKURA, S. & KANDA, T. 2010. Effect of a centrally active angiotensin-converting enzyme inhibitor, perindopril, on cognitive performance in a mouse model of Alzheimer's disease. *Brain research,* 1352**,** 176-186.

YESAVAGE, J. 1988. Geriatric Depression Scale. *Psychopharmacology bulletin,* 24**,** 709.

YESAVAGE, J. A., BRINK, T., ROSE, T. L., LUM, O., HUANG, V., ADEY, M. & LEIRER, V. O. 1983. Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of psychiatric research,* 17**,** 37-49.

YLIKOSKI, R., ERKINJUNTTI, T., SULKAVA, R., JUVA, K., TILVIS, R. & VALVANNE, J. 1992. Correction for age, education and other demographic variables in the use of the Mini Mental State Examination in Finland. *Acta Neurologica Scandinavica,* 85**,** 391-396.

YOUDEN, W. 1950. Index for rating diagnostic tests. *Cancer,* 3**,** 32-35.

ZHAN, H. J. 2013. Population Aging and Long-Term Care in China. *Generations,* 37**,** 53-58.

ZHANG, D., WANG, Y., ZHOU, L., YUAN, H. & SHEN, D. 2011. Multimodal classification of Alzheimer's disease and mild cognitive impairment. *Neuroimage,* 55**,** 856-867.

ZHOU, X.-H., OBUCHOWSKI, N. A. & MCCLISH, D. K. 2011. *Statistical methods in diagnostic medicine*, Wiley. com.

ZI, M., CARMICHAEL, N. & LYE, M. 2003. The effect of quinapril on functional status of elderly patients with diastolic heart failure. *Cardiovascular drugs and therapy,* 17**,** 133-139.

ZOU, K. H., HALL, W. & SHAPIRO, D. E. 1997. Smooth non‐parametric receiver operating characteristic (ROC) curves for continuous diagnostic tests. *Statistics in medicine,* 16**,** 2143-2156.

APPENDIX

A. Publication List

Peer reviewed journals:

O'CAOIMH, R., HEALY, L., **GAO, Y**., SVENDROVSKI, A., KERINS, D. M., EUSTACE, J., KEHOE, P. G., GUYATT, G. & MOLLOY, D. W. 2014. Effects of Centrally acting Angiotensin Converting Enzyme Inhibitors on Functional Decline in Patients with Alzheimer's Disease. *Journal of Alzheimer's Disease.*

GAO, Y., O'CAOIMH, R., HEALY, L., KERINS, D. M., EUSTACE, J., GUYATT, G., SAMMON, D. & MOLLOY, D. W. 2013a. Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia. *BMJ open,* 3.

O'CAOIMH, R., SVENDROVSKI, A., JOHNSTON, B. C., **GAO, Y.**, MCGLADE, C., EUSTACE, J., TIMMONS, S., GUYATT, G. & MOLLOY, D. W. 2013. The Quick Mild Cognitive Impairment screen correlated with the Standardized Alzheimer's Disease Assessment Scale–cognitive section in clinical trials. *Journal of Clinical Epidemiology.*

O'CAOIMH, R., **GAO, Y.**, GALLAGHER, P. F., EUSTACE, J., MCGLADE, C. & MOLLOY, D. W. 2013a. Which part of the Quick mild cognitive impairment screen (Qmci) discriminates between normal cognition, mild cognitive impairment and dementia? *Age and ageing,* 42**,** 324-330.

O'CAOIMH, R., **GAO, Y.**, MCGLADE, C., HEALY, L., GALLAGHER, P., TIMMONS, S. & MOLLOY, D. W. 2012c. Comparison of the quick mild cognitive impairment (Qmci) screen and the SMMSE in

screening for mild cognitive impairment. *Age and ageing,* 41**,** 624-629.

Abstracts:

O'CAOIMH, R., **GAO, Y.**, MCGLADE, C., HEALY, L., GALLAGHER, P., TIMMONS, S. & MOLLOY, D. W. The Quick Mild Cognitive Impairment (Qmci) Screen: A New Screening Tool for Mild Cognitive Impairment. *Irish journal of medical science*, 2012. SPRINGER LONDON LTD 236 GRAYS INN RD, 6TH FLOOR, LONDON WC1X 8HL, ENGLAND, S228-S229.

GAO, Y., O'CAOIMH, R., HEALY, L., KERINS, D. M., EUSTACE, J., GUYATT, G., SAMMON, D. & MOLLOY, D. W. 2013. Effects of Centrally Acting Angiotensin Converting EnzymeInhibitors on the Rate of Cognitive Decline and Activities of Daily Living in Dementia. *Irish Gerontological Society meeting 2013*. Dublin, Ireland.

Presentations:

GAO, Y., O'CAOIMH, R. & MOLLOY, D. W. 2012. The Quick Behaviour Score, Qbehaviour: Assessing the Frequency of Behaviours that Challenge to Differentiate Mild Cognitive Impairment and Dementia from Depression. *The 15th Asia-Pacific Regional Conference of Alzheimer's Disease International (ADI) & 2012 Annual Conference of Alzheimer's Disease Chinese (ADC)*. Beijing, China.

O'CAOIMH, R., **GAO, Y.**, MCGLADE, C., HEALY, L., GALLAGHER, P., TIMMONS, S. & MOLLOY, D. W. 2012d. The Quick Mild Cognitive Impairment (Qmci) screen: a New Screening Tool for Mild Cognitive Impairment. *The 15th Asia-Pacific Regional Conference of Alzheimer's Disease International (ADI) & 2012 Annual Conference of Alzheimer's Disease Chinese (ADC)*. Beijing,

China.

Unpublished Papers:

GAO, Y., O'CAOIMH, R., KEHOE, P. G., SAMMON, D. & MOLLOY, D. W. Centrally Acting Angiotensin Converting Enzyme Inhibitors and Functional Decline in Dementia: Do they Affect Instrumental or Basic ADLs?

O'CAOIMH, R., GAO, Y., GALLAGHER, P. F., EUSTACE, J. & MOLLOY, D. W. Adjusting cut-off scores for age and education in patients presenting with symptomatic memory loss.

B. Published Journals

BMJ open

Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia

Yang Gao,[1,2] Rónán O'Caoimh,[1] Liam Healy,[1] David M Kerins,[3,4] Joseph Eustace,[5] Gordon Guyatt,[6] David Sammon,[2] D William Molloy[1,7]

To cite: Gao Y, O'Caoimh R, Healy L, *et al*. Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia. *BMJ Open* 2013;**3**:e002881. doi:10.1136/bmjopen-2013-002881

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2013-002881).

Received 14 March 2013
Revised 9 May 2013
Accepted 14 May 2013

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 3.0 Licence; see http://bmjopen.bmj.com

For numbered affiliations see end of article.

Correspondence to
Professor D William Molloy; w.molloy@ucc.ie

ABSTRACT

Objectives: There is growing evidence that antihypertensive agents, particularly centrally acting ACE inhibitors (CACE-Is), which cross the blood–brain barrier, are associated with a reduced rate of cognitive decline. Given this, we compared the rates of cognitive decline in clinic patients with dementia receiving CACE-Is (CACE-I) with those not currently treated with CACE-Is (NoCACE-I), and with those who started CACE-Is, during their first 6 months of treatment (NewCACE-I).

Design: Observational case–control study.

Setting: 2 university hospital memory clinics.

Participants: 817 patients diagnosed with Alzheimer's disease, vascular or mixed dementia. Of these, 361 with valid cognitive scores were included for analysis, 85 CACE-I and 276 NoCACE-I.

Measurements: Patients were included if the baseline and end-point (standardised at 6 months apart) Standardised Mini-Mental State Examination (SMMSE) or Quick Mild Cognitive Impairment (Qmci) scores were available. Patients with comorbid depression or other dementia subtypes were excluded. The average 6-month rates of change in scores were compared between CACE-I, NoCACE-I and NewCACE-I patients.

Results: When the rate of decline was compared between groups, there was a significant difference in the median, 6-month rate of decline in Qmci scores between CACE-I (1.8 points) and NoCACE-I (2.1 points) patients (p=0.049), with similar, non-significant changes in SMMSE. Median SMMSE scores improved by 1.2 points in the first 6 months of CACE treatment (NewCACE-I), compared to a 0.8 point decline for the CACE-I (p=0.003) group and a 1 point decline for the NoCACE-I (p=0.001) group over the same period. Multivariate analysis, controlling for baseline characteristics, showed significant differences in the rates of decline, in SMMSE, between the three groups, p=0.002.

Conclusions: Cognitive scores may improve in the first 6 months after CACE-I treatment and use of CACE-Is is associated with a reduced rate of cognitive decline in patients with dementia.

ARTICLE SUMMARY

Article focus

- Treatment options for dementia, including Alzheimer's disease, remain limited. The purpose of this study was to examine the effect of centrally acting ACE inhibitors (CACE-Is) on the rate of cognitive decline in patients with dementia.
- This study also examined the acute effect of CACE-Is on cognition, during the first 6 months of treatment.

Key messages

- Reduced rates of cognitive decline were seen in an unselected outpatient sample, prescribed CACE-Is, irrespective of the blood pressure readings or diagnosis of hypertension.
- The rate of decline was reduced in patients in the 6 months after starting CACE-Is, compared to those already established on them.

Strengths and limitations of this study

- This study used observational data collected in a 'real world' setting, where treatments, including antihypertensive agents, were administered on the basis of clinical judgement.
- The study investigated the effects of CACE-Is in an unselected clinic sample of older adults with different dementia subtypes, whose mean age approached 80 years.
- Although most patients in the database had Qmci or SMMSE recorded, large numbers lacked results at the baseline or end point, limiting the numbers that could be included in the analysis.
- Change over 6 months of treatment was analysed. Different effects may have been demonstrated over a longer period.

INTRODUCTION

As populations age worldwide, the incidence of dementia will increase. By 2040, approximately 81 million people worldwide will be affected.[1] Until now, no agents have been identified that prevent, modify or reverse dementia, and available treatments for dementia are predominantly symptomatic.[2] There is growing recognition of the role of cardiovascular risk factors, especially in midlife, in the conversion and progression of mild cognitive impairment (MCI)

and dementia.[3–5] Blood pressure (BP) control, in particular, is associated with both a reduced incidence of cognitive impairment (CI) and rate of cognitive decline.[6–9] Several antihypertensive agents are associated with a lower risk of developing dementia, including calcium channel blockers (CCBs),[10 11] diuretics,[8] angiotensin receptor blockers (ARBs)[12–14] and ACE inhibitors (ACE-Is).[15 16] ACE-Is and ARBs affect the renin angiotensin system and may lower dementia risk, independent of their BP lowering properties.[17] Results of clinical trials investigating the potential role of antihypertensives are limited and conflicting.[18] The Perindopril Protection against Recurrent Stroke Study (PROGRESS) demonstrated that a combination of perindopril (ACE-I) and indapamide (diuretic) was associated with a significant reduction in the incidence of stroke and in cognitive decline, compared to placebo.[8] The Systolic Hypertension in Europe (Syst-Eur) study found that the combination of enalapril (ACE-I), nitrendipine (CCB) and/or hydrochlorothiazide (diuretic) reduced the incidence of dementia by 55%, compared to placebo.[19 20] Monotherapy with the ARB, candesartan, in the Study on Cognition and Prognosis in the Elderly (SCOPE) also showed modest effects.[14] Not all studies have shown cognitive benefits with antihypertensive agents; some implicate them in the worsening of cognition.[21] The ONTARGET and TRANSCEND trials, two parallel studies involving more than 25 000 patients, found that ACE-Is did not have any measurable effects on cognition.[22] Although the evidence is limited, treatment with antihypertensives has been associated with reduced rates of cognitive[23 24] and functional decline[25] in those with established Alzheimer's disease (AD).

ACE-Is were one of the first antihypertensives to be studied, particularly in AD, the most prevalent form of dementia.[26] Patients with AD have abnormal cleavage of amyloid precursor protein resulting in a pathological accumulation of amyloid β (Aβ).[27] The relationship between ACE and the accumulation of Aβ is complex and different polymorphisms have been postulated to either increase,[28] or decrease,[29] the risk of developing AD. ACE activity is increased in AD, proportional to the Aβ load.[30] Centrally acting ACE-Is (CACE-Is) that cross the blood–brain barrier may have a greater impact than those that do not. The CACE-I perindopril, administered to mouse models, showed a significant protective effect[31] and reversed CI more than did the non-centrally acting imidapril and enalapril.[32] Patients receiving CACE-Is have a reduced rate of cognitive decline compared to both non-centrally acting ACE-Is and CCBs.[15] The Cardiovascular Health Study demonstrated no reduced risk in the incidence of dementia in those taking CACE-Is compared to other classes of antihypertensives.[33] Those prescribed CACE-Is had a reduced rate of cognitive decline and less impairment in instrumental activities of daily living compared to those taking non-centrally acting agents.[34] Prescription of ARBs and ACE-Is is also associated with reduced incidence of both vascular dementia and mixed dementia subtypes.[35 36]

Outside of clinical trials, there are few data on the effects of CACE-Is on the rate of cognitive decline in patients with dementia. Given this, and the growing evidence for antihypertensive agents, particularly CACE-Is, in reducing the incidence and rate of cognitive decline, we compared the rates of decline in patients taking CACE-Is (called CACE-I) with those not currently prescribed CACE-Is (called NoCACE-I), in those with established dementia, attending a memory clinic. We also examined whether patients started on CACE-Is while attending clinic (called NewCACE-I), behaved differently during their first 6 months of treatment, compared to the NoCACE-I group and those already established on CACE-Is.

METHODS

Data collection

Data were analysed from the Geriatric Assessment Tool (GAT) database, a customised software application that automates physicians' clinic assessments. Data were collected in memory clinics in two university hospitals in Ontario, Canada. The database contains over 8000 individual assessments from 1749 people aged 41–104 years. GAT data, collected between 1999 and 2010, includes age, gender, education, medical diagnosis, BP, laboratory findings, medications, etc and the scores of two cognitive screening tests, the Standardised Mini-Mental State Examination (SMMSE)[37 38] and the Quick Mild Cognitive Impairment (Qmci) screen,[39 40] a new cognitive screen, more sensitive and specific for differencing MCI from normal cognition and dementia than the SMMSE.[39] Both tests were administered to patients by trained raters (clinic nurses) blind to the diagnosis, prior to each assessment, to monitor progression.

The Qmci has six subtests covering five cognitive domains: orientation, working memory, semantic memory (verbal fluency for animals), visual spatial (clock drawing) and two tests of episodic memory (delayed recall and immediate recall logical memory). It is scored out of 100 points.

Subjects

Patients with dementia were diagnosed by a consultant geriatrician using NINCDS[41] and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.[42] Only patients with AD, vascular or mixed dementias (Alzheimer's/vascular) were included in this analysis. As there is little evidence that antihypertensive medications affect other dementia subtypes, patients with Parkinson's disease dementia,[43 44] frontotemporal dementia,[45] Lewy body dementia,[46] alcohol-related dementia, post-trauma and post-anaesthetic dementia were excluded. Patients with MCI, n=235, defined as those with subjective and corroborated memory loss, without obvious loss of function,[47] were

excluded. Patients with MCI were excluded because few, n=12, had baseline and end-point Qmci scores available. Although the SMMSE was available, it is insensitive to MCI,[39] and rates of cognitive decline vary, depending on the cognitive measures used.[48] Patients with normal cognition, n=181 and depression, n=397 were also excluded. Participants were screened for depression using the 15-point Geriatric Depression Scale.[49] As there is limited evidence that ACE-Is affect comorbid depression,[50] while depression negatively affects the results of cognitive testing,[51] 397 participants with depression were excluded: 260 with CI and comorbid depression and 137 with normal cognition and depression. Patients with depression were predominantly (63%) women and were significantly younger than patients without depression, mean age 72.7 (SD 10.7), p<0.001. Patients were also excluded if they did not have the results of either the Qmci or SMMSE available at both the baseline and end point. Changes between the baseline and end-point (last visit) scores were standardised at 6 months to facilitate comparison between all groups. In total, 56% (n=456) of patients with dementia did not have the same cognitive test recorded at two visits and were therefore excluded. Regression analysis, adjusting for baseline characteristics (age, gender, education and BP) between participants without follow-up and those included, showed no significant difference in baseline SMMSE (p=0.06) or Qmci scores (p=0.51). Patient selection is presented graphically in figure 1. The CACE-I group included patients currently prescribed the following CACE-Is: perindopril, ramipril, trandolapril, captopril, fosinopril, lisinopril, prinivil and monopril.[34 52]

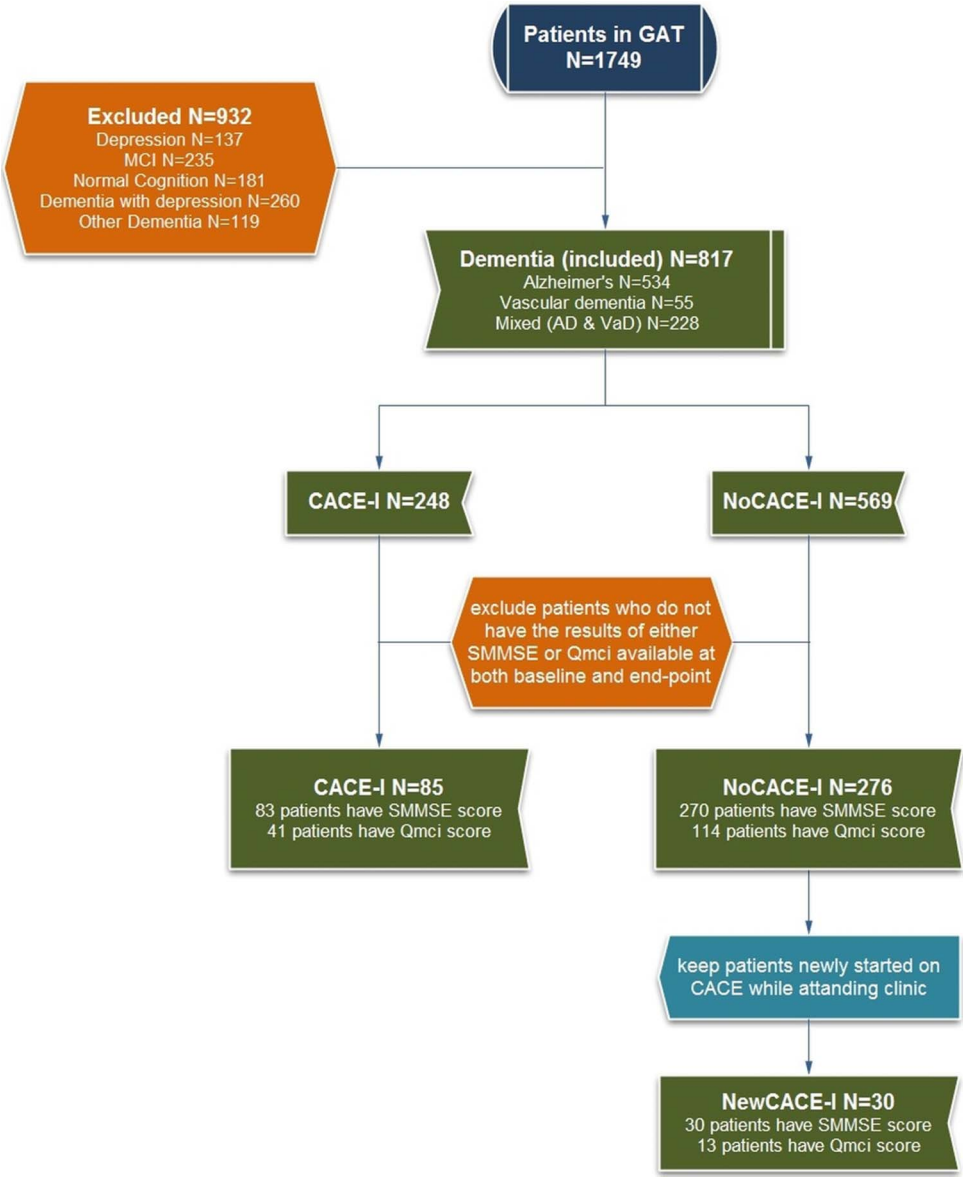


Figure 1 Flow chart demonstrating the breakdown of the patients included in the Geriatric Assessment Tool (GAT) database.

NoCACE-I included patients who were not currently receiving CACE-Is, irrespective of the BP readings, diagnosis of hypertension or whether they were receiving other antihypertensive medications.

Analysis

Our goal was to determine whether there were differences in rates of change, from the baseline to the end point (the time point when cognitive scores were last available), in Qmci and SMMSE scores between patients in the NoCACE-I, NoCACE-I and NewCACE-I groups while attending clinic. Given that regulatory authorities like the US Food and Drug Administration require evidence of change in cognitive tests over 6 months[41 53] to confirm benefit from new medications, we used change scores from the baseline, on a six-monthly basis, according to the formula:

$$\text{Rate of decline} = (\text{Baseline score} - \text{end - point score}) \times 6/\text{duration in months}$$

We also used multivariate regression to compare end-point cognitive scores (SMMSE and Qmci), adjusted for the baseline cognitive scores and characteristics (age, years of education, duration of follow-up and BP), between the three groups (CACE-I, NoCACE-I and NewCACE-I). Data were analysed using SPSS V.18.0. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality. Non-normally distributed data were compared with the Mann-Whitney U test. Categorical data were analysed with χ^2 tests.

RESULTS

Baseline characteristics

In total, there were 817 patients with dementia. Of these, 361 with SMMSE and Qmci scores recorded at two or more visits were included for analysis, 85 receiving CACE-Is and 276 receiving NoCACE-Is. The mean age of those included was 77.9 years with an SD of 8.1 years. Half (50.3%) were men and the mean time spent in education was 11.2 years. The mean age of patients taking CACE-Is was 77.2 years compared to 77 years for the NoCACE-Is group. Men represented 51.8% of the CACE-I group compared to 49.6% of the NoCACE-I group. Within the NoCACE-I group, 30 participants had been started on ACE-Is while attending clinic (NewCACE-I). Table 1 shows the baseline characteristics, including demographics and medication use, for the CACE-I, NoCACE-I or NewCACE-I groups.

Both SMMSE and Qmci scores were available for 147 participants at the baseline and end point, while 206 participants had SMMSE scores only and 8 had Qmci scores alone. For the participants included, the mean SMMSE scores at the baseline and end point were 21.6 (SD±5.6) and 18.1 (SD±8.0), respectively. Mean Qmci scores were 36.8 (SD±13.6) and 31.3 (SD±18.3), respectively. Table 2 presents the baseline and end-point Qmci and SMMSE scores for the CACE-I, NoCACE-I or NewCACE-I groups. After adjusting for the baseline characteristics (age, education, duration of follow-up and BP), there were no significant differences in the baseline cognitive scores (SMMSE and Qmci) between the three groups (CACE-I, NoCACE-I and NewCACE-I).

In relation to medications, 88.2% of the CACE-I group, 82.6% of the NoCACE-I group and 80% of those in the NewCACE-I group were receiving cholinesterase inhibitors (CholEIs). A smaller percentage was currently prescribed memantine. There was no difference in the distribution of CholEIs (p=0.40) or memantine (p=0.98) between the CACE-I, NoCACE-I and NewCACE-I groups.

Rate of decline

The median change in SMMSE scores between the baseline and end point for those included was 0.69 points per 6 months (IQR of 2). The median SMMSE score differences for the CACE-I, NoCACE-I and NewCACE-I groups were 0.8, 1.0 and −1.2, respectively, per 6 months. For the Qmci, the median change was 2 points per 6 months, with median Qmci score differences for the CACE-I and NoCACE-I groups of 1.8 and 2.1, respectively, per 6 months.

There was a small but non-significant difference in the SMMSE median rate of decline over 6 months for patients taking CACE-Is, compared to NoCACE-I patients, p=0.77. The difference in the median rates of

Table 1 Baseline characteristics of CACE-I, NoCACE-I or NewCACE-I patients

Groups	CACE-I	NoCACE-I	NewCACE-I
Number	85	276	30
Age (mean±SD)	77.2±6.4	77.0±7.6	77.3±8.2
Male (%)	44 (51.8)	137 (49.6)	15 (50)
Education (mean±SD)	10.6±3.8	11.4±4.0	12.1±3.9
Systolic BP in mm Hg (mean±SD)	133.4±21.2	135.5±16.9	141.1±16.2
Diastolic BP in mm Hg (mean±SD)	70.1±12.6	72.5±11.5	78.1±17.0
Cholinesterase inhibitor use (%)	75 (88.2)	228 (82.6)	24 (80)
Memantine use (%)	23 (27.1)	72 (26.1)	8 (26.7)

BP, blood pressure; CACE-I, patients currently receiving ACE inhibitors; NewCACE-I, patients who were newly started on CACE-Is; NoCACE-I, patients who are not currently prescribed CACE-Is.

Table 2 Baseline and end-point (last visit) SMMSE and Qmci scores

		N	Baseline age, mean (±SD)	Gender (male, %)	Duration of follow-up in months, median (Q3–Q1)	Baseline score, median (Q3–Q1)	End-point score, median (Q3–Q1)
SMMSE	CACE-I	83	77.3 (±6.6)	53	17 (34–7)	22 (25–19)	20 (25–14)
	NoCACE-I	270	77.1 (±7.6)	49.3	18 (31–9)	23 (26–19)	20 (25–13)
	NewCACE-I	30	77.3 (±8.2)	50	6 (7–4)	23 (27–18)	24 (27–19)
Qmci	CACE-I	41	78.9 (±6.1)	56.1	16 (31–7)	36 (44–23)	29 (49–15)
	NoCACE-I	114	78.0 (±7.6)	49.1	11 (24–6)	38 (47–27)	32 (45–17)

CACE-I, patients currently receiving ACE inhibitors; NewCACE-I, patients who were newly started on CACE-Is; NoCACE-I, patients who are not currently prescribed CACE-Is; Qmci, Quick Mild Cognitive Impairment; SMMSE, Standardised Mini-Mental State Examination.

decline in Qmci scores reached borderline significance, p=0.049. The median decline in scores (rate per 6 months) for the NewCACE-I group, on the SMMSE, was −1.2 points for the NewCACE-I group, significantly less than for the CACE-I group (median 0.8); p=0.003 and NoCACE-I group (median 1.0), p=0.001. The Qmci could not be compared for the NewCACE-I group, as the numbers were too small. These results are presented in table 3. Multivariate regression analysis was used to compare the end-point cognitive scores (SMMSE and Qmci), adjusting for baseline cognitive scores (SMMSE and Qmci) and patient characteristics (age, education, duration of follow-up and BP). There were significant differences in end-point scores for the SMMSE (p=0.002) between all three groups (CACE-I, NoCACE-I and NewCACE-I). No significant difference was seen, for the Qmci, comparing the CACE-I and NoCACE-I groups, (p=0.172).

CONCLUSION

This study demonstrates a small reduction in the rate of cognitive decline, measured with the SMMSE and Qmci, in patients taking CACE-Is compared to the NoCACE-I group. The changes in Qmci scores over 6 months were small but statistically significant. The SMMSE scores, while non-significant, suggested a possible slower progression among those currently receiving CACE-Is. NewCACE-I patients, started on CACE-Is while attending clinic, showed a median improvement rather than a decline in SMMSE scores, over the first 6 months of treatment, compared to those already taking CACE-Is and those not currently treated with CACE-Is. These results confirm an association between the use of CACE-Is, particularly during the first 6 months of treatment, and a reduced rate of cognitive decline. This is the first study to demonstrate that cognitive scores improve in patients starting on CACE-Is, compared to those already established on maintenance treatment. This may have been related to better medication compliance, the effects of improved BP control or increased cerebrovascular perfusion after initial treatment.[54 55]

The strength of the study lies in its large numbers and inclusion of different (AD, vascular and mixed) dementia subtypes. The study also investigates the effects of CACE-Is in an unselected clinic sample of older adults, whose mean age approached 80 years. It has a number of limitations. This study is an analysis of observational data collected in a 'real world' setting, where treatments, including antihypertensive agents, were administered on the basis of clinical judgement. Observational studies like this are subject to bias in that those who receive treatment may be systematically different from those

Table 3 Comparison of differences in Qmci and SMMSE scores between baseline and end point

	Groups	Mann-Whitney U test (p Values)
Changes in Qmci	CACE-I (53) vs NoCACE-I (102) median = 1.8* vs median = 2.1*	0.049
Changes in SMMSE	CACE-I (113) vs NoCACE-I (240) median = 0.8* vs median = 1.0*	0.77
	NewCACE-I (30) vs NoCACE-I (240) median = −1.2* vs median = 1.0*	0.001
	NewCACE-I (30) vs CACE-I† (83) median = −1.2* vs median = 0.8*	0.003

*Median score shows the change in six months for CACE-I, NoCACE-I and NewCACE-I
†CACE-I group excluding NewCACE-I patients.
CACE-I, patients currently receiving ACE inhibitors; NewCACE-I, patients who were newly started on CACE-Is; NoCACE-I, patients who are not currently prescribed CACE-Is; Qmci, Quick Mild Cognitive Impairment; SMMSE, Standardised Mini-Mental State Examination.

who do not. That said, the baseline demographic characteristics of the groups were similar and few participants, in the NewCACE-I group, received other medications that could have accounted for the differences observed. Compliance with antihypertensive treatment, which has been shown to reduce with time,[56 57] could also have been a confounding factor and may have accounted for the improvement in the NewCACE-I group. Similarly, duration of treatment with antihypertensive medications, prior to attending clinic, could not be established for the CACE-I and NoCACE-I groups in this retrospective analysis.

Although most patients in the database had a Qmci or SMMSE recorded, large numbers lacked results at the baseline or end point, limiting the numbers that could be included in the analysis. It is possible that the results would have differed with more complete data on all patients. However, the baseline cognitive scores were similar between those included and excluded because of missing data. In the comparison of the subgroup scores, change over the first 6 months of treatment was analysed as this is the accepted time scale to show evidence of benefit in clinical drug trials.[53] Although a small percentage (9%) had a shorter interval between the baseline and end-point scores, the duration of follow-up was standardised at 6 months to facilitate comparison. The accepted standard for measuring cognitive change is the ADAS-cog.[58] As this was an observational study in a clinic setting, only the Qmci and the commonly used SMMSE were available. The ADAS-cog is not an ideal test[59] and the Qmci has been shown to be as sensitive to change as its standardised version, the SADAS-cog.[60] Significant differences, between NewCACE-I and the other groups' scores, using the SMMSE, could not be replicated with the Qmci, as the numbers were too small to analyse.

In summary, this study demonstrates an association between the use of CACE-Is and reduced rates of cognitive decline, in an unselected sample of clinic patients with dementia, particularly in the first 6 months of treatment. This supports the growing body of evidence for the use of ACE-Is and other antihypertensive agents in the management of dementia.[18] Although the differences were small and of uncertain clinical significance, if sustained over years, the compounding effects may well have significant clinical benefits. However, this may be tempered by recent evidence suggesting that ACE-Is, by interfering with degradation of Aβ, could contribute to increased amyloid burden,[61–63] potentially accelerating dementia severity and rates of cognitive decline.[34] Indeed, ACE-Is may even increase mortality in patients with CI, suggesting that if ACE-Is are proven to be beneficial in dementia, not all patients will benefit.[64] Further study with an appropriately powered randomised trial is needed to confirm these findings and determine if and for how long these effects are sustained.[65] If these data can be reproduced in a randomised trial of sufficient length incorporating appropriate outcome measures, such as an amyloid positron emission tomography, then these agents are likely to have significant benefits in delaying or even preventing dementia.

Author affiliations
[1]Centre for Gerontology and Rehabilitation, University College Cork, St Finbarrs' Hospital, Cork City, Ireland
[2]Department of Business Information Systems, University College Cork, Cork, Ireland
[3]Department of Pharmacology and Therapeutics, University College Cork, Cork, Ireland
[4]Mercy University Hospital, Cork, Ireland
[5]Clinical Research Facility, Mercy University Hospital, Cork, Ireland
[6]Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada
[7]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Contributors YG performed the data processing, statistical analysis and cowrote the paper with ROC. ROC also assisted with the submission of the manuscript. LH was responsible for performing the literature search and writing the introduction. DMK advised on the pharmacology of ACE inhibitors and contributed to writing the manuscript. JE and GG were involved in the data analysis plan, oversight of statistical analysis and preparation of the manuscript. DS gave input in statistical analysis and was the joint supervisor of YG. DWM contributed to collection of patient data, gave input in the preparation of the manuscript, and was the joint supervisor of YG and ROC. All authors have read and approved the final version of the manuscript.

Funding The Centre for Gerontology and Rehabilitation is funded by Atlantic Philanthropies, the Health Services Executive Ireland, the Irish Hospice Foundation and the Canadian Institutes of Health Research.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Ferri CP, Prince M, Brayne C, *et al*. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;366:2112–17.
2. Sloane PD, Zimmerman S, Suchindran C, *et al*. The public health impact of Alzheimer's disease, 2000–2050: potential implication of treatment advances. *Annu Rev Public Health* 2002;23:213–31.
3. Whitmer R, Sidney S, Selby J, *et al*. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005;64:277–81.
4. Breteler MMB, Claus JJ, Grobbee DE, *et al*. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam study. *BMJ* 1994;308:1604–8.
5. Rozzini L, Vicini Chilovi B, Trabucchi M, *et al*. Antihypertensive medications influence the rate of conversion from mild cognitive impairment to Alzheimer disease. *Arch Neurol* 2008;65:993.
6. Duron E, Rigaud AS, Dubail D, *et al*. Effects of antihypertensive therapy on cognitive decline in Alzheimer's disease. *Am J Hypertens* 2009;22:1020–4.
7. Ligthart SA, Van Charante EPM, Van Gool WA, *et al*. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. *Vasc Health Risk Manag* 2010;6:775.
8. Collaborative P, Neal B, MacMahon S. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003;163:1069–75.
9. Oveisgharan S, Hachinski V. Hypertension, executive dysfunction, and progression to dementia: the Canadian Study of Health and Aging. *Arch Neurol* 2010;67:187.
10. Tollefson GD. Short-term effects of the calcium channel blocker nimodipine (Bay-e-9736) in the management of primary degenerative dementia. *Biol Psychiatry* 1990;27:1133–42.
11. Kennelly S, Abdullah L, Kenny RA, *et al*. Apolipoprotein E genotype-specific short-term cognitive benefits of treatment with the antihypertensive nilvadipine in Alzheimer's patients—an open-label trial. *Int J Geriatr Psychiatry* 2012;27:415–22.

12. Hajjar I, Brown L, Mack WJ, *et al*. Impact of angiotensin receptor blockers on Alzheimer disease neuropathology in a large brain autopsy series. *Arch Neurol* 2012;69:1632–8.
13. Li NC, Lee A, Whitmer RA, *et al*. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ* 2010;340:65465.
14. Lithell H, Hansson L, Skoog I, *et al*. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21:875–86.
15. Ohrui T, Tomita N, Sato-Nakagawa T, *et al*. Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression. *Neurology* 2004;63:1324–5.
16. Rozzini L, Chilovi BV, Bertoletti E, *et al*. Angiotensin converting enzyme (ACE) inhibitors modulate the rate of progression of amnestic mild cognitive impairment. *Int J Geriatr Psychiatry* 2006;21:550–5.
17. Hajjar I, Hart M, Milberg W, *et al*. The rationale and design of the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial in elderly hypertensives with early cognitive impairment: role of the renin angiotensin system inhibition. *BMC Geriatr* 2009;9:48.
18. Poon IO. Effects of antihypertensive drug treatment on the risk of dementia and cognitive impairment. *Pharmacotherapy* 2008;28:366–75.
19. Staessen JA, Fagard R, Thijs L, *et al*. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350:757–64.
20. Forette F, Seux ML, Staessen JA, *et al*. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2002;162:2046.
21. Maxwell CJ, Hogan DB, Ebly EM. Calcium-channel blockers and cognitive function in elderly people: results from the Canadian Study of Health and Aging. *CMAJ* 1999;161:501–6.
22. Teo K, Yusuf S, Sleight P, *et al*. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J* 2004;148:52.
23. Mielke M, Rosenberg P, Tschanz J, *et al*. Vascular factors predict rate of progression in Alzheimer disease. *Neurology* 2007;69:1850–8.
24. Bellew KM, Pigeon JG, Stang PE, *et al*. Hypertension and the rate of cognitive decline in patients with dementia of the Alzheimer type. *Alzheimer Dis Assoc Disord* 2004;18:208–13.
25. Rosenberg P, Mielke M, Tschanz J, *et al*. Effects of cardiovascular medications on rate of functional decline in Alzheimer disease. *Am J Geriatr Psychiatry* 2008;16:883.
26. Brunnström H, Gustafson L, Passant U, *et al*. Prevalence of dementia subtypes: a 30-year retrospective survey of neuropathological reports. *Arch Gerontol Geriatr* 2009;49:146–9.
27. Hardy J. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. *J Neurochem* 2009;110:1129–34.
28. Kehoe PG, Russ C, McIlory S, *et al*. Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. *Nat Genet* 1999;21:71.
29. Lehmann DJ, Cortina-Borja M, Warden DR, *et al*. Large meta-analysis establishes the ACE insertion-deletion polymorphism as a marker of Alzheimer's disease. *Am J Epidemiol* 2005;162:305–17.
30. Miners J, Ashby E, Van Helmond Z, *et al*. Angiotensin-converting enzyme (ACE) levels and activity in Alzheimer's disease, and relationship of perivascular ACE-1 to cerebral amyloid angiopathy. *Neuropathol Appl Neurobiol* 2007;34:181–93.
31. Dong YF, Kataoka K, Tokutomi Y, *et al*. Perindopril, a centrally active angiotensin-converting enzyme inhibitor, prevents cognitive impairment in mouse models of Alzheimer's disease. *FASEB J* 2011;25:2911–20.
32. Yamada K, Uchida S, Takahashi S, *et al*. Effect of a centrally active angiotensin-converting enzyme inhibitor, perindopril, on cognitive performance in a mouse model of Alzheimer's disease. *Brain Res* 2010;1352:176–86.
33. Fried LP, Borhani NO, Enright P, *et al*. The cardiovascular health study: design and rationale. *Ann Epidemiol* 1991;1:263–76.
34. Sink KM, Leng X, Williamson J, *et al*. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med* 2009;169:1195.
35. Hanes DS, Weir MR. Usefulness of ARBs and ACE inhibitors in the prevention of vascular dementia in the elderly. *Am J Geriatr Cardiol* 2007;16:175–82.
36. Davies NM, Kehoe PG, Ben-Shlomo Y, *et al*. Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *J Alzheimers Dis* 2011;26:699–708.
37. Molloy DW, Alemayehu E, Roberts R. Reliability of a standardized mini-mental state examination compared with the traditional mini-mental state examination. *Am J Psychiatry* 1991;148:102–5.
38. Molloy DW, Standish TIM. A guide to the standardized Mini-Mental State Examination. *Int Psychogeriatr* 1997;9:87–94.
39. O'Caoimh R, Gao Y, McGlade C, *et al*. Comparison of the quick mild cognitive impairment (Qmci) screen and the SMMSE in screening for mild cognitive impairment. *Age Ageing* 2012;41:624–9.
40. O'Caoimh R, Gao Y, Gallagher PF, *et al*. Which part of the quick mild cognitive impairment screen (Qmci) discriminates between normal cognition, mild cognitive impairment and dementia? *Age Ageing* 2013;42:324–30.
41. McKhann G, Drachman D, Folstein M, *et al*. Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–44.
42. First MB. *Diagnostic and statistical manual of mental disorders*. DSM IV-4th edn APA 1994:97–327.
43. Louis ED, Benito-León J, Bermejo-Pareja F. Antihypertensive agents and risk of Parkinson's disease, essential tremor and dementia: a population-based prospective study (NEDICES). *Neuroepidemiology* 2009;33:286–92.
44. Simon KC, Chen H, Schwarzschild M, *et al*. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology* 2007;69:1688–95.
45. Rosso S, Landweer E, Houterman M, *et al*. Medical and environmental risk factors for sporadic frontotemporal dementia: a retrospective case–control study. *J Neurol Neurosurg Psychiatry* 2003;74:1574–6.
46. Londos E, Passant U, Gustafson L. Blood pressure and drug treatment in clinically diagnosed Lewy body dementia and Alzheimer's disease. *Arch Gerontol Geriatr* 2000;30:35–46.
47. Portet F, Ousset P, Visser P, *et al*. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2006;77:714–18.
48. Monsell SE, Liu D, Weintraub S, *et al*. Comparing measures of decline to dementia in amnestic MCI subjects in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set. *Int Psychogeriatr* 2012;24:1553.
49. Yesavage J. Geriatric Depression Scale. *Psychopharmacol Bull* 1988;24:709.
50. Rogers D, Pies R. General medical drugs associated with depression. *Psychiatry (Edgmont)* 2008;5:28.
51. Porter RJ, Gallagher P, Thompson JM, *et al*. Neurocognitive impairment in drug-free patients with major depressive disorder. *Br J Psychiatry* 2003;182:214–20.
52. Solfrizzi V, Scafato E, Frisardi V, *et al*. Angiotensin-converting enzyme inhibitors and incidence of mild cognitive impairment. The Italian Longitudinal Study on Aging. *Age (Dordr)* 2013(2):441–53.
53. Matthews HP, Korbey J, Wilkinson DG, *et al*. Donepezil in Alzheimer's disease: eighteen month results from Southampton Memory Clinic. *Int J Geriatr Psychiatry* 2000;15:713–20.
54. Hatazawa J, Shimosegawa E, Osaki Y, *et al*. Long-term angiotensin-converting enzyme inhibitor perindopril therapy improves cerebral perfusion reserve in patients with previous minor stroke. *Stroke* 2004;35:2117–22.
55. Lipsitz LA, Gagnon M, Vyas M, *et al*. Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertension* 2005;45:216–21.
56. Chapman RH, Benner JS, Petrilla AA, *et al*. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* 2005;165:1147.
57. Conlin PR, Gerth WC, Fox J, *et al*. Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. *Clin Ther* 2001;23:1999–2010.
58. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984.

59. Connor DJ, Sabbagh MN. Administration and scoring variance on the ADAS-Cog. *J Alzheimers Dis* 2008;15:461–4.
60. O'Caoimh R, Svendrovski A, Johnston B, *et al*. Comparison of the *Qmci* to the SADAS-Cog. *J Clin Epidemiol* 2013. In press.
61. Hu J, Igarashi A, Kamata M, *et al*. Angiotensin-converting enzyme degrades Alzheimer amyloid β-peptide (Aβ); retards Aβ aggregation, deposition, fibril formation; and inhibits cytotoxicity. *J Biol Chem* 2001;276:47863–8.
62. Kehoe PG, Passmore PA. The renin-angiotensin system and antihypertensive drugs in Alzheimer's disease: current standing of the angiotensin hypothesis? *J Alzheimers Dis* 2012;30:S251–68.
63. Fournier A, Oprisiu-Fournier R, Serot J-M, *et al*. Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. *Expert Rev Neurother* 2009;9:1413–31.
64. Kehoe PG, Davies NM, Martin RM, *et al*. Associations of angiotensin targeting antihypertensive drugs with mortality and hospitalization in primary care patients with dementia. *J Alzheimers Dis* 2013;33:999–1008.
65. Todd S, McGuinness B, Passmore AP. Designing appropriate clinical trials to assess ACEI use and cognitive decline in older adults with hypertension. *Arch Intern Med* 2010;170:107.

Journal of Alzheimer's Disease 40 (2014) 595–603
DOI 10.3233/JAD-131694
IOS Press

Effects of Centrally Acting Angiotensin Converting Enzyme Inhibitors on Functional Decline in Patients with Alzheimer's Disease

Rónán O'Caoimh[a,*], Liam Healy[a], Yang Gao[a], Anton Svendrovski[b], David M. Kerins[c,d], Joseph Eustace[e], Patrick Gavin Kehoe[f], Gordon Guyatt[b] and D. William Molloy[a]
[a]*Centre for Gerontology and Rehabilitation, University College Cork, St Finbarrs Hospital, Cork, Ireland*
[b]*Department of Clinical Epidemiology & Biostatistics, McMaster University, ON, Canada*
[c]*Department of Pharmacology and Therapeutics, University College Cork, Cork, Ireland*
[d]*Mercy University Hospital, Cork, Ireland*
[e]*Clinical Research Facility, Mercy University Hospital, Cork, Ireland*
[f]*Dementia Research Group, School of Clinical Sciences, University of Bristol, Frenchay Hospital, Bristol, UK*

Accepted 10 December 2013

Abstract.
Background: Centrally acting angiotensin converting enzyme inhibitors (CACE-Is) are associated with reduced rates of cognitive decline in patients with dementia. CACE-Is may also improve exercise tolerance in functionally impaired older adults with normal cognition, suggesting that CACE-Is may positively influence activities of daily living (ADL) in dementia.
Objective: To compare rates of decline in patients with mild to moderate Alzheimer's disease (AD) receiving CACE-Is to those not currently treated with CACE-Is (NoCACE-I), included in the Doxycycline and Rifampicin for Alzheimer's Disease study ($n = 406$).
Methods: Patients were included if baseline and end-point (twelve months apart) scores were available for measures including the Standardized Alzheimer's Disease Assessment Scale – Cognitive Subscale; Quick Mild Cognitive Impairment screen; Clinical Dementia Rating Scale (CDR-SB), and Lawton-Brody ADL Scale.
Results: There was a significant, 25% difference (median one-point) in the 12-month rate of decline in ADL scores in patients taking CACE-Is ($n = 91$), compared to the NoCACE-I group ($n = 274$), $p = 0.024$. This remained significant after adjusting for age, gender, education, and blood pressure, $p = 0.034$. When individual CACE-Is were compared to the NoCACE-I group, a significant reduction in the rate of decline in ADLs (median one versus four points), were only observed for perindopril, $p = 0.01$. The CDR-SB was also reduced (median one-point) for the perindopril compared to the NoCACE-I group, $p = 0.04$.
Conclusion: This observational study suggests that CACE-Is, and potentially perindopril in particular, are associated with a reduced rate of functional decline in patients with AD, without an association with mood or behavior. This suggests that CACE-Is may slow disease progression in AD.

Keywords: ACE inhibitors, Alzheimer's disease, cognitive, dementia, function, psychological decline

INTRODUCTION

Although higher midlife blood pressure (BP) is associated with increased risk of dementia [1], it is not a simple association [2]. Authors have suggested that a variety of anti-hypertensives improve cognition in

*Correspondence to: Rónán O'Caoimh, Centre for Gerontology and Rehabilitation, University College Cork, St Finbarrs Hospital, Douglas Road, Cork City, Ireland. Tel.: +353 86 3241795; Fax: +353 21 492309; E-mail: rocaoimh@hotmail.com.

ISSN 1387-2877/14/$27.50 © 2014 – IOS Press and the authors. All rights reserved
This article is published online with Open Access and distributed under the terms of the Creative Commons Attribution Non-Commercial License.

older adults with elevated BP [3, 4] and have potential as therapeutic agents in dementia [5–11]. Results are however, inconsistent [12–14] with some observational studies even suggesting harm [15, 16].

Dementia and angiotensin converting enzyme

Angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) may lower dementia risk or slow progression independent of their BP lowering properties [9, 10, 17, 18]. Centrally acting ACE-Is (CACE-Is), which cross the blood-brain barrier, are associated in observational studies with a reduced incidence of mild cognitive impairment (MCI) [19, 20] and dementia [14], and slower rates of cognitive decline in Alzheimer's disease (AD), relative to non-centrally acting ACE-Is [21, 22]. In patients with AD, CACE-Is may modulate the pathological accumulation of amyloid-β (Aβ), a key neuropathological hallmark of AD [23]. ACE gene polymorphisms are associated with increased risk of AD [24, 25]: alleles putatively associated with AD are also associated with low levels of plasma ACE [26, 27]. Pre-clinical studies suggest that ACE degrades Aβ [28–30], and marked increases in ACE activity have been reported in the frontal cortex of patients with AD [31–33]. More recently, lack of evidence from large scale genetic studies [5, 16] has diminished interest in ACE [24] while interest in Angiotensin II, the potent vasoconstrictor formed by ACE action in AD pathology, has increased [35, 36].

Centrally-acting ACE–Is and cognition

The strongest pre-clinical evidence to date for the utility of ACE-Is in affecting cognitive decline is for the CACE-I perindopril. Perindopril reversed Aβ-induced cognitive impairment [37], inhibited brain ACE activity, elevating extracellular acetylcholine levels in mice [38], while two non-centrally acting ACE-Is did not. Perindopril, but not other ACE-Is, significantly inhibited hippocampal ACE and prevented cognitive impairment in mouse models of AD [39, 40, 41]. Clinically, the Cardiovascular Health Study reported observational data that perindopril, rather than non-centrally acting ACE-Is or calcium channel blockers, decreased the rate of decline in patients with mild to moderate AD [14]. Results, however, are inconsistent. Secondary analysis of randomized trials have failed to detect an effect of ACE-Is [42] or ARBs on cognition [12, 43]. Furthermore, a small placebo controlled clinical trial in non-demented offspring of AD patients showed no effect on cognition [44].

Effects of CACE-Is on ADLs and the behavioral and psychological symptoms of dementia (BPSD)

Observational studies suggest that beta-blockers are associated with reduced rates of functional decline in patients with established AD [45]. Although, there is no association for ACE-Is [14, 45], they are associated with increased exercise tolerance, muscle strength [46], and lower falls risk [46, 47], suggesting effects independent of their BP lowering properties. Furthermore, the discontinuation of ACE-Is in those with AD is associated with increased rates of functional decline [48]. Studies investigating ACE genotypes in functional decline suggest both increased [49] and decreased disability [50]. There is also evidence that ACE-Is modulate mood, including anxiety [51] and depression in hypertensive patients with normal cognition [52]. Again, evidence is inconsistent [53, 54].

Objective

The aim of this paper was to compare rates of cognitive, functional, and neuropsychological decline in patients with AD receiving CACE-Is (called CACE-Is) to those not currently treated with CACE-Is (NoCACE-I) by conducting a secondary analysis of data from a randomized control trial.

METHODS

Data collection

We performed a secondary analysis of data from the Doxycycline and Rifampin for Alzheimer's Disease (DARAD) trial [55], a multi-center, blinded, randomized 2 × 2 factorial controlled trial, conducted between 2006 and 2010, comparing two antibiotics (doxycycline and rifampicin) to placebo, to investigate if these can delay progression of AD [55]. The co-primary outcomes were the Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale (SADAS-cog) [56] and the Clinical Dementia Rating scale-Sum of the Boxes (CDR-SB) [57]. Secondary outcomes included the Standardized Mini-Mental State Examination (SMMSE) [58, 59], Quick Mild Cognitive Impairment screen (Q*mci*) [60–62], the Geriatric Depression Scale (GDS) [63], Cornell Scale for Depression in Dementia (CSDD) [64], Lawton-Brody ADL Scale [65], and the Dysfunctional Behaviour Rating Instrument (DBRI),

frequency (DBRIF) and reaction (DBRIR), subscales [66, 67]. The SADAS-cog, CDR-SB, Q*mci*, Lawton-Brody ADL Scale, and DBRI were available at one, three, six, nine, and twelve months (end-point). The SMMSE was recorded at screening and end-point, the GDS at baseline and end-point and the CSDD at baseline, six-months and end-point only.

The SADAS-cog is a standardized version of the ADAS-cog [68], the existing, accepted standard for measuring cognitive function in clinical trials [69]. Consisting of 11 domains (including word recall, object naming, command following, construction, orientation, word recognition, language, speech comprehension, word finding and recall), the SADAS-cog improved inter-rater reliability using explicit administration and scoring guidelines. Scored from 0–70, scores $\geq$13 indicate increasing cognitive impairment [56]. The CDR-SB, a measure of global function, is scored from 0–18 with a score of 0 indicating no impairment, 0.5–4.0 possible impairment, and 4.5–9.0, 9.5–15.5, and 16.0–18.0 suggesting mild, moderate, and severe impairment, respectively [57]. The Q*mci* screen is a short (3–5 min), cognitive screening instrument composed of six subtests, covering five domains: orientation, registration, clock drawing, delayed recall, verbal fluency (naming animals) and logical memory (immediate verbal recall of a short story), scored out of 100 points. It has superior accuracy for detecting MCI compared to the SMMSE [60] and similar accuracy as the Montreal Cognitive Assessment (O'Caoimh 2013 unpublished work). The Lawton-Brody ADL Scale, combining both basic (Physical Self-Maintenance Scale) and instrumental ADLs, covering 14 categories, is scored out of 64 points, with higher scores suggesting greater independence [65]. The GDS short-form is scored from 0–15 with a score $\geq$5 suggesting depression [63, 70]. The CSDD is a 19-item scale, range of 0–39: normal <6, probable depression 10–17, definite depression $\geq$18. The DBRI, completed by caregivers, scores the frequency of (from 'never' to 'greater than five times per day') and reaction to (impact from 'no problem' to 'great deal of a problem') 25 behaviors [66].

Participants

In total, 406 patients with mild to moderate AD (SMMSE scores between 14 and 26) were included from 14 geriatric outpatient clinics in Canada [55]. All patients were aged 50 years or more and met the National Institute of Neurological Disorders and Stroke (NINCDS) criteria for AD [71]. In this study, patients were subdivided into a CACE-I group, including patients currently prescribed centrally acting ACE-Is: ramipril (n = 57), perindopril (n = 21), lisinopril (n = 9), trandolapril (n = 3), and fosinopril (n = 1) [14, 19], and a NoCACE-I group not currently receiving CACE-Is, irrespective of BP readings, diagnosis of hypertension, or receipt of other anti-hypertensives.

Analysis

The average 12-month rate of change in outcomes, measured as the difference between baseline and 12-month scores, were compared between patients receiving CACE-Is and the NoCACE-I group. For the Q*mci*, CSDD, GDS, and Lawton-Brody ADL Scale, change was calculated as the baseline minus the 12-month score. The SADAS-cog, CDR-SB, DBRIF, and DBRIR scales were calculated as the score at month 12 minus the baseline. In this way, irrespective of the scoring instructions, positive change denoted improvement. The SMMSE, used as an inclusion criterion, was not used in the analysis. Data were analyzed using SPSS 20.0. Non-normally distributed numerical data were compared using the independent samples median test, while chi-square tests were used for categorical data. Multivariate regression analysis was used to compare baseline measurement scores, adjusted for baseline characteristics; age, years of education, and BP (systolic and diastolic), between the CACE-I and NoCACE-I groups and CACE-I subgroups: perindopril and other CACE-Is. Multivariate regression was also used to compare the rate of decline, in each measure, between the subgroups.

RESULTS

Baseline demographics

Co-primary outcome measures were available for 365 patients at 12 months; for most, secondary outcomes were also available. The remaining 41 patients were lost to follow-up because of death (n = 13), refusal (n = 14), adverse events (n = 6), withdrawal from the trial (n = 5), and other reasons (moved, caregiver death, n = 3). Table 1 presents patients' baseline characteristics. Of the 365 patients included, 91 were taking CACE-Is during the course of the trial: 21 receiving perindopril and 70 other CACE-Is (Figure 1). Although no difference in baseline outcome measure scores were present between the CACE-I and NoCACE-I groups, when the CACE-I subgroups (perindopril and other CACE-Is) were compared to the NoCACE-I group,

Table 1
Differences in baseline demographic characteristics and outcome measures of patients receiving centrally acting ACE inhibitors (CACE-I) to those not currently treated with CACE-Is (NoCACE-I)

	CACE ($n=91$) Median (IQR)	NoCACE ($n=274$) Median (IQR)	Perindopril ($n=21$) Median (IQR)	Other CACE-Is ($n=70$) Median (IQR)	p-value[1]	p-value[2]
Age	79 (8)	78 (10)	78 (9)	79 (10)	0.90	0.72
Gender (male %)	45.1%	51.1%	23.8%	51.4%	0.46	0.05
Education (years)	12 (4)	12 (5)	12 (5)	12 (3.5)	0.06	0.15
Blood pressure systolic	138 (19)	134 (22.5)	140 (19)	135.5 (17.25)	0.41	0.45
Blood pressure diastolic	70 (14)	72 (14)	70 (11)	70 (12.5)	0.41	0.66
Cholinesterase inhibitor use (%)	89.0%	92.3%	76.2%	92.9%	0.32	0.03
Memantine use (%)	15.4%	15.3%	14.2%	15.7%	0.64	0.99
SMMSE	23 (4.5)	22.5 (5)	24 (2)	23 (5)	0.14	0.22
Q*mci*	39.5 (18)	39 (19)	40 (12)	39 (20)	0.74	0.90
SADAS-cog	18 (12)	21 (11)	16 (9)	19 (12)	0.05	0.04
Lawton-Brody ADL	51 (10)	52 (10)	52 (9)	51 (11)	0.34	0.57
CDR-SB	5 (4)	5 (4)	4.5 (4)	6 (4)	0.74	0.23
CSDD	3 (5)	3 (4)	4 (8)	3 (5)	0.09	0.23
GDS	1 (2)	1 (3)	2 (2)	1 (2)	0.74	0.82
DBRIF	4 (13)	5 (10)	3 (11)	4 (13)	0.61	0.88
DBRIR	11 (12)	13 (11)	12 (16)	11 (12)	0.45	0.75

[1]p-values are provided for independent samples median test (numerical data) or Chi-square test (categorical data) for comparison between CACE-I and NoCACE-I groups; [2]p-values are provided for independent samples median test (numerical data) or Chi-square test (categorical data) for comparison between perindopril, other CACE-Is and NoCACE-I groups; ADL, activities of daily living; CDR-SB, Clinical Dementia Rating scale-Sum of the Boxes; CSDD, Cornell Scale for Depression in Dementia; DBRIF, Dysfunctional Behaviour Rating Instrument-frequency; DBRIR, Dysfunctional Behaviour Rating Instrument-reaction; GDS, Geriatric Depression Scale; IQR, interquartile range; *Qmci*, Quick Mild Cognitive Impairment screen; SADAS-cog, Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale; SMMSE, Standardized Mini-Mental State Examination.

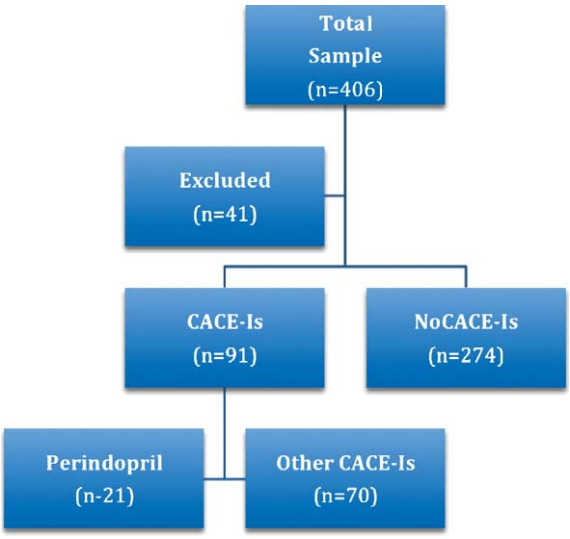


Fig. 1. Flow diagram demonstrating the breakdown of the patients included from the Doxycycline and Rifampin for Alzheimer's Disease (DARAD) trial database receiving centrally acting ACE inhibitors (CACE-Is: perindopril and others) and those not currently treated with CACE-Is (NoCACE-I).

there was a marginal statistically significant difference in baseline characteristics for gender ($p=0.05$), cholinesterase inhibitor use ($p=0.03$), and SADAS-cog scores ($p=0.04$) (Table 2).

Table 2
Comparison of the rate of decline, from baseline to one year, between patients receiving centrally acting ACE inhibitors (CACE-I) and those not currently treated with CACE-Is (NoCACE-I)

Variable	CACE-I Median (IQR)	NoCACE-I Median (IQR)	p-value[1]	p-value[2]
Blood pressure systolic	0 (30)	1.5 (24)	0.38	0.69*
Blood pressure diastolic	0 (20)	0 (18)	0.69	0.71*
SADAS-cog	2 (9)	4 (8)	0.41	0.86
CDR-SB	2 (4)	1.5 (3.5)	0.83	0.84
Q*mci*	4 (12)	5 (13)	0.15	0.49
Lawton-Brody (ADL)	3 (6)	4 (7)	0.024	0.034
CSDD	0 (3)	1 (4)	0.13	0.001
GDS	0 (2)	0 (2)	0.95	0.94
DBRIF	0 (9)	0 (8)	0.50	0.24
DBRIR	4 (13)	2 (11)	0.50	0.44

[1]p-values are provided for unadjusted comparisons between CACE-I and NoCACE-I groups; [2]p-values are provided for multivariate regression (adjusted for age, gender, education, and blood pressure) for comparison between the CACE-I and NoCACE-I groups; *Adjusted for age, gender, and education; ADL, activities of daily living; CDR-SB, Clinical Dementia Rating scale-Sum of the Boxes; CSDD, Cornell Scale for Depression in Dementia; DBRIF, Dysfunctional Behaviour Rating Instrument-frequency; DBRIR, Dysfunctional Behaviour Rating Instrument-reaction; GDS, Geriatric Depression Scale; IQR, interquartile range; *Qmci*, Quick Mild Cognitive Impairment screen; SADAS-cog, Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale.

Rate of decline

Patients receiving CACE-Is had a median decline of three points (IQR six) in ADL scores between baseline and 12 months, in comparison to a decline of four points (IQR seven) in the NoCACE-I group ($p = 0.024$). No statistically significant differences in decline were evident for the other outcome measures in the unadjusted analysis. However, patients taking CACE-Is demonstrated a median decline in Q*mci* screen scores of four (IQR 12) versus five (IQR 13) points in the NoCACE-I group ($p = 0.15$). The deterioration in CDR-SB and CSDD scores was also less marked in the CACE-I group relative to the NoCACE-I group, although again differences were not statistically significant (Table 2). Adjusting for age, education, gender, and BP confirmed a significant difference in ADL scores ($p = 0.034$). The adjusted analysis also showed a significant one point difference in the rate of decline between groups in the CSDD scores ($p = 0.001$, Table 2): 57% ($n = 52$) of CACE-I improved or remained the same, compared to 47% ($n = 128$) in the NoCACE-I group.

When individual CACE-Is were compared to the NoCACE-I group, a significant median reduction in the rate of decline in ADLs, one point compared to four points, was observed for those receiving perindopril ($p = 0.01$). The CDR-SB was also reduced by a median of one point ($p = 0.04$) for the perindopril compared to the NoCACE-I group. Median decline in CDR-SB scores was 0.5 (IQR 3) in patients receiving perindopril versus 2.5 (IQR 4) in those receiving other CACE-Is ($p = 0.05$). Patients receiving other CACE-Is showed a median decline in ADL scores of three points (IQR seven), compared to one point (IQR six) for perindopril ($p = 0.09$). Patients reported few adverse events that could possibly be related to ACE-I treatment. Of those taking CACE-Is, six noted a fall, while none reported cough or orthostatic symptoms.

DISCUSSION

This study found a small (25%, three versus four points) reduction in the rate of decline in ADL scores, measured with the Lawton-Brody ADL Scale, over a 12-month period, in patients taking CACE-Is compared to those not currently receiving CACE-Is. Other outcomes measures were also associated with a decreased progression for the CACE-I compared to the NoCACE-I group, although only changes in ADL and CSSD scores were statistically significant. In particular, the Q*mci* screen scores declined 20% less (four versus five points respectively), for the CACE-I group over one year, not inconsistent with other studies demonstrating a slower rate of cognitive decline in persons with dementia receiving CACE-Is [21, 22, 72].

Investigators have not previously reported a reduced rate of decline in ADLs in patients with established dementia receiving CACE-Is, although the effect has been shown with beta-blockers [45]. Since we found no significant changes in BP over the 12-month follow-up period, these benefits are likely to be independent of an anti-hypertensive effect. There are a number of possible mechanisms by which CACE-Is could impact upon ADLs. Perindopril improves exercise tolerance in older adults with normal cognition, with [73] and without heart failure [46]. This might be explained by the reported ability of ACE-Is to reduce inflammation and to improve endothelial function, increasing muscle blood flow and glucose delivery [74] to both skeletal and cardiac muscle, thereby improving exercise tolerance and capacity. Previous trials have demonstrated benefits, equivalent to six months of training, with four weeks exposure to ACE-Is [46]. These effects appear to be unique to ACE-Is, when compared to other classes of anti-hypertensives [75], further supporting that the benefits are independent of the drugs BP lowering properties. In addition, individuals with polymorphisms, resulting in low ACE activity, have an enhanced response to training [76] although this contrasts with the observations of increased ADL disability for the same gene variants in older populations [49]. The association between treatment with either ACE-Is and/or ARBs, with a lower incidence of falls also supports the theory that these medications may produce global effects on physical function [47]. Therefore, one year of ACE-I treatment could, theoretically, result in improvements in muscle strength and function, sufficient to alter the rate of decline in ADLs.

Other studies, however, contradict these findings. Results from the Cardiovascular Health Study, investigating incidence of dementia, suggest that exposure to ACE-Is and non-CACE-Is in particular, are associated with an increased dependency in ADLs [14]. Although these reductions may have been relative to smaller disimprovements with other anti-hypertensives, such as calcium channel blockers, which are also associated with reduced incidence of dementia [77, 78] and possibly reduced progression that is currently being tested in clinical trials [Nilvad registered trial EudraCT Number: 2012-002764-27]. The TRAIN study demonstrated no benefit in muscle strength or

exercise performance for fosinopril over placebo in patients with high cardiovascular risk but normal cognition [79].

In this study, the use of perindopril was associated with a slower rate of decline in measures of cognition (SADAS-cog and Q*mci*), global function (CDR-SB), and ADLs compared to other CACE-Is, although only the CDR-SB reached statistical significance. The potential benefits of perindopril on exercise tolerance over other ACE-Is has been commented upon previously [79], with most studies reporting positive findings using perindopril [46, 73, 79] and negative findings using other agents such as fosinopril [79] or quinapril [81].

The results presented here also suggest that depressive symptoms (measured using the CSDD) were more likely to improve or remain unchanged in patients receiving CACE-Is. Although reductions in the adjusted one-year rate of decline were statistically significant for the CSDD, between the CACE-I and NoCACE-I groups, the effects were small (both had a median three-point change over the year, see Table 2). The frequency of the BPSD, as measured by the DBRIF and DBRIR, reduced for both CACE-I and NoCACE-I groups, although this did not achieve statistical significance. Thus, minimal or no effects of CACE-Is on mood or the BPSD were demonstrated in this study. Both the CACE-I and NoCACE-I groups appeared to demonstrate little difference in rates of decline in their GDS, CSDD, and DBRI scores over the year of follow-up. Although more patients in the CACE-I group compared to the NoCACE-I group showed a significant improvement in CSDD scores (57% versus 47%) over one year, CSDD scores were significantly higher in the CACE-I group at baseline. These data support the current evidence that ACE-Is, in general, have little effect on mood and depression [53, 54].

Strengths of our study include that the data were collected as part of a clinical trial, with rigorous interviewer training and quality checks. Furthermore, the DARAD trial had a relatively low loss to follow-up and good compliance with measurements throughout [55]. Other strengths include the large numbers, regular assessment, and measurement of a wide variety of outcomes over one year [55]. Limitations to this study included the fact that patients had established dementia, median SMMSE of 23, and may have been taking CACE-Is for many years. Another limitation is that as this was an observational study, derived from the secondary analyses of data from a randomized control trial; it was not possible to identify duration or previous history of anti-hypertensive treatment. Furthermore, compliance with anti-hypertensive medications, which has been shown to reduce with time, may also have been a confounder [82, 83]. A percentage of patients in the NoCACE-I group (41%) were not receiving any anti-hypertensive treatment. By lowering BP, which is associated with progression of cognitive and functional impairment [45], these medications may have caused bias from confounding by indication favoring those currently receiving them. However, baseline characteristics including BP were similar between the CACE-I and NoCACE-I groups and were not associated with rates of decline. Likewise, most anti-hypertensive drugs have been linked with reduced rates of cognitive and or functional decline [9, 10, 14, 17, 18, 45]. There were marginal differences of borderline significance between the three groups (CACE-I, NoCACE-I, and perindopril) in gender, cholinesterase inhibitor use, and SADAS-cog scores. However, the difference in deterioration in ADLs remained after adjustment for these variables. The marker of ADLs used, the Lawton-Brody ADL Scale score, is not a gold standard outcome measure, but it is still a widely used instrument that incorporates both instrumental and basic activities of daily living [14, 65, 84]. Indeed, like most instruments measuring ADLs, it is subject to potential bias arising from self or informant reporting rather than a demonstration of ability, and insensitivity to small changes in function. Another limitation and perhaps most important, is that inferences regarding treatment effects are limited by the small effects, the borderline significance of the findings, and the multiple comparisons increasing the likelihood of chance findings. Small effects may however also reflect that this analysis was conducted in patients with more advanced disease. Therefore greater effects may be gained from longer treatment periods in patients with less advanced pathology or people with early stages of cognitive impairment (e.g., MCI), where cognitive benefits have previously been reported [19, 20].

Overall, this study suggests the possibility of benefit for patients with established AD taking CACE-Is compared to a group not currently treated with CACE-Is, across a range of outcome measures, particularly ADLs. The finding of a reduced rate of progression in ADL disability is small and if real of uncertain significance and with an unclear mechanism. Nevertheless, if such an effect were sustained over years, patient-important benefit may result. Our data provide modest support for the hypothesis that CACE-Is, and perhaps perindopril in particular, may slow disease progression in patients with dementia. At present no anti-hypertensive agents have been licensed for the

treatment of AD. These data support the need for further study.

ACKNOWLEDGMENTS

Funding for this study is from Atlantic Philanthropy, and the Canadian Institute of Health Research (CIHR).

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2056).

REFERENCES

[1] Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K (2005) Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* **64**, 277-281.

[2] Joas E, Backman K, Gustafson D, Ostling S, Waern M, Guo X, Skoog I (2012) Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. *Hypertension* **59**, 796-801.

[3] Fogari R, Mugellini A, Zoppi A, Derosa G, Pasotti C, Fogari E, Preti P (2003) Influence of losartan and atenolol on memory function in very elderly hypertensive patients. *J Hum Hypertens* **17**, 781-785.

[4] Fogari R, Mugellini A, Zoppi A, Marasi G, Pasotti C, Poletti L, Rinaldi A, Preti P (2004) Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension. *Eur J Clin Pharmacol* **59**, 863-868.

[5] Kehoe PG, Passmore PA (2012) The renin-angiotensin system and antihypertensive drugs in Alzheimer's disease: current standing of the angiotensin hypothesis? *J Alzheimers Dis* **30**, 251-268.

[6] Fournier A, Oprisiu-Fournier R, Serot JM, Godefroy O, Achard JM, Faure S, Mazouz H, Temmar M, Albu A, Bordet R, Hanon O, Gueyffier F, Wang J, Black S, Sato N (2009) Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. *Expert Rev Neurother* **9**, 1413-1431.

[7] Goodison WV, Frisardi V, Kehoe PG (2012) Calcium channel blockers and Alzheimer's disease: potential relevance in treatment strategies of metabolic syndrome. *J Alzheimers Dis* **30**, 269-282.

[8] Khachaturian AS, Zandi PP, Lyketsos CG, Hayden KM, Skoog I, Norton MC, Tschanz JT, Mayer LS, Welsh-Bohmer KA, Breitner JC (2006) Antihypertensive medication use and incident Alzheimer disease: The Cache County Study. *Arch Neurol* **63**, 686-692.

[9] Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM (2011) Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *J Alzheimers Dis* **26**, 699-708.

[10] Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, Wolozin B (2010) Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ* **340**, b5465.

[11] Ohrui T, Matsui T, Yamaya M, Arai H, Ebihara S, Maruyama M, Sasaki H (2004) Angiotensin-converting enzyme inhibitors and incidence of Alzheimer's disease in Japan. *J Am Geriatr Soc* **52**, 649-650.

[12] Staessen JA, Thijs L, Richart T, Odili AN, Birkenhager WH (2011) Placebo-controlled trials of blood pressure-lowering therapies for primary prevention of dementia. *Hypertension* **57**, e6-e7.

[13] Poon IO (2008) Effects of antihypertensive drug treatment on the risk of dementia and cognitive impairment. *Pharmacotherapy* **28**, 366-375.

[14] Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, Yasar S, Atkinson H, Robbins M, Psaty B, Goff DC Jr (2009) Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med* **169**, 1195-1202.

[15] Kehoe PG, Davies NM, Martin RM, Ben-Shlomo Y (2013) Associations of angiotensin targeting antihypertensive drugs with mortality and hospitalization in primary care patients with dementia. *J Alzheimers Dis* **33**, 999-1008.

[16] Kehoe P, Miners S, Love S (2009) Angiotensins in Alzheimer's disease-friend or foe? *Trends Neurosci* **32**, 619-628.

[17] Hajjar I, Hart M, Milberg W, Novak V, Lipstz L (2009) The rationale and design of the antihypertensives and vascular, endothelial, and cognitive function (AVEC) trial in elderly hypertensives with early cognitive impairment: Role of the renin angiotensin system inhibition. *BMC Geriatr* **9**, 48.

[18] Hajjar I, Hart M, Chen Y, Mack W, Milberg W, Chui H, Lipsitz L (2012) Effect of antihypertensive therapy on cognitive function in early executive cognitive impairment: A Double-Blind Randomized Clinical Trial. *Arch Intern Med* **172**, 442-444.

[19] Solfrizzi V, Scafato E, Frisardi V, Seripa D, Logroscino G, Kehoe PG, Imbimbo BP, Baldereschi M, Crepaldi G, Di Carlo A, Galluzzo L, Gandin C, Inzitari D, Maggi S, Pilotto A, Panza F; Italian. Longitudinal Study on Aging Working Group (2013) Angiotensin-converting enzyme inhibitors and incidence of mild cognitive impairment. The Italian Longitudinal Study on Aging. *Age (Dordr)* **35**, 441-453.

[20] Rozzini L, Chilovi BV, Bertoletti E, Conti M, Del Rio I, Trabucchi M, Padovani A (2006) Angiotensin converting enzyme (ACE) inhibitors modulate the rate of progression of amnestic mild cognitive impairment. *Int J Geriatr Psychiatry* **21**, 550-555.

[21] Ohrui T, Tomita N, Sato-Nakagawa T, Matsui T, Maruyama M, Niwa K, Arai H, Sasaki H (2004) Effects of brain-penetrating ACE inhibitors on Alzheimer disease progression. *Neurology* **63**, 1324-1325.

[22] Gao Y, O'Caoimh R, Healy L, Kerins D, Guyatt G, Eustace J, Sammon D, Molloy DW (2013) Effects of centrally acting angiotensin converting enzyme inhibitors on the rate of cognitive decline in dementia. *BMJ Open* **3**, e002881.

[23] Hardy J (2009) The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. *J Neurochem* **110**, 1129-1134.

[24] Kehoe PG, Russ C, McIlory S, Williams H, Holmans P, Holmes C, Liolitsa D, Vahidassr D, Powell J, McGleenon B, Liddell M, Plomin R, Dynan K, Williams N, Neal J, Cairns NJ, Wilcock G, Passmore P, Lovestone S, Williams J, Owen MJ (1999) Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. *Nat Genet* **21**, 71-72.

[25] Lehmann DJ, Cortina-Borja M, Warden DR, Smith AD, Sleegers K, Prince van Duijn CM, Kehoe PG (2005) Large meta-analysis establishes the ACE insertion-deletion polymorphism as a marker of Alzheimer's disease. *Am J Epidemiol* **162**, 305-317.

[26] Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F (1990) An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the

variance of serum enzyme levels. *J Clin Invest* **86**, 1343-1346.

[27] Tiret L, Rigat B, Visvikis S, Breda C, Corvol P, Cambien F, Soubrier F (1992) Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. *Am J Hum Genet* **51**, 197-205.

[28] Hemming ML, Selkoe DJ (2005) Amyloid beta -protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. *J Biol Chem* **280**, 37644-37650.

[29] Hu J, Igarashi A, Kamata M, Nakagawa H (2001) Angiotensin-converting enzyme degrades Alzheimer amyloid beta-peptide (A beta); retards A beta aggregation, deposition, fibril formation; and inhibits cytotoxicity. *J Biol Chem* **276**, 47863-47868.

[30] Oba R, Igarashi A, Kamata M, Nagata K, Takano S, Nakagawa H (2005) The N-terminal active centre of human angiotensin-converting enzyme degrades Alzheimer amyloid beta-peptide. *Eur J Neurosci* **21**, 733-740.

[31] Miners JS, Ashby E, Van Helmond Z, Chalmers KA, Palmer LE, Love S, Kehoe PG (2008) Angiotensin-converting enzyme (ACE) levels and activity in Alzheimer's disease, and relationship of perivascular ACE-1 to cerebral amyloid angiopathy. *Neuropathol Appl Neurobiol* **34**, 181-193.

[32] Miners S, Ashby E, Baig S, Harrison R, Tayler H, Speedy E, Prince JA, Love S, Kehoe PG (2009) Angiotensin-converting enzyme levels and activity in Alzheimer's disease: differences in brain and CSF ACE and association with ACE1 genotypes. *Am J Transl Res* **1**, 163-177.

[33] Miners JS, van Helmond Z, Raiker M, Love S, Kehoe PG (2010) ACE variants and association with brain Abeta levels in Alzheimer's disease. *Am J Transl Res* **3**, 73-80.

[34] Belbin O, Brown K, Shi H, Medway C, Abraham R, Passmore P, Mann D, Smith AD, Holmes C, McGuiness B, Craig D, Warden D, Heun R, Kölsch H, Love S, Kalsheker N, Williams J, Owen MJ, Carrasquillo M, Younkin S, Morgan K, Kehoe PG (2011) A multi-center study of ACE and the risk of late-onset Alzheimer's disease. *J Alzheimers Dis* **24**, 587-597.

[35] Tian M, Zhu D, Xie W, Shi J (2012) Central angiotensin II-induced Alzheimer-like tau phosphorylation in normal rat brains. *FEBS Lett* **586**, 3737-7345.

[36] Zhu D, Shi J, Zhang Y, Wang B, Liu W, Chen Z, Tong Q (2011) Central angiotensin II stimulation promotes β amyloid production in Sprague Dawley rats. *PLoS One* **6**, e16037.

[37] Yamada K, Uchida S, Takahashi S, Takayama M, Nagata Y, Suzuki N, Shirakura S, Kanda T (2010) Effect of a centrally active angiotensin-converting enzyme inhibitor, perindopril, on cognitive performance in a mouse model of Alzheimer's disease. *Brain Res* **1352**, 176-186.

[38] Yamada K, Horita T, Takayama M, Takahashi S, Takaba K, Nagata Y, Suzuki N, Kanda T (2011) Effect of a centrally active angiotensin converting enzyme inhibitor, perindopril, on cognitive performance in chronic cerebral hypo-perfusion rats. *Brain Res* **1421**, 110-120.

[39] Dong YF, Kataoka K, Tokutomi Y, Nako H, Nakamura T, Toyama K, Sueta D, Koibuchi N, Yamamoto E, Ogawa H, Kim-Mitsuyama S (2011) Perindopril, a centrally active angiotensin-converting enzyme inhibitor, prevents cognitive impairment in mouse models of Alzheimer's disease. *FASEB J* **25**, 2911-2920.

[40] Tota S, Nath C, Najmi AK, Shukla R, Hanif K (2012) Inhibition of central angiotensin converting enzyme ameliorates scopolamine induced memory impairment in mice: Role of cholinergic neurotransmission, cerebral blood flow and brain energy metabolism. *Behav Brain Res* **232**, 66-76.

[41] Ferrington L, Palmer LE, Love S, Horsburgh KJ, Kelly PA, Kehoe PG (2012) Angiotensin II-inhibition: effect on Alzheimer's pathology in the aged triple transgenic mouse. *Am J Transl Res* **4**, 151-164.

[42] Teo K, Yusuf S, Sleight P, Anderson C, Mookadam F, Ramos B, Hilbrich L, Pogue J, Schumacher H, ONTARGET/TRANSCEND Investigators (2004) Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Patients with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J* **148**, 52-61.

[43] Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A, SCOPE Study Group (2003) The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* **21**, 875-886.

[44] Wharton W, Stein JH, Korcarz C, Sachs J, Olson SR, Zetterberg H, Dowling M, Ye S, Gleason CE, Underbakke G, Jacobson LE, Johnson SC, Sager MA, Asthana S, Carlsson CM (2012) The effects of ramipril in individuals at risk for Alzheimer's disease: results of a pilot clinical trial. *J Alzheimers Dis* **32**, 147-156.

[45] Rosenberg P, Mielke M, Tschanz J, Cook L, Corcoran C, Hayden KM, Norton M, Rabins PV, Green RC, Welsh-Bohmer KA, Breitner JCS, Munger R, Lyketsos CG (2008) Effects of cardiovascular medications on rate of functional decline in Alzheimer disease. *Am J Geriatric Psychiatry* **16**, 883-892.

[46] Sumukadas D, Witham MD, Struthers AD, McMurdo MET (2007) Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. *CMAJ* **177**, 867-874.

[47] Wong AKW, Lord SR, Sturnieks DL, Delbaere K, Trollor JN, Close JCT (2013) Angiotensin system–blocking medications are associated with fewer falls over 12 months in community-dwelling older people. *J Am Geriatr Soc* **61**, 776-781.

[48] Regan C, Katona C, Walker Z, Hooper J, Donovan J, Livingston G (2006) Relationship of vascular risk to the progression of Alzheimer disease. *Neurology* **67**, 1357-1362.

[49] Seripa D, Paroni G, Matera MG, Gravina C, Scarcelli C, Corritore M, D'Ambrosio LP, Urbano M, D'Onofrio G, Copetti M, Kehoe PG, Panza F, Pilotto A (2011) Angiotensin-converting enzyme (ACE) genotypes and disability in hospitalized older patients. *Age (Dordr)* **33**, 409-419.

[50] Kritchevsky SB, Nicklas BJ, Visser M, Simonsick EM, Newman AB, Harris TB, Lange EM, Penninx BW, Goodpaster BH, Satterfield S, Colbert LH, Rubin SM, Pahor M (2005) Angiotensin-converting enzyme insertion/deletion genotype, exercise, and physical decline. *JAMA* **294**, 691-698.

[51] Gard PR (2004) Angiotensin as a target for the treatment of Alzheimer's disease, anxiety and depression. *Expert Opin Ther Targets* **8**, 7-14.

[52] Braszko JJ, Karwowska-Polecka W, Halicka D, Gard PR (2003) Captopril and enalapril improve cognition and depressed mood in hypertensive patients. *J Basic Clin Physiol Pharmacol* **14**, 323-343.

[53] Deary IJ, Capewell S, Hajducka C, Muir AL (1991) The effects of captopril vs atenolol on memory, information processing and mood: a double-blind crossover study. *Br J Clin Pharmacol* **32**, 347-353.

[54] Rogers D, Pies R (2008) General medical drugs associated with depression. *Psychiatry (Edgmont)* **5**, 28.
[55] Molloy DW, Standish TI, Zhou Q, Guyatt G (2013) A multi-centre, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. *Int J Geriatr Psychiatry* **28**, 463-470.
[56] Standish TI, Molloy DW, Bédard M, Layne EC, Murray EA, Strang D (1996) Improved reliability of the Standardized Alzheimer's Disease Assessment Scale (SADAS) compared with the Alzheimer's Disease Assessment Scale (ADAS). *J Am Geriatr Soc* **44**, 712-716.
[57] Schafer KA, Tractenberg RE, Sano M, Mackell JA, Thomas RG, Gamst A, Thal LJ, Morris JC, Alzheimer's Disease Cooperative, Study (2004) Reliability of monitoring the Clinical Dementia Rating in multicenter clinical trials. *Alzheimer Dis Assoc Disord* **18**, 219-222.
[58] Molloy DW, Alemayehu E, Roberts RS (1991) Reliability of a standardized mini-mental state examination compared with the traditional mini-mental state examination. *Am J Psychiatry* **148**, 102-105.
[59] Molloy DW, Standish TIM (1997) A guide to the standardized mini-mental state examination. *Int Psychogeriatrics* **9**, 87-94.
[60] O'Caoimh R, Gao Y, McGlade C, Healy L, Gallagher P, Timmons S, Molloy DW (2012) Comparison of the quick mild cognitive impairment (Q*mci*) screen and the SMMSE in screening for mild cognitive impairment. *Age Ageing* **41**, 624-629.
[61] O'Caoimh R, Gao Y, Gallagher P, Eustace J, McGlade C, Molloy DW (2013) Which part of the quick mild cognitive impairment screen (Q*mci*) discriminates between normal cognition, mild cognitive impairment and dementia? *Age Ageing* **42**, 324-330.
[62] O'Caoimh R, Svendrovski A, Johnston B, Gao Y, McGlade C, Timmons S, Eustace J, Guyatt G, Molloy DW (2014) The quick mild cognitive impairment screen correlated with the standardised Alzheimer's disease assessment scale-cognitive section in clinical trials. *J Clin Epidemiol* **67**, 87-92.
[63] Yesavage JA (1988) Geriatric depression scale. *Psychopharmacol Bull* **24**, 709-711.
[64] Alexopoulos GA, Abrams RC, Young RC, Shamoian CA (1988) Cornell scale for depression in dementia. *Biol Psych* **23**, 271-284.
[65] Lawton MP, Brody EM (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.
[66] Molloy DW, McIlroy WE, Guyatt GH, Lever JA (1991) Validity and reliability of the dysfunctional behavior rating instrument. *Acta Psychiatr Scand* **84**, 103-106.
[67] Molloy DW, Bédard M, Guyatt GH, Lever JA (1996) Dysfunctional behaviour rating instrument. *Int Psychogeriatr* **8**, 333-341.
[68] Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**, 1356-1364.
[69] Weyer G, Erzigkeit H, Kanowski S, Ihl R, Hadler D (1997) Alzheimer's Disease Assessment Scale: reliability and validity in a multicenter clinical trial. *Int Psychogeriatrics* **9**, 123-138.
[70] Marc LG, Raue PJ, Bruce ML (2008) Screening performance of the geriatric depression scale (GDS-15) in a diverse elderly home care population. *Am J Geriatr Psychiatry* **16**, 914-921.
[71] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.
[72] Hanes DS, Weir MR (2007) Usefulness of ARBs and ACE inhibitors in the prevention of vascular dementia in the elderly. *Am J Geriatr Cardiol* **16**, 175-182.
[73] Henriksen EJ, Jacob S (2003) Modulation of metabolic control by angiotensin converting enzyme (ACE) inhibition. *J Cell Physiol* **196**, 171-179.
[74] Onder G, Penninx BW, Balkrishnan R, Fried LP, Chaves PH, Williamson J, Carter C, Di Bari M, Guralnik JM, Pahor M (2002) Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. *Lancet* **359**, 926-930.
[75] Montgomery H, Clarkson P, Barnard M, Bell J, Brynes A, Dollery C, Hajnal J, Hemingway H, Mercer D, Jarman P, Marshall R, Prasad K, Rayson M, Saeed N, Talmud P, Thomas L, Jubb M, World M, Humphries S (1999) Angiotensin-converting-enzyme gene insertion/deletion polymorphism and response to physical training. *Lancet* **353**, 541-545.
[76] Tollefson GD (1990) Short-term effects of the calcium channel blocker nimodipine (Bay-e-9736) in the management of primary degenerative dementia. *Biol Psychiatry* **27**, 1133-1142.
[77] Kennelly S, Abdullah L, Kenny RA, Mathura V, Luis CA, Mouzon B, Crawford F, Mullan M, Lawlor B (2012) Apolipoprotein E genotype-specific short-term cognitive benefits of treatment with the antihypertensive nilvadipine in Alzheimer's patients – an open label trial. *Int J Geriatr Psychiatry* **27**, 415-422.
[78] Cesari M, Pedone C, Incalzi RA, Pahor M (2010) ACE inhibition and physical function. results from the trial of angiotensin converting enzyme inhibition and novel cardiovascular risk factors (TRAIN) study. *J Am Med Dir Assoc* **11**, 26.
[79] Hutcheon SD, Gillespie ND, Crombie IK, Struthers AD, McMurdo ME (2002) Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomised double blind placebo controlled trial. *Heart* **88**, 373-377.
[80] Zi M, Carmichael N, Lye M (2003) The effect of quinapril on functional status of elderly patients with diastolic heart failure. *Cardiovasc Drugs Ther* **17**, 133-139.
[81] Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* **27**, 2338-2345.
[82] Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, Schwartz JS (2005) Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* **165**, 1147-1152.
[83] Conlin PR, Gerth WC, Fox J, Roehm JB, Boccuzzi SJ (2001) Four-year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. *Clin Ther* **23**, 1999-2010.
[84] Sheehan B (2012) Assessment scales in dementia. *Ther Adv Neurol Disord* **5**, 349-358.

Age and Ageing 2012; **41:** 624–629
doi: 10.1093/ageing/afs059
Published electronically 18 May 2012

© The Author 2012. Published by Oxford University Press on behalf of the British Geriatrics Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Comparison of the quick mild cognitive impairment (Q*mci*) screen and the SMMSE in screening for mild cognitive impairment

RÓNÁN O'CAOIMH[1], YANG GAO[1], CIARA MCGLADE[1], LIAM HEALY[1], PAUL GALLAGHER[2], SUZANNE TIMMONS[1], D. WILLIAM MOLLOY[1]

[1]Department of Gerontology and Rehabilitation, St Finbarrs Hospital, Douglas Road, Cork City, Ireland
[2]Department of Geriatric Medicine, Cork University Hospital, Wilton, Cork City, Ireland

Address correspondence to: D. W. Molloy. E-mail: w.molloy@ucc.ie

Abstract

Introduction: differentiating mild cognitive impairment (MCI) from normal cognition (NC) is difficult. The AB Cognitive Screen (ABCS) 135, sensitive in differentiating MCI from dementia, was modified to improve sensitivity and specificity, producing the quick mild cognitive impairment (Q*mci*) screen.
Objective: this study compared the sensitivity and specificity of the Q*mci* with the Standardised MMSE and ABCS 135, to differentiate NC, MCI and dementia.
Methods: weightings and subtests of the ABCS 135 were changed and a new section 'logical memory' added, creating the Q*mci*. From four memory clinics in Ontario, Canada, 335 subjects (154 with MCI, 181 with dementia) were recruited and underwent comprehensive assessment. Caregivers, attending with the subjects, without cognitive symptoms, were recruited as controls ($n = 630$).
Results: the Q*mci* was more sensitive than the SMMSE and ABCS 135, in differentiating MCI from NC, with an area under the curve (AUC) of 0.86 compared with 0.67 and 0.83, respectively, and in differentiating MCI from mild dementia, AUC of 0.92 versus 0.91 and 0.91. The ability of the Q*mci* to identify MCI was better for those over 75 years.
Conclusion: the Q*mci* is more sensitive than the SMMSE in differentiating MCI and NC, making it a useful test, for MCI in clinical practice, especially for older adults.

Keywords: *quick mild cognitive impairment screen, mild cognitive impairment, standardised mini-mental state examination, AB cognitive screen 135, sensitivity*

Introduction

Mild cognitive impairment (MCI) represents a heterogeneous group of disorders of memory impairment [1]. Individuals with MCI have variable, subtle, cognitive changes. Although many go on to develop dementia, the rate of progression varies considerably. The annual conversion rate from MCI to dementia is estimated at between 5 and 10% [2]. The reason for this is partly due to variability in the definitions used [3] and in the diagnostic methods employed. When people present with memory loss, it is important to differentiate between MCI and dementia, as treatment choices differ. In particular, patients with dementia benefit from cholinesterase inhibitors, while those with MCI do not have a sustained response [4]. Clinical and functional assessments are used to differentiate between these two groups. While those with MCI generally do not have functional impairment, evidence suggests that subtle functional changes are present in 31% [5].

Several cognitive screening tools have been used in an attempt to differentiate normal cognition (NC), and MCI from dementia [6, 7]. Not all are able to distinguish

between dementia and MCI, and it has been suggested that no single screening tool will fit all situations [8]. One of the most widely employed tools is the Folstein Mini-Mental State Examination (MMSE) [9]. The Standardised Mini-Mental State Examination (SMMSE) improved inter-rater reliability by the inclusion of explicit administration and scoring guidelines [10, 11]. The MMSE and SMMSE have a limited role in identifying MCI [12], lacking sufficient sensitivity to differentiate between NC and MCI, in particular, where individuals have higher levels of academic achievement [13]. The AB Cognitive Screen 135 (ABCS 135) was developed to address this problem [6].

Description of the ABCS 135

The ABCS 135, a short screening test, administered in 3–5 min, is more sensitive in differentiating NC from dementia, and more importantly, MCI from dementia than the SMMSE. The ABCS 135 evaluates five domains, orientation, registration, clock drawing, delayed recall (DR) and verbal fluency (VF) [6] (Table 1). Although, the ABCS 135 is sensitive and quick to employ, it could be argued, that much of the test is redundant. All the domains differentiate NC and MCI from dementia, but orientation, registration and clock drawing did not enhance the discriminatory properties of the test in differentiating NC from MCI. For this reason, the Quick Mild Cognitive Impairment (Q*mci*) screen was developed to enhance the sensitivity of the ABCS 135.

Development of the Q*mci*

The Q*mci*, is a modified version of the ABCS 135, scored out of 100 points, placing greater emphasis on verbal memory and fluency, along with DR, (Supplementary data are available in *Age and Ageing* online, Appendix 1). As analysis of the ABCS 135 subtests found that DR and VF, were more sensitive at differentiating MCI from NC than orientation, registration and clock drawing [14], these three subtests had their weightings reduced by a factor of 2.5, 5 and 2, respectively (Table 1). Logical memory (LM), which is highly sensitive and specific in differentiating NC from MCI [15] was added and given the largest weighting, necessitating the reduction of weightings for all the other subtests.

Table 1. Comparison of ABCS version 135 and Q*mci*

ABCS 135	Score	Q*mci*	Score
Orientation	25	Orientation	10
Registration	25	Registration	5
Clock drawing	30	Clock drawing	15
Delayed recall	25	Delayed recall	20
Verbal fluency	30	Verbal fluency	20
		Logical memory	30

LM is a linguistic memory test (for stories) [16] and is unaffected by age or education [17]. VF and DR are highly sensitive tests for distinguishing MCI from NC [14], and although their weighting were cut, by a factor of 0.66 and 0.8 respectively, to allow for the introduction of LM, their relative weighting, compared to the other subtests, increased.

The Q*mci*, has six domains; five orientation items (country, year month, day and date), five registration items and a clock drawing test, each scored within 1 min. It also has a recall section (timed at 20 s), a test of VF (60 s) and a LM test with 30 s for administration and 30 s for response. It can be administered and scored in 5 min.

The primary objective of this study was to compare the sensitivity and specificity of the new Q*mci* with the ABCS 135 and SMMSE to distinguish individuals with NC from those with MCI and dementia.

Methods

Subjects

Subjects attending four memory clinics across Ontario, Canada (Hamilton, Paris, Niagara Falls and Grand Bend) referred for the investigation of cognitive loss were recruited between 2004 and 2010. Normal controls were selected by convenience sampling. All caregivers, or those attending with the subjects, were asked if they themselves had memory problems. Those without memory problems were invited to participate as normal controls. A diagnosis of dementia was based on NINCDS [18] and DSM-IV criteria [19]. Dementia severity was correlated with the Reisberg FAST scale [20]. A diagnosis of MCI was made by a consultant geriatrician if patients had recent, subjective but corroborated memory loss without obvious loss of social or occupational function. Subjects were excluded if they were under 55 years of age, unable to communicate verbally in English, if they had depression (as defined by a Geriatric Depression Scale greater than seven [21]), or if a reliable collateral was not available. Subjects with Parkinson's disease and Lewy body dementia were excluded as these typically present with exaggerated functional deficits and a different MCI syndrome [22]. Ethics approval was obtained and subjects provided verbal consent. Assent was obtained from individuals with cognitive impairment.

Data collection

Each subject had demographic data collected which included age, gender and number of years of education. Each had a physical examination and work-up for causes of cognitive impairment including a brain CT (computerised tomogram) scan, an electrocardiogram and blood tests. Each subject had the SMMSE and the Q*mci* administered sequentially but randomly by the same trained rater, who was blind to the eventual diagnosis.

Statistical analysis

Data were entered into SPSS version 16.0 [23]. Subjects were subdivided according to age, > or <75 years and educational level achieved, > or <12 years (approximating high school/secondary school level). ABCS 135 data, based on the Q*mci*, were reconstituted from data collected from the Q*mci*. The Shapiro–Wilk test was used to test normality and found that the majority of data were non-parametric. This was analysed using the Mann–Whitney *U* test, whereas Student's *t*-tests compared scores for parametric data. Data were also analysed using Receiver operating characteristics (ROC) curves.

Results

A total of 965 participants, 551 females (57%) and 414 males (43%), were included in the study. Overall, 630 subjects had NC (65%), 154 had MCI (16%) and 181 (19%) had dementia. The median age of the total population was 70.5 years; those with NC had a mean age 67 years compared with 75.5 for the MCI group and 79 for the dementia group. The dementia group was older than the NC ($P < 0.001$) and MCI ($P < 0.001$) groups. They also had spent less time in education, 10 years compared with the normal control (13 years, $P < 0.001$) and MCI (12 years, $P < 0.005$) populations. Dementia was divided into mild ($n = 141$), moderate ($n = 33$) and severe cognitive impairment ($n = 7$). The normal population had a median SMMSE score of 29 and a median Q*mci* score of 76, the MCI group scored 28 and 62 and the dementia group scored 22 and 36 on the SMMSE and Q*mci*, respectively. These results and demographics are summarised with inter-quartile range (IQR) in Table 2. All three cognitive tests (SMMSE, ABCS 135 and the Q*mci*) were sensitive in differentiating MCI from NC. The Q*mci* was best able to do this in a clinically useful way. The median difference in scores between subjects with either MCI or NC was one for the SMMSE compared with 14 for the Q*mci*. This represents a difference of 3.33% of the total score of 30 with the SMMSE and a 14% difference for the Q*mci* (scored out of 100).

All three tests distinguished dementia from MCI. Patients with MCI, scored a median 26 points more on the Q*mci* than those with dementia ($P < 0.001$), whereas there was a 40 point difference in the Q*mci* between those with NC and dementia ($P < 0.001$). Figure 1 shows two ROC curves demonstrating the sensitivities and specificities of the Q*mci,* ABCS 135 and SMMSE in differentiating MCI from NC and MCI from dementia. Although the Q*mci*, ABCS 135 and the SMMSE were able to distinguish MCI from NC, the Q*mci* was more sensitive with an area under the curve (AUC) of 0.86 (95% CI: 0.83–0.89) compared with 0.83 (95% CI: 0.79–0.86) for the ABCS 135 and 0.67 (95% CI: 0.62–0.72) for the SMMSE. The Q*mci* was also more sensitive at differentiating MCI from dementia, AUC of 0.92 (95% CI: 0.89–0.95) versus 0.91 (95% CI: 0.88–0.94) for the ABCS 135 and 0.91 (95% CI: 0.88–0.94) for the SMMSE. When moderate and severe dementia cases were removed from analysis, the AUC of the Q*mci* and SMMSE for differentiating MCI from mild dementia cases alone was unchanged at 0.92 (95% CI: 0.89–0.95) and 0.90 (95% CI: 0.85–0.93), respectively.

Subanalysis for age (> or < 75 years of age) and education (> or <12 years) showed that the Q*mci* was more sensitive, with a larger AUC, than the SMMSE. The Q*mci* was best for distinguishing MCI from NC in an older age group, (over 75 years), with more time, (>12 years), in education, with an AUC of 0.86 (95% CI: 0. 79–0.92)

Table 2. Characteristics of the normal, MCI and dementia groups, including median Q*mci*, SMMSE and ABCS 135 scores and inter-quartile range (IQR), (Q1–Q3 = IQR; Q1 = 1st Quartile, Q3 = 3rd Quartile)

Group	Normal	MCI	Dementia
Number of subjects	630	154	181
Age			
Mean	67.4	73.6	78.1
Median	67	75.5	79
Range	44–92	50–88	49–93
Proportion female (57.0%) $n = 551$			
Mean age	67.0	73.3	78.7
Median age	66.5	75	80
Range	50–92	50–87	49–93
Proportion male (43.0%) $n = 414$			
Mean age	68.0	73.9	77.6
Median age	68	76	79
range	44–85	51–88	53–92
Education (years in education)			
Mean	13.8	12.2	11.0
Median	13	12	10
Range	5–29	5–26	3–20
Q*mci* (median with IQR)	76 (83–69 = 14)	62 (68–53 = 15)	36 (45–23 = 22)
SMMSE (median with IQR)	29 (30–28 = 2)	28 (29–27 = 2)	22 (25–18 = 7)
ABCS 135 (median with IQR)	115.5 (121–109 = 12)	102 (111–94 = 17)	70 (83.5–45.5 = 38)

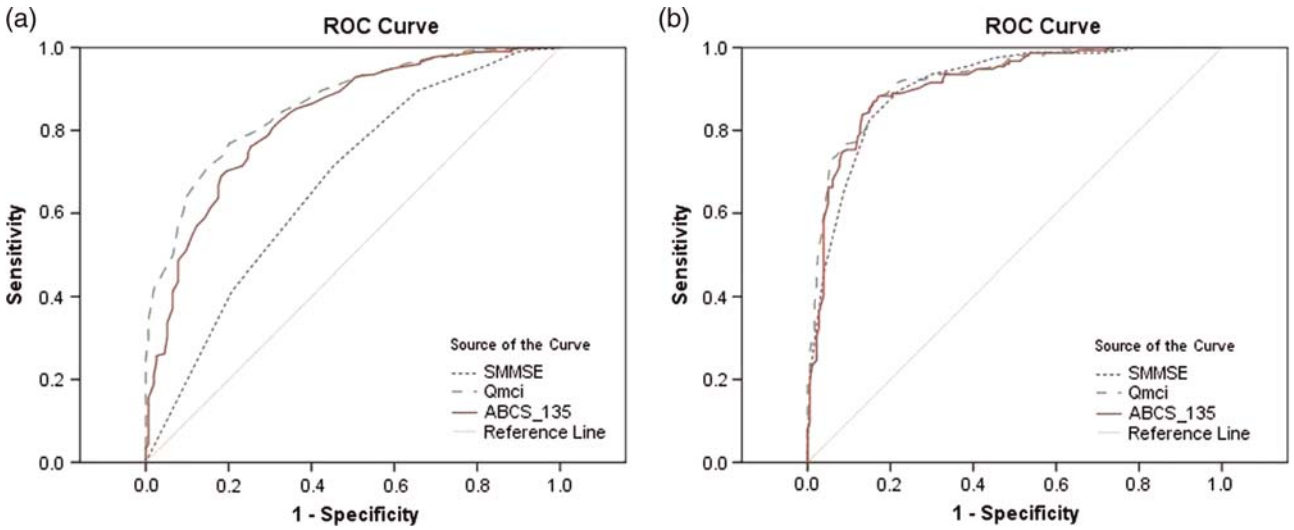


Figure 1. ROC curve demonstrating sensitivities and specificities of the Q*mci,* ABCS 135 and SMMSE in differentiating (a). MCI from normal cognition, (b). MCI and dementia.

compared with 0.55 (95% CI: 0.44–0.66) for the SMMSE. The only subjects where the difference in sensitivity between the Q*mci* and SMMSE was less obvious was for younger individuals, (<75 years) with less than 12 years in education, AUC of 0.72 (95% CI: 0.62–0.82) for the Q*mci* versus 0.65 (95% CI: 0.54–0.76) for the SMMSE. The SMMSE, ABCS 135 and Q*mci* were all able to differentiate MCI from dementia, irrespective of age or educational status ($P < 0.001$).

Conclusion

This study compares the refined ABCS tool, the newly developed Q*mci*, to the established SMMSE and the original ABCS 135 in their ability to discriminate NC and MCI from dementia. The results presented here show that the Q*mci* is more sensitive than the SMMSE and the ABCS 135 in differentiating MCI from NC, whereas all three are able to distinguish NC from dementia. Although, the SMMSE was useful in differentiating MCI and NC groups, from dementia subjects, it was not able to separate MCI from NC. The small percentage difference (3.33%) of the total score for the SMMSE between those with NC and MCI shows that the SMMSE is not clinically useful in distinguishing MCI from normals. The Q*mci* had a wider and more clinically significant percentage difference in median scores to help discriminate MCI from dementia. Similarly, the median SMMSE score for MCI cases and controls, even taking the IQR into account, at 28 out of 30 (IQR: 29–27 = 2) lies within the accepted cut-off interval for NC, at greater than 25 out of 30 [11, 24]. This again suggests that the SMMSE is not adequately sensitive in detecting MCI. The Q*mci* was also more sensitive than the SMMSE in differentiating MCI from NC among older adults, over 75 years, especially those with more than 12 years in education.

Of note, age and educational level did not affect the ability of the Q*mci* or SMMSE to discriminate between MCI and dementia. The dementia group in this study was significantly older and had spent less time in formal education than either the MCI group or the NC group. The dementia group was weighted towards the mild spectrum of dementia. This is important, as differentiating MCI from mild dementia is more challenging than differentiating it from severe dementia. Removing moderate and severe dementia cases from analysis, showed that the Q*mci* retains and even improves its increased sensitivity, for differentiating MCI from mild dementia, confirming that this tool is useful across the whole range of the cognitive impairment spectrum.

Our paper has several limitations. First, we cannot be certain that all patients were classified appropriately as having normal or impaired cognition. This is difficult to do, especially where controls are drawn from a sample of convenience. Controls in this study did not have any complaints of memory loss. We acknowledge that one of the major clinical challenges is to separate symptomatic patients with NC from those with MCI, especially as approximating 50%, attending some memory clinics with subjective memory problems, have NC [25]. However, within the confines of a sample of convenience, the subjects chosen as normal controls were tested rigorously, screened for cognitive impairment and depression and underwent the same detailed assessment as cases with MCI and dementia. Future validation of the Q*mci*, will target controls with NC, referred to the memory clinic.

Second, we used NINCDS and DSM IV criteria to make a diagnosis of dementia. While there is no defined gold standard, these criteria are broadly accepted and have been validated internationally [26]. Third, the diagnosis of dementia was based on a single assessment

which may have reduced accuracy and one rater scored both cognitive tests which may have led to 'practice' effects. However, the raters were blind to the eventual diagnosis made at the clinical assessment. Finally, we compared the Q*mci* to the SMMSE and ABCS 135 which are not gold standards for differentiating MCI from NC or dementia. This said, the SMMSE is the most widely used screen for dementia and no gold standard yet exists for the diagnosis of MCI.

The strengths of this study are the large sample size, comprehensive assessment and bigger number of controls than the original ABCS 135 validation paper. The diagnosis of MCI and diagnosis and grading of dementia are based on both functional and cognitive assessments. This study was performed at multiple sites. Future research will focus on comparing the Q*mci* to other short cognitive tests such as the Montreal Cognitive Assessment [27] and further refinement of the different domains in the test.

The study confirms that the Q*mci*, a short cognitive screen, is more sensitive in differentiating NC from MCI, than the widely used SMMSE. Compared with the ABCS 135, the Q*mci* is more sensitive in differentiating MCI, takes the same time to complete and is conveniently scored out of 100, making it easy to interpret in clinical practice.

Key points

- The Qmci is more sensitive than the SMMSE in differentiating MCI from NC.
- The Qmci is more sensitive than the SMMSE in differentiating MCI from dementia.
- The Qmci is more sensitive at differentiating MCI from NC in older adults, over 75.
- The Qmci needs to be compared with other short-cognitive screening tools.

Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

References

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Int Med 2004; 256: 183–94.
2. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia–meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 2009; 119: 252–65.
3. Fisk JD, Merry HR, Rockwood K. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. Neurology 2003; 61: 1179–84.
4. Peterson RC, Thomas RG, Grundman M *et al.*, for the Alzheimer's Disease Cooperative Study Group. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Eng J Med 2005; 352: 2379–88.
5. Artero S, Touchon J, Ritchie K. Disability and mild cognitive impairment: a longitudinal, population-based study. Int J Geriatr Psychiatry 2001; 16: 1092–7.
6. Molloy DW, Standish TIM, Lewis DL. Screening for mild cognitive impairment: comparing the SMMSE and the ABCS. Can J Psychiatry 2005; 50: 52–58.
7. Lonie JA, Tierney KM, Ebmeier KP. Screening for mild cognitive impairment: a systematic review. Int J Geriatr Psychiatry 2009; 24: 902–15.
8. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry 2007; 78: 790–9.
9. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
10. Molloy DW, Alemayehu E, Roberts R. Reliability of a standardized Mini-Mental State Examination compared with the traditional Mini-Mental State Examination. Am J Psychiatry 1991; 148: 102–5.
11. Molloy DW, Standish TIM. A guide to the Standardized Mini-Mental State Examination. Int Psychogeriatr 1997; 9 (S1): 87–94.
12. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res 2009; 43: 411–31.
13. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993; 269: 2386–91.
14. Standish T, Molloy DW, Cunje A, Lewis DL. Do the ABCS 135 short cognitive screen and its subtests discriminate between normal cognition, mild cognitive impairment and dementia? Int J Geriatr Psychiatry 2007; 22: 189–94.
15. Cunje A, Molloy DW, Standish TI, Lewis DL. Alternative forms of logical memory and verbal fluency tasks for repeated testing in early cognitive changes. Int Psychogeriatr 2007; 19: 65–75.
16. Wechsler D. Wechsler Memory Scale—Third Edition Manual. San Antonio, TX, USA: The Psychological Corporation, 1997.
17. Lichtenberg PA, Christensen B. Extended normative data for the logical memory subtests of the Wechsler Memory Scale–Revised: responses from a sample of cognitively intact elderly medical patients. Psychol Rep 1992; 71: 745–6.
18. McKhann G, Drachman DA, Folstein MF *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939–44.
19. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DC: American Psychiatric Association, 1994.
20. Reisberg B. Functional Assessment Staging (FAST). Psychopharmacol Bull 1988; 24: 653–59.
21. Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull 1988; 24: 709–11.
22. Caviness JN, Driver-Dunckley E, Connor DJ *et al.* Defining mild cognitive impairment in Parkinson's disease. Mov Disord 2007; 22: 1272–7.
23. SPSS Inc. SPSS for Windows 16.0. Chicago IL: SPSS Inc, 2008.
24. Mungas D. In-office mental status testing: a practical guide. Geriatrics 1991; 46: 54–8. 63, 66.

25. Steenland K, Macneil J, Bartell S, Lah J. Analyses of diagnostic patterns at 30 Alzheimer's disease centers in the US. Neuroepidemiology 2010; 35: 19–27.
26. O Connor DW, Blessed G, Cooper B, Jonker C, Morris JC. Cross-national interrater reliability of dementia diagnosis in the elderly and factors associated with disagreement. Neurology 1996; 47: 1194–9.
27. Nasreddine ZS, Philips NA, Bedirian V *et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53: 695–9.

Received 18 October 2011; accepted in revised form 8 February 2012

Age and Ageing 2012; **41:** 629–634
doi: 10.1093/ageing/afs060
Published electronically 15 May 2012

© The Author 2012. Published by Oxford University Press on behalf of the British Geriatrics Society. All rights reserved. For Permissions, please email: journals.permissions@oup.com

Preventing delirium in an acute hospital using a non-pharmacological intervention

Felipe Tomas Martinez[1], Catalina Tobar[1], Carlos Ignacio Beddings[1], Gustavo Vallejo[1], Paola Fuentes[2]

[1]Escuela de Medicina, Universidad de Valparaiso, Valparaiso, Chile
[2]Escuela de Medicina, Universidad Andres Bello, Viña del Mar, Chile

Address correspondence to: F. T. Martinez, 5 Norte 1096, Apartment N°202, Viña del Mar, Chile. Tel: +56 32 2480830. Email: ranoih@gmail.com

Abstract

Background: delirium is a clinical syndrome associated with multiple short and long-term complications and therefore prevention is an essential part of its management. This study was designed to assess the efficacy of multicomponent intervention in delirium prevention.
Methods: a total of 287 hospitalised patients at intermediate or high risk of developing delirium were randomised to receive a non-pharmacological intervention delivered by family members (144 patients) or standard management (143 patients). The primary efficacy outcome was the occurrence of delirium at any time during the course of hospitalisation. Three validated observers performed the event adjudication by using the confusion assessment method screening instrument.
Results: there were no significant differences in the baseline characteristics between the two groups. The primary outcome occurred in 5.6% of the patients in the intervention group and in 13.3% of the patients in the control group (relative risk: 0.41; confidence interval: 0.19–0.92; $P = 0.027$).
Conclusion: the results of this study show that there is a benefit in the non-pharmacological prevention of delirium using family members, when compared with standard management of patients at risk of developing this condition.

Keywords: *delirium, primary prevention, elderly*

Introduction

Delirium is a clinical syndrome characterised by an altered level of consciousness and cognitive disorders that develop over a short period of time (usually over hours or days) and tend to fluctuate during the course of the day [1]. The etiology of this syndrome is often multifactorial.

What makes delirium important is not only its high occurrence rate among hospitalied patients but also its consequences. The occurrence rate ranges from 6 to 56% [2, 3] in hospitalised patients. Its consequences include the contribution to increased morbidity and mortality, being cause of distress to patients and their families and increased costs [3]. An example of this is that the presence of delirium in hospitalisation is an independent factor for mortality 1 year

prospective population-based study. BMC Public Health 2010; 10: 396.
18. Isoaho R, Puolijoki H, Huhti E, Kivelä SL, Tala E. Prevalence of asthma in elderly Finns. J Clin Epidemiol 1994; 47: 1109–18.
19. Piirtola M, Vahlberg T, Isoaho R, Aarnio P, Kivelä SL. Predictors of fractures among the aged: a population-based study with 12-years follow-up in a Finnish municipality. Aging Clin Exp Res 2008; 20: 242–52.
20. Classification of Medicines (ATC) and Defined Daily Doses (DDD) 2000. Helsinki, Finland: National Agency of Medicines, 2000.
21. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. Am J Epidemiol 1998; 148: 887–92.
22. Kamal-Bahl SJ, Stuart BC, Beers MH. Propoxyphene use and risk for hip fractures in older adults. Am J Geriatr Pharmacother 2006; 4: 219–26.
23. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with the use of morphine and opiates. J Intern Med 2006; 260: 76–87.
24. Vestergaard P, Tigaran S, Rejnmark L, Tigaran C, Dam M, Mosekilde L. Fracture risk is increased in epilepsy. Acta Neurol Scand 1999; 99: 269–75.
25. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia 2004; 45: 1330–7.
26. Sirven JI. Acute and chronic seizures in patients older than 60 years. Mayo Clin Proc 2001; 76: 175–83.
27. Kinjo M, Setoguchi S, Schneeweiss S, Solomon DH. Bone mineral density in subjects using central nervous system-active medications. Am J Med 2005; 118: 1414.
28. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain 2002; 3: 377–384.
29. Ali II, Schuh L, Barkley GL, Fates JR. Antiepileptic drugs and reduced bone mineral density. Epilepsy Behav 2004; 5: 296–300.
30. Kiebzak GM, Beinard GA, Perser K, Ambrose CG, Siff SJ, Heggeness MH. Undertreatment of osteoporosis in men with hip fracture. Arch Intern Med 2002; 162: 2217–22.

Received 12 March 2012; accepted in revised form 21 November 2012

Age and Ageing 2013; **42:** 324–330
doi: 10.1093/ageing/aft044

© The Author 2013. Published by Oxford University Press on behalf of the British Geriatrics Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by-nc/3.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Which part of the Quick mild cognitive impairment screen (Q*mci*) discriminates between normal cognition, mild cognitive impairment and dementia?

Rónán O'Caoimh[1], Yang Gao[1], Paul Francis Gallagher[2], Joesph Eustace[3], Ciara McGlade[1], D. William Molloy[1]

[1]Centre for Gerontology and Rehabilitation, St Finbarrs Hospital, Douglas Road, Cork City, Ireland
[2]Department of Geriatric Medicine, School of Medicine, Cork University Hospital, University College Cork, Cork, Ireland
[3]Clinical Research Facility, College of Medicine and Health, University College Cork, Cork, Ireland

Address correspondence to: R. O'Caoimh. Tel: 00353 86 3241795. Email: rocaoimh@hotmail.com

Abstract

Introduction: the Q*mci* is a sensitive and specific test to differentiate between normal cognition (NC), mild cognitive impairment (MCI) and dementia. We compared the sensitivity and specificity of the subtests of the Q*mci* to determine which best discriminated NC, MCI and dementia.
Objective: the objective was to determine the contribution each subtest of the Q*mci* makes, to its sensitivity and specificity in differentiating MCI from NC and dementia, to refine and shorten the instrument.

Methods: existing data from our previous study of 965 subjects, testing the Q*mci,* was analysed to compare the sensitivity and specificity of the Q*mci* subtests.
Results: all the subtests of the Q*mci* differentiated MCI from NC. Logical memory (LM) performed the best (area under the receiver operating curve of 0.80), registration the worst, (0.56). LM and verbal fluency had the largest median differences (expressed as percentage of total score) between MCI and NC, 20 and 25%, respectively. Other subtests did not have clinically useful differences. LM was best at differentiating MCI from NC, irrespective of age or educational status.
Conclusion: the Q*mci* incorporates several important cognitive domains making it useful across the spectrum of cognitive impairment. LM is the best performing subtest for differentiating MCI from NC.

Keywords: *Quick mild cognitive impairment screen, mild cognitive impairment, standardised Mini-Mental State Examination, sensitivity and specificity, cognitive domains*

Introduction

As time is limited in clinical practice, short cognitive screens help to improve diagnostic efficiency and are useful in detecting and quantifying cognitive impairment. One of the major challenges in cognitive testing has been the development of rapid screening tests to differentiate mild cognitive impairment (MCI) from normal cognition (NC). Tools, such as the Folstein MMSE [1] and standardised Mini-Mental State Examination (SMMSE) [2, 3], are useful in distinguishing NC and MCI from dementia, but take time to complete, and are less able to distinguish MCI from NC [4, 5]. Identifying MCI is important as it can be a prodrome to dementia [6] and allows earlier recognition of individuals at risk [7]. Although treatment options are limited, a diagnosis of MCI should prompt the search for reversible causes of cognitive impairment. The International Working Group on MCI suggested that population screening cannot be recommended at present, as there is insufficient evidence for sensitive and specific tools, including cognitive tests [7]. Few tools used for detecting MCI are specific for the condition, because they were developed as dementia screening tests [8]. Some, such as the Montreal Cognitive Assessment (MoCA) [9], the Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-cog) [10] and the AB Cognitive Screen 135 (ABCS 135) [5], have shown improved sensitivity for detecting MCI when compared with the SMMSE.

The MoCA is widely used and valid in different clinical settings including Parkinson's disease, cerebrovascular disease [11] and Huntington's disease [12], but takes at least 10 min to perform. The ADAS-cog [10] also screens for MCI [13], but takes up to 45 min, requires trainings [14] and has ceiling effects, possibly limiting its usefulness [15, 16]. The addition of executive function and functional ability subtests has recently improved its sensitivity [16]. The ABCS 135 is more sensitive and shorter than the SMMSE at differentiating MCI from NC and dementia [5]. It is composed of five subtests, orientation, registration, clock drawing, delayed recall for words (DR) and verbal fluency (VF) for animals. The Q*mci*, the Quick mild cognitive impairment screening test, was developed to improve upon the ABCS 135 and is more sensitive and specific in differentiating MCI from NC [4].

Development of the Q*mci*

The Q*mci* was created from the ABCS 135, by reweighting the original subtests and adding a logical memory (LM) section. Previous analysis of the ABCS 135 subtests found that DR and VF were more sensitive than orientation, registration and clock drawing, in distinguishing MCI from NC [17]. LM, a verbal memory test, using immediate recall, was added because it is highly sensitive and specific in differentiating MCI from NC [18]. The original subtests had their absolute scores reduced, to allow for the introduction of LM, with the weightings of DR and VF increasing relative to the others. Orientation scores 10 points, registration 5, clock drawing 15, DR and VF 20 each and LM 30. The Q*mci* total score of 100 points is easier to use than a total score of 135, in the original ABCS 135.

The Q*mci*, therefore, has six subtests covering the following cognitive domains: orientation, working memory (registration), visuospatial/executive function (clock drawing), semantic memory (VF) and two episodic memory domains (DR and LM). The Q*mci* can be completed in 3–5 min, median time 4.24, and is more sensitive than the SMMSE and ABCS 135 in discriminating MCI from NC and dementia [4]. It is more clinically useful than these other tests, as it has greater median percentage differences between subjects with MCI and NC [4].

The primary objective of this study was to compare the sensitivity and specificity of different subtests of the Q*mci* in differentiating between NC, MCI and dementia. The secondary objective was to assess the effect of age and educational attainment on the sensitivity and specificity of individual Q*mci* subtests.

Methods

Subjects

Subjects were recruited between 2004 and 2010 from patients attending four memory clinics in Ontario, Canada. A total of 1,006 subjects were assessed, 53 were excluded, 965 individuals were included; 16% ($n = 154$) had MCI, 19% ($n = 181$) dementia and 65% ($n = 630$) NC. Normal controls, selected by convenience sampling, comprised exclusively of caregivers attending with the subjects, without

symptoms of memory loss. Subjects were excluded if they were unable to communicate verbally in English ($n = 12$), if they had depression ($n = 33$), including 21 controls with subjective memory loss but NC, or if a reliable collateral history was unavailable ($n = 8$). Parkinson's disease and Lewy body dementia cases were excluded as they typically present with marked functional impairment and a different MCI syndrome [19].

Dementia was diagnosed based on NINCDS [20] and DSM-IV criteria [21] and was correlated with the Reisberg FAST scale [22]. The majority (78%) of dementia cases were mild ($n = 141$). Removing moderate and severe cases did not affect sensitivity [4]. As no consensus on diagnostic criteria exists [23], MCI was diagnosed clinically, by a consultant geriatrician following a comprehensive assessment of patients with recent, subjective and or corroborated memory loss without obvious loss of function. Assessment included comprehensive history, physical examination, laboratory screening, functional assessment, behavioural scores and depression screening (Geriatric Depression Scale, GDS, greater than seven [24]). No objective cognitive test was used in the classification of MCI. This in keeping with criteria previously proposed by the MCI Working Group of the European Consortium on Alzheimer's Disease (EADC) [25], but differs from others such as the International Working group on MCI [7] which suggests the use of objective cognitive testing. Cognitive tests were performed in random order, by trained raters, blind to the diagnosis and prior to the assessment.

The functional level was measured using the Quick Activity of Daily Living (Q*adl*) score, unpublished work, measuring basic and instrumental ADLs. Unless there was co-existing physical disability, all subjects with MCI had normal Q*adl* scores. Subjects with dementia varied, depending upon stage and physical disability. Behaviours were recorded using the Quick Behaviour score, unpublished work, which condenses 12 items from the Dysfunctional Behaviour Rating Instrument [26]. The most frequent behaviour reported was repetition, 81.9% for dementia, 82.1% for MCI, $P = 0.36$. Statistically significant differences were seen for social withdrawal, 47.5% for dementia versus 22.4% for MCI, $P = 0.003$, sleep disturbance (61.4 versus 46%, $P = 0.05$) and aggression (10.5 versus 1.5%, $P = 0.038$). Ethical approval was obtained and subjects provided consent.

Data analysis

Data were analysed using SPSS 16.0. Subgroup analysis was performed for age (greater and less than 75 years, to provide balance in sample size between groups) and for years of formal education (greater or less than 12 years, based upon UNESCO data [27]). Normality was tested using the Shapiro–Wilk test. The majority of the data were not normally distributed and were analysed using a Mann–Whitney *U* test. Normally distributed data were analysed using Student's *t*-tests. Pearson Chi-squared tests were used to establish the difference between the distributions when it was not possible to analyse differences in medians. Receiver operating characteristics (ROC) curves were constructed based upon the sensitivity and specificity of the Q*mci* subtests. Area under the curve (AUC) was calculated for each subtest and analysed for age and years of education. Nine subjects, without complete data, were excluded from this analysis. Test–retest reliability was demonstrated by measuring the Q*mci* on two separate occasions, 1 week apart, for a small sample of subjects, chosen by simple randomisation, $n = 20$. Pearson's correlation coefficient showed good test–retest correlation, 0.86.

Results

Figure 1 shows box plot distributions for each Q*mci* subtest, with median and inter-quartile range (IQR) scores for subjects with dementia, MCI and NC. The VF and LM subtests of the Q*mci* clearly distinguish between dementia, MCI and NC. Orientation and registration did not show a median difference between MCI and NC. All individual subtests had statistically significant differences, $P < 0.001$, in distributions between NC, MCI and dementia.

Table 1 shows the median scores and IQR's for the Q*mci* subtests along with the *P*-value of the median difference between the scores of subjects with either MCI and NC or MCI and dementia. The overall median scores and differences are also shown for the Q*mci* as a whole. Although there were statistically significant differences between Q*mci* subtests scores, they were not all able to differentiate MCI and NC in a clinically useful way. The median difference in scores between MCI and NC was clinically useful for DR (four point difference), VF (four points) and LM (7.5 points). These differences, expressed as a percentage of the total score for each subtest, are 20% (four point difference out of a total score of 20), for DR, 20% for VF and 25% for LM. There was a median one point difference for clock drawing (6.66%), and no difference (0%), for orientation and registration, between MCI and NCs, suggesting that these three subtests are clinically less useful.

ROC curves in Figure 2a illustrate the sensitivity and specificity of the Q*mci* in differentiating NC from MCI, compared with the ABCS 135 and the SMMSE. The Q*mci* performs better in distinguishing NC from MCI with an AUC of 0.86, compared with the ABCS 135 (0.82), and the SMMSE (0.67). Taken in isolation, the LM component of the Q*mci*, scored higher than the ABCS 135 and SMMSE (AUC of 0.80 and 0.67, respectively). We also examined the individual subtests of the Q*mci* to assess their accuracy. The ROC curves in Figure 2b compare the ability of the subtests to discriminate between MCI and NC. The most accurate subtest is LM (AUC of 0.80), followed by VF (0.77), and DR (0.73). Registration (0.56), orientation (0.57) and clock drawing (0.66) were the least accurate subtests. The best performing SMMSE subtest was short-term memory (0.66), the worst registration (0.51).

The Q*mci* (total), ABCS 135, SMMSE and LM subtest had similar performance in differentiating MCI from

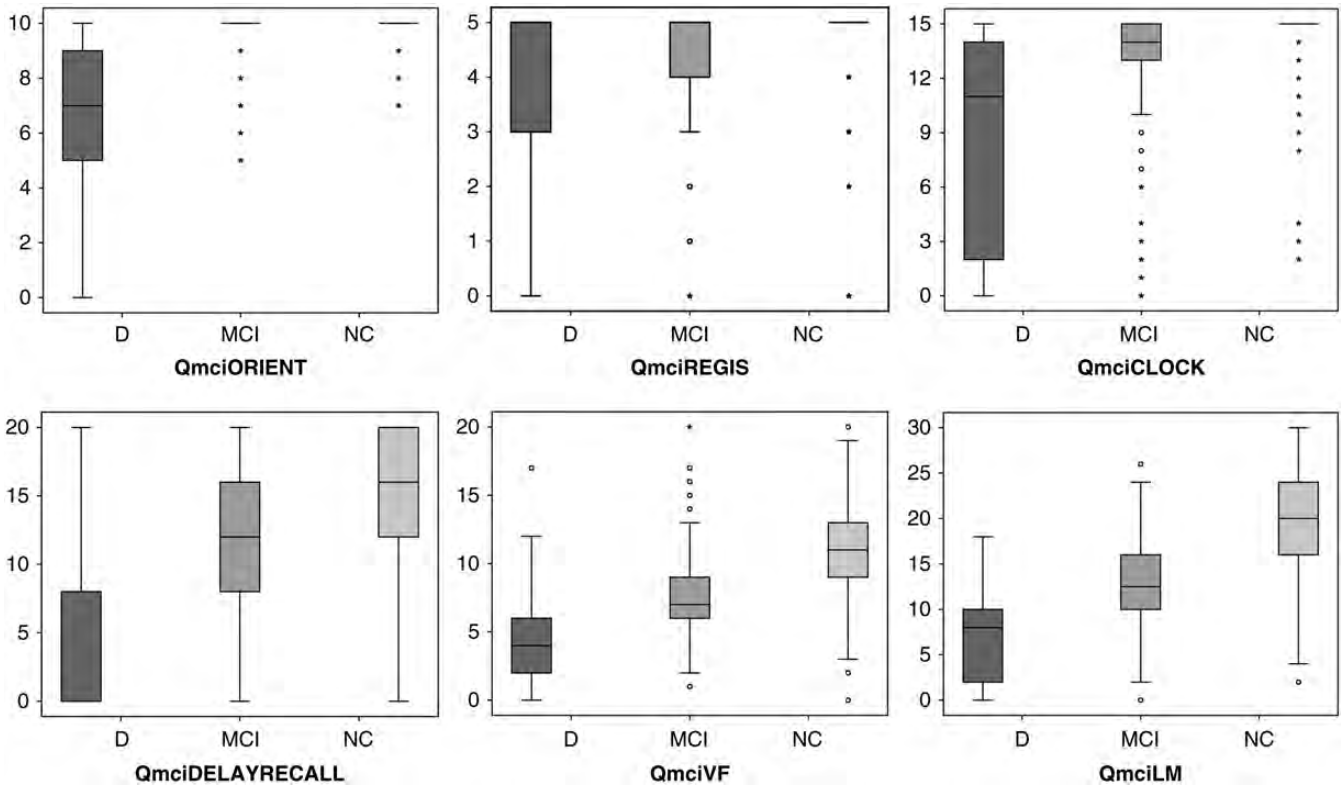


Figure 1. Box plots distributions for each subtest of the Q*mci* showing the median and inter-quartile range scores for dementia (D), mild cognitive impairment (MCI) and normal cognition (NC).

Table I. Q*mci* subtests: median scores and IQR (Q1 = 1st Quartile, Q3 = 3rd Quartile) by diagnosis, and *P*-value of the median difference between MCI and NC, dementia and MCI, along with AUC scores for SMMSE and the best performing Q*mci* subtest, LM, by age and education, for differentiating NC from MCI

Item	NC median (Q3-Q1 = IQR) (*n* = 630)	MCI median (Q3-Q1 = IQR) (*n* = 154)	Dementia median (Q3-Q1 = IQR) (*n* = 181)	*P*-value of the median diff between MCI-NC	*P*-value of the median diff between MCI-Dementia
Q*mci* total	76 (83–69 = 14)	62 (68–53 = 15)	36 (45–23 = 22)	$P < 0.001$	$P < 0.001$
Q*mci* subtests (score out of)					
Orientation (10)	10 (10–10 = 0)	10 (10–9 = 1)	7 (9–5 = 4)	$P < 0.001$	$P < 0.001$
Registration (5)	5 (5–5 = 0)	5 (5–4 = 1)	5 (5–3 = 2)	$P < 0.001$	$P = 0.002$
Clock drawing (15)	15 (15–15 = 0)	14 (15–13 = 2)	11 (14–2 = 12)	$P < 0.001$	$P < 0.001$
Delayed recall (20)	16 (20–12 = 8)	12 (16–8 = 8)	0 (8–0 = 8)	$P < 0.001$	$P < 0.001$
Verbal fluency (20)	11 (13–9 = 4)	7 (9–6 = 3)	4 (6–2 = 4)	$P < 0.001$	$P < 0.001$
Logical memory (30)	20 (24–16 = 8)	12.5 (16–10 = 6)	8 (10–2 = 8)	$P < 0.001$	$P < 0.001$
Group (MCI and NC, *n* = X)	Test variables	Area under curve (95% CI)	Median diff MCI and NC (*P*-value)		
Age ≤75 with education <12 years *n* = 127	SMMSE	0.65 (0.54–0.76)	29 ($P = 0.011$)		
	LM	0.72 (0.62–0.82)	15.49[a] (mean) ($P < 0.001$)		
Age ≤75 with education ≥12 years *n* = 449	SMMSE	0.66 (0.57–0.75)	29 ($P < 0.001$)		
	LM	0.79 (0.73–0.86)	20 ($P < 0.001$)		
Age >75 with education <12 years *n* = 71	SMMSE	0.64 (0.51–0.77)	28 ($P = 0.034$)		
	LM	0.74 (0.62–0.85)	14.35[a] (mean) ($P < 0.001$)		
Age >75 with education ≥12 years *n* = 127	SMMSE	0.55 (0.44–0.66)	29 ($P = 0.350$)		
	LM	0.79 (0.71–0.88)	16.91[a] (mean) ($P < 0.001$)		
Overall	SMMSE	0.67 (0.62–0.72)	29 ($P < 0.001$)		
	LM	0.80 (0.76–0.84)	18 ($P < 0.001$)		

[a]Normally distributed data.

dementia. LM, alone, performed particularly well with an AUC of 0.82. The AUC for the Q*mci* total score was 0.92 (95% CI: 0.89–95), suggesting it has similar accuracy, in differentiating MCI from dementia, to the ABCS 135 (AUC 0.91; 95% CI: 0.88–0.94) and the SMMSE (0.91; 95% CI: 0.86–0.94). Each of the subtests of the Q*mci*

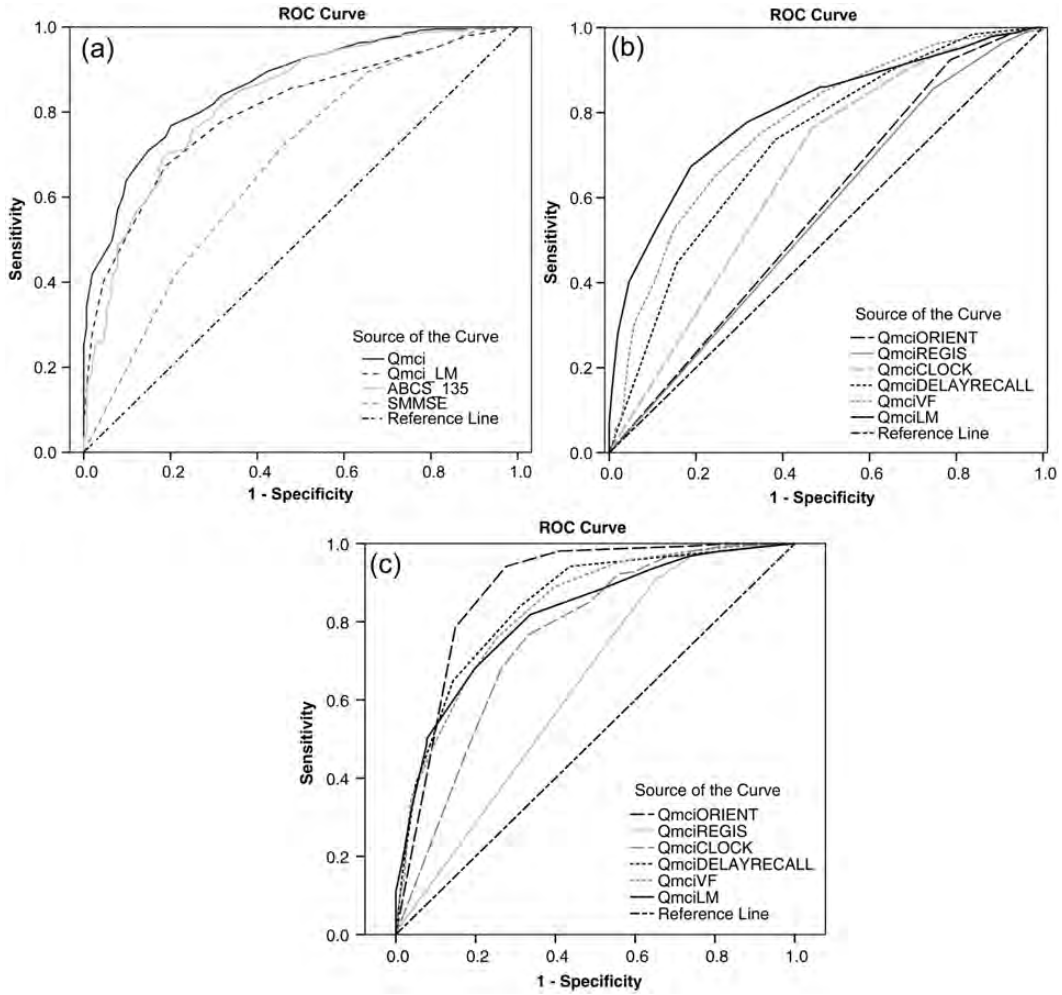


Figure 2. ROC curves illustrating the sensitivities and specificities of (*a*) Q*mci*, logical memory component (LM) of the Q*mci*, ABCS 135 and SMMSE in differentiating MCI from NC (*b*) Q*mci* subtests in differentiating MCI from NC and (*c*) Q*mci* subtests, in differentiating dementia from MCI. *Area under the curve (AUC).

accurately distinguished MCI from dementia, (see Figure 2c). The best tests were orientation (AUC of 0.88) and DR (0.84). Registration was again the worst performing test (AUC of 0.64). The best performing SMMSE subtest was orientation (0.82) and the worst was registration (0.54).

Table 1 also shows AUC values for the SMMSE compared with the best performing subtest, LM. The AUC for the LM was superior to the SMMSE, in differentiating MCI from NC, irrespective of the educational level, or age (over or under 75 years) of subjects. The improved performance of LM over the SMMSE was more evident for the older age group (age over 75) who had over 12 years of formal education, AUC of 0.79 (95% CI: 0.71–0.88) versus 0.55 (95% CI: 0.44–0.66). There was a significant difference between the median scores for LM, for the MCI and NC groups, irrespective of age or educational status. This difference was not significant for the SMMSE for older people, >75 years with >12 years in education ($P = 0.350$).

Conclusion

The importance of MCI is only matched by difficulties in its diagnosis, particularly in its differentiation from NC. The Q*mci* can differentiate MCI from NC and is more sensitive and specific than the SMMSE and ABCS 135 in distinguishing MCI from NC and dementia [4]. The Q*mci* includes a battery of subtests, but not all differentiate MCI from NC in a clinically useful way. This study found that subtests with the greatest median differences between MCI from NC, expressed as a percentage of their total scores, were DR, VF and LM. LM, added to the original ABCS 135, improved the sensitivity of the test in differentiating MCI from NC and is the most useful subtest of the Q*mci*. Orientation, registration and clock drawing, as individual subtests, do not enhance the discriminating power of the tool to the same extent. These subtests have lower ceilings and are insensitive to early cognitive changes [17]. When age and education were taken into account, the best performing subtest, LM, was more accurate than the SMMSE

in differentiating MCI from NC, suggesting that alone, it may be better at distinguishing MCI in the oldest and most educated subjects. All subtests could differentiate dementia from MCI and NC. None of the SMMSE subtests performed better than the complete SMMSE or LM.

From the results, we conclude that tests targeting episodic memory (DR and LM) best discriminate MCI from NC, whereas orientation is best for assessing dementia, allowing the Q*mci* accurately monitor disease progression. The remaining subtests, further enhance sensitivity, structure the test and may enhance its ability to identify MCI syndromes that convert to different dementia subtypes.

The strength of this study is that it included large numbers of patients with MCI and dementia, and that the tool was validated in a clinical sample in a busy memory clinic, increasing the generalisability of these results. A weakness is that it compares the Q*mci* to the SMMSE and ABCS 135, which are not gold standards for diagnosing MCI or dementia. No objective cognitive testing was used in the diagnosis of MCI which may also have led to bias although the diagnosis and criteria remain ill-defined [23]. The GDS, used to support a diagnosis of depression, is limited in advanced dementia [28], although the majority of subjects in this study were at an early stage. Subjects were only classified with MCI if there was no evidence of functional impairment. This may have created bias given that evidence suggests that up to 30% of subjects with MCI may have subtle impairment in instrumental ADLs [29]. Another limitation is that the reweighting of the subtests in favour of DR, VF and LM, may have overestimated their contribution to the sensitivity of the Q*mci*, minimising the role of the other subtests. However, the overall improved sensitivity of the Q*mci* over the ABCS 135, in differentiating MCI from NC, suggests that the reweighting and addition of LM, have enhanced the test as a whole. Including only caregivers, attending with subjects, as normal controls, could also have led to bias, as the challenge in diagnosing MCI lies in differentiating MCI from persons with subjective memory problems who have NC. This population accounts for up to 50% of referrals in memory clinics [30], but accounted for <10% of our clinic population.

In summary, this study confirms that reweighting the Q*mci* subtests and adding LM, improved the ability of the original ABCS 135, to differentiate subjects with MCI and NC. This paper further highlights and describes some attributes of an ideal short cognitive screening test for MCI that can be used in everyday clinical practice. The Q*mci* incorporates several important cognitive domains, across the spectrum of cognition and its subtests allow discrimination of MCI from both NC and dementia, allowing monitoring of progression. The Q*mci* also has the advantage of being quick to administer, easily translatable (linguistically and culturally), and of having alternative forms. Other tools, such as the SMMSE and the ABCS 135, are less sensitive and because of their scoring range, are less practical for use clinically. Comparison with other rapid screening tools, such as the MoCA, is now required.

Key points

- All subtests of the Q*mci* differentiated MCI from NC and dementia.
- LM is the best performing test, registration the worst.
- LM is the best subtest at distinguishing mild cognitive impairment in the oldest and most educated people.

Conflicts of interest

None declared.

Funding

The Centre for Gerontology and Rehabilitation is funded by Atlantic Philanthropies and the Health Service Executive of Ireland.

References

1. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
2. Molloy DW, Alemayehu E, Roberts R. Reliability of a standardized Mini-Mental State Examination compared with the traditional Mini-Mental State Examination. Am J Psychiatry 1991; 148: 102–5.
3. Molloy DW, Standish TIM. A guide to the Standardized Mini-Mental State Examination. Int Psychogeriatrics 1997; 9: 87–94.
4. O'Caoimh R, Gao Y, McGlade C *et al*. Comparison of the Quick Mild Cognitive Impairment (Q*mci*) screen and the SMMSE in Screening for mild cognitive impairment. Age Ageing 2012; 41(5): 624–9.
5. Molloy DW, Standish TIM, Lewis DL. Screening for mild cognitive impairment: comparing the SMMSE and the ABCS. Can J Psychiatry 2005; 50: 52–8.
6. Morris JC, Storandt M, Miller JP *et al*. Mild cognitive impairment represents early-stage Alzheimer's disease. Arch Neurol 2001; 58: 397–405.
7. Winblad B, Palmer K, Kivipelto M *et al*. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Int Med 2004; 256: 240–46.
8. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. Neurology 2001; 56: 37–42.
9. Nasreddine ZS, Philips NA, Bedirian V *et al*. The Montreal Cognitive Assessment, MoCA: a Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc 2005; 53: 695–9.
10. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984; 141: 1356–64.
11. Videnovic A, Bernard B, Fan W, Jaglin J, Leurgans S, Shannon KM. The Montreal Cognitive Assessment as a screening tool for cognitive dysfunction in Huntington's disease. Mov Disord 2010; 25: 401–4.

12. Wong A, Xiong YY, Kwan PWL *et al*. The Validity, Reliability and Clinical Utility of the Hong Kong Montreal Cognitive Assessment (HK-MoCA) in patients with cerebral small vessel disease. Dement Geriatr Cogn Disord 2009; 28: 81–7.
13. Perneczky R, Pohl C, Sorg C *et al*. Complex activities of daily living in mild cognitive impairment: conceptual and diagnostic issues. Age Ageing 2006; 35: 240–5.
14. Peña-Casanova J. Alzheimer's Disease Assessment Scale—cognitive in clinical practice. Int Psychogeriatrics 1997; 9: 105–14.
15. Mohs RC, Knopman D, Petersen RC *et al*. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11(Suppl. 2): S13–21.
16. Skinner J, Carvalho JO, Potter GG *et al*.; for the Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. Brain Imaging Behav 2012; 6(4): 489–501.
17. Standish T, Molloy DW, Cunje A, Lewis DL. Do the ABCS 135 short cognitive screen and its subtests discriminate between normal cognition, mild cognitive impairment and dementia? Int J Geriatr Psychiatry 2007; 22: 189–94.
18. Cunje A, Molloy DW, Standish TI, Lewis DL. Alternative forms of logical memory and verbal fluency tasks for repeated testing in early cognitive changes. Int Psychogeriatrics 2007; 19: 65–75.
19. Caviness JN, Driver-Dunckley E *et al*. Mov Disord 2007; 22: 1272–1277.
20. McKhann G, Drachman DA, Folstein MF *et al*.. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939–44.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. American Psychiatric Association: Washington, DC, 1994.
22. Reisberg B. Functional Assessment Staging (FAST). Psychopharmacol Bull 1988; 24: 653–9.
23. Morris JC. Revised criteria for mild cognitive impairment may compromise the diagnosis of Alzheimer disease dementia. Arch Neurol 2012; 69: 700–708.
24. Yesavage JA. Geriatric depression scale. Psychopharmacol Bull 1988; 24: 709–11.
25. Portet F, Ousset PJ, Visser PJ *et al*., the MCI Working Group of the European Consortium on Alzheimer's Disease (EADC). Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. J Neurol Neurosurg Psychiatry 2006; 77: 714–8.
26. Molloy DW, Bédard M, Guyatt GH, Lever J. Dysfunctional Behavior Rating Instrument (DBRI). Int Psychoger 1997; 8: 333–41.
27. Average years of schooling of adults by country', UNESCO. Retrieved from: http://www.NationMaster.com/graph/edu_ave_yea_of_sch_of_adu-education-average-years-schooling-adults.
28. Artero S, Touchon J, Ritchie K. Disability and mild cognitive impairment: a longitudinal, population-based study. Int J Geriatr Psychiatry 2001; 16: 1092–7.
29. Burke WJ, Houston MJ, Boust SJ, Roccaforte WH. Use of the Geriatric Depression Scale in dementia of the Alzheimer type. J Am Geriatr Soc 1989; 37: 856–60.
30. Steenland K, Macneil J, Bartell S, Lah J. Analyses of diagnostic patterns at 30 Alzheimer's disease centers in the US. Neuroepidemiology 2010; 35: 19–27.

Received 12 March 2012; accepted in revised form 21 November 2012

Age and Ageing 2013; **42:** 330–338
doi: 10.1093/ageing/afs196

© World Health Organization [2013]. All rights reserved.
The World Health Organization has granted the Publisher permission for the reproduction of this article.

Socio-demographic determinants of caregiving in older adults of low- and middle-income countries

AHMAD REZA HOSSEINPOOR, NICOLE BERGEN, SOMNATH CHATTERJI

Department of Health Statistics and Information Systems, World Health Organization, 20, Ave. Appia, Geneva, Switzerland

Address correspondence to: A. R. Hosseinpoor. Tel: +41 22 791 3205; Fax: +41 22 791 1584. E-mail: hosseinpoora@who.int

Abstract

Background: caregivers make substantial contributions to health and social systems, but many low-resource settings lack reliable data about the determinants and experiences of older adults who are caregivers.

ELSEVIER

Journal of Clinical Epidemiology 67 (2014) 87–92

Journal of Clinical Epidemiology

The Quick Mild Cognitive Impairment screen correlated with the Standardized Alzheimer's Disease Assessment Scale–cognitive section in clinical trials☆

Rónán O'Caoimh[a,*], Anton Svendrovski[b], Bradley C. Johnston[b], Yang Gao[a], Ciara McGlade[a], Joseph Eustace[c], Suzanne Timmons[a], Gordon Guyatt[b], D. William Molloy[a]

[a]*Department of Gerontology and Rehabilitation, St Finbarr's Hospital, Douglas Road, Cork City, Ireland*
[b]*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*
[c]*Clinical Research Facility, College of Medicine and Health, University College Cork, Mercy University Hospital, Grenville Place, Cork City, Ireland*

Accepted 9 July 2013; Published online 25 September 2013

Abstract

Objectives: The Alzheimer's Disease Assessment Scale–cognitive section and its standardized version (SADAS-cog) are the current standard for assessing cognitive outcomes in clinical trials of dementia. This study compares a shorter cognitive instrument, the Quick Mild Cognitive Impairment (Q*mci*) screen, with the SADAS-cog as outcome measures in clinical trials.

Study Design and Setting: The SADAS-cog, Q*mci*, Clinical Dementia Rating (CDR) scale, and the Lawton–Brady activities of daily living (ADL) scale were assessed at multiple time points, over 1 year in a multicenter randomized clinical trial of 406 patients with mild to moderate Alzheimer's dementia. Correlations were estimated using regression at each time point, all time points, and mean values across time. Responsiveness was assessed using the standardized response mean (SRM).

Results: Regression for pooled time points showed strong and significant correlation between the SADAS-cog and Q*mci* ($r = -0.75$, $P < 0.001$). Correlations remained strong for mean values across time and at each time point. The SADAS-cog and Q*mci* also correlated with CDR and ADL scores. There was no difference in SRMs between the SADAS-cog and Q*mci* [$t(357) = -0.32$, $P = 0.75$].

Conclusion: The Q*mci* correlated strongly with the SADAS-cog and both were equally responsive to deterioration. We suggest that clinicians and investigators can substitute the shorter Q*mci* for the SADAS-cog. © 2014 The Authors. Published by Elsevier Inc. All rights reserved.

Keywords: Quick Mild Cognitive Impairment (Q*mci*) screen; Standardized Alzheimer's Disease Assessment Scale–cognitive section (SADAS-cog); Clinical Dementia Rating (CDR) scale; Short cognitive screen; Correlation; Clinical trials

1. Introduction

A number of cognitive screening instruments are used in clinical care and research. To standardize assessments and allow comparison between settings, there is a need for valid and reliable cognitive assessment tools. No single cognitive screening instrument is ideal, and to date, none are established as the standard [1]. Several are limited by their inability to detect significant variations between patients with respect to age and/or educational status [2]. Researchers and clinicians require short instruments that are reliable, valid, and responsive to change across a wide range of cognitive function. They need multiple standardized scoring formats that measure changes early (high ceiling) and in the later stages of dementia (low floor).

The existing accepted standard for measuring cognitive function in clinical trials in dementia is the Alzheimer's Disease Assessment Scale–cognitive section (ADAS-cog) [3–5]. The ADAS-cog has 11 domains, including word recall, object naming, command following, construction and ideational praxis, orientation, word recognition, language, speech comprehension, word finding and recall, and takes 30–40 minutes to complete [3]. Total scores range from 0 to 70; higher scores (≥18) indicate greater cognitive impairment. The minimal important change has been determined to be

Financial disclosure: This project was supported by an unrestricted grant from Atlantic Philanthropies (R14297). The original DARAD trial was supported by the Canadian Institutes of Health Research (FRN 79779).

Conflict of interest: The authors report no conflict of interest.

The DARAD trial is registered at www.controlled-trials.com—ISRCTN15039674.

☆ This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike License, which permits non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

* Corresponding author. Tel.: +353 86-324-1795.
E-mail address: rocaoimh@hotmail.com (R. O'Caoimh).

0895-4356/$ - see front matter © 2014 The Authors. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jclinepi.2013.07.009

What is new?

Key findings

- The Quick Mild Cognitive Impairment (Q*mci*) screen correlates strongly and significantly to the Standardized Alzheimer's Disease Assessment Scale−cognitive section (SADAS-cog) over time.
- The Q*mci* had moderate correlation with the Clinical Dementia Rating scale and activities of daily living.

What this adds to what was known?

- This study confirms that short screening tools can be used instead of longer cognitive assessments in clinical trials.
- The Q*mci*, specifically designed to identify mild cognitive impairment, can be used to identify and measure cognitive impairment in clinical trials, potentially improving the ability to detect early cognitive changes in clinical trials.

What is the implication and what should change now?

- This study suggests that investigators could substitute the shorter Q*mci* for the SADAS-cog as a cognitive outcome measure in clinical trials, particularly where differentiating mild cognitive impairment from normal cognition and dementia is important.

approximately four points and many regulatory authorities, including the US Food and Drug Administration, require evidence of such change at 6 months to confirm the benefit of any new medication [6−8].

The ADAS-cog, although comprehensive and useful at different stages of dementia, has limitations. The ADAS-cog is long, requires training, and there is concern about the instruments' interrater reliability [9]. It also has a ceiling effect, limiting usefulness in the initial stages of dementia [10]. To overcome these limitations, the Standardized Alzheimer's Disease Assessment Scale−cognitive section (SADAS-cog) was developed, to improve interrater reliability using explicit administration and scoring guidelines [11]. The SADAS-cog is equally lengthy, taking up to 45 minutes.

1.1. The Quick Mild Cognitive Impairment screen

The Quick Mild Cognitive Impairment (Q*mci*) screen was developed to screen for mild cognitive impairment (MCI). The Q*mci* was refined from the AB Cognitive Screen (ABCS 135) [12], by reweighting the original subtests and adding a logical memory section. It measures cognition across a full range of cognition from normal cognition (NC) to MCI and severe dementia. The Q*mci* has six domains: orientation, registration, clock drawing, delayed recall, verbal fluency, and logical memory scored as follows: orientation (10), registration (5), clock drawing (15), registration (20), verbal fluency (20), and logical memory (30). It takes 3−5 minutes to complete. The Q*mci* is more sensitive and specific than the Standardized Mini-Mental State Examination (SMMSE) [13,14] at differentiating MCI from NC and dementia [12]. The Q*mci* is scored out of 100, and depending on age and educational levels, 50 is the cutoff for dementia. The Q*mci* can be completed in 3−5 minutes, median time of 4.24 minutes [15].

1.2. The DARAD trial

The doxycycline and rifampicin for Alzheimer's Disease (DARAD) was a multicenter, blinded, randomized controlled trial comparing two antibiotics, rifampicin and doxycycline, with placebo to confirm if preliminary evidence, suggesting that these antibiotics can delay the progression of Alzheimer's disease [16], was correct [17]. Outcome measures included functional, mood, behavioral, and two cognitive assessments, the SADAS-cog and Q*mci*.

We used data from the DARAD trial to compare the Q*mci* and SADAS-cog to determine if the Q*mci* is an alternative to the SADAS-cog as an outcome in clinical trials. We also investigated the extent to which the two tests were correlated and compared their validity and responsiveness (sensitivity to change).

2. Methods

2.1. Study sample

The DARAD trial investigated the use of two antibiotics, doxycycline and rifampicin, in 406 patients with mild to moderate Alzheimer's dementia. Subjects were randomized into four arms: doxycycline 100 mg twice daily with rifampicin 300 mg daily, doxycycline 100 mg twice daily with placebo rifampicin daily, rifampicin 300 mg daily with placebo doxycycline twice daily, or placebo doxycycline twice daily with placebo rifampicin daily [17]. Patients were recruited from 14 Canadian geriatric clinics between 2006 and 2010. The DARAD database contains data for a range of variables at 1, 3, 6, 9, and 12 months. Patients aged 50 years or more, meeting the National Institute of Neurological Disorders and Stroke (NINCDS) criteria for Alzheimer's disease [6], and with SMMSE scores between 14 and 26 were included. Patients were excluded if they were unable to communicate verbally in English.

2.2. Measures

The coprimary outcomes in the DARAD trial were the SADAS-cog and the Clinical Dementia Rating scale (CDR)

using the sum of the boxes technique [18,19]. Secondary outcomes included the Q*mci* and the Lawton–Brody activities of daily living (ADL) scale [20]. The Lawton–Brody scale measures both basic (Physical Self-Maintenance Scale) and instrumental (Lawton IADL scale) ADLs and has excellent interrater reliability [21]. The SADAS-cog, Q*mci*, and CDR were administered by a trained rater, in a random sequence, blinded to each study arm.

2.3. Data analysis

Data from the DARAD database were analyzed using SPSS, version 18 (SPSS, Chicago, IL, USA) [22]. The Shapiro–Wilk test was used to test normality and found that most data were approximately symmetrical, having a small deviation from normality. The median and interquartile range (IQR) were reported for skewed continuous data (age and SMMSE). This analysis included only those patients who had complete data. The correlations between the Q*mci* and the SADAS-cog were calculated using the data collected at 1, 3, 6, 9, and 12 months. The original values were standardized to remove within-subject variations, and simple regression analyses were run to estimate correlation coefficients. To address the validity of the two instruments, the relationship between both the SADAS-cog and the Q*mci* and two other variables (ADL and CDR) were analyzed using different analytical approaches. Correlations were analyzed at each time point, then for all time points together, and finally for mean values across time. Fisher's *Z* test was used to determine differences in correlations between tests.

To compare the responsiveness of the two instruments, at each time point, the standardized response mean (SRM), the mean score change divided by the standard deviation (SD) of the score change using baseline as the initial score, were calculated for the SADAS-cog and Q*mci*. Paired-samples *t* tests were performed to detect if a statistically significant difference existed in the SRM between the SADAS-cog and Q*mci*.

3. Results

Overall, 365 of the 406 patients who entered the DARAD study completed 1 year [17]. Median age of the total population was 79 years, IQR 10. Median SMMSE score at baseline was 23, IQR 5. More than 90% were taking a cholinesterase inhibitor and 13%, the N-Methyl-D-aspartate receptor antagonist, memantine. Three hundred sixty patients had complete data for the Q*mci* and 363 for the SADAS-cog, 364 for the ADL screen, and 360 for the CDR. Three hundred fifty-eight patients had complete data for the Q*mci* and SADAS-cog, at each time point, over the year.

Correlation coefficients between the outcome measures along with their confidence intervals (CIs), at each time point, at all time points, and using mean values across time

Table 1. Demonstrating correlation coefficients, with 95% confidence intervals, between the SADAS-cog and Q*mci*, Lawton–Brody activities of daily living (ADL) scale, and CDR using different analysis methods

Analysis method	Month	SADAS-cog to Q*mci* [correlation coefficient (95% CI)]	SADAS-cog to ADL [correlation coefficient (95% CI)]	Q*mci* to ADL [correlation coefficient (95% CI)]	Fisher *Z* test for difference in correlations with ADL	SADAS-cog to CDR [correlation coefficient (95% CI)]	Q*mci* to CDR [correlation coefficient (95% CI)]	Fisher *Z* test for difference in correlations with CDR
Correlations at each time point	1	−0.69 (−0.62, −0.76)	−0.31 (−0.21, −0.40)	0.26 (0.17, 0.36)	$z = 0.66$, $P = 0.51$	0.41 (0.32, 0.50)	−0.38 (−0.29, −0.47)	$z = 0.44$, $P = 0.66$
	3	−0.75 (−0.69, −0.82)	−0.41 (−0.32, −0.50)	0.32 (0.22, 0.42)	$z = 1.39$, $P = 0.17$	0.45 (0.36, 0.54)	−0.48 (−0.39, −0.57)	$z = -0.52$, $P = 0.60$
	6	−0.76 (−0.69, −0.83)	−0.44 (−0.34, −0.53)	0.34 (0.24, 0.44)	$z = 1.45$, $P = 0.15$	0.56 (0.48, 0.65)	−0.55 (−0.46, −0.64)	$z = 0.28$, $P = 0.78$
	9	−0.78 (−0.71, −0.85)	−0.46 (−0.36, −0.56)	0.39 (0.29, 0.49)	$z = 1.14$, $P = 0.25$	0.59 (0.50, 0.68)	−0.56 (−0.46, −0.65)	$z = 0.70$, $P = 0.48$
	12	−0.76 (−0.70, −0.83)	−0.49 (−0.40, −0.58)	0.45 (0.36, 0.55)	$z = 0.65$, $P = 0.51$	0.57 (0.49, 0.66)	−0.55 (−0.46, −0.64)	$z = 0.42$, $P = 0.67$
Unadjusted correlations using all time points together		−0.75 (−0.72, −0.78)	−0.42 (−0.37, −0.46)	0.37 (0.33, 0.42)	$z = 1.67$, $P = 0.09$	0.51 (0.47, 0.55)	−0.52 (−0.48, −0.56)	$z = -0.28$, $P = 0.78$
Unadjusted correlations using mean values across time		−0.80 (−0.74, −0.86)	−0.43 (−0.34, −0.52)	0.38 (0.29, 0.47)	$z = 0.75$, $P = 0.45$	0.54 (0.46, 0.62)	−0.54 (−0.46, −0.62)	$z = -0.02$, $P = 0.98$

Abbreviations: SADAS-cog, Standardized Alzheimer's Disease Assessment Scale–cognitive section; Q*mci*, Quick Mild Cognitive Impairment; CDR, Clinical Dementia Rating; CI, confidence interval.

are reported in Table 1. The correlation coefficients demonstrated significant strong correlation between the Q*mci* and the SADAS-cog, at each time point ($r = -0.69$; 95% CI: −0.62, −0.78; $P \leq 0.001$ for the first month and −0.76; 95% CI: −0.70; −0.83; $P \leq 0.001$ for the last month). The data most closely correlated at 9 months ($r = -0.78$; $P \leq 0.001$). Each patient was included five times (corresponding to each time point) in the calculation, which would be expected to inflate the value of the correlation coefficient. However, estimating correlations between measures overall, at all time points, pooled together, showed that the correlations between the SADAS-cog and Q*mci* remained strong and significant ($r = -0.75$; 95% CI: 0.72, 0.78; $P \leq 0.001$). Correlations increased to −0.8 using mean values across time.

The relationship between the SADAS-cog and Q*mci* and the other measures, ADL and CDR, at each of the five time points, showed modest to strong significant correlations. Correlations between the CDR and SADAS-cog (range from 0.41 to 0.59) were stronger than those between the ADL and SADAS-cog (range from −0.31 to −0.49). Fig. 1 provides the correlations between the SADAS-cog and Q*mci* and between the Q*mci* and SADAS-cog and the other variables, ADL and CDR, at each time point. CIs for correlations between the outcome measures at different time points overlap, indicating no difference between them. Fisher's *Z* test confirmed that there was no statistically significant difference in correlations between the SADAS-cog and Q*mci* with either ADL ($z = 1.67$; $P = 0.09$) or CDR scores ($z = -0.28$; $P = 0.78$). The correlation between the SADAS-cog and itself (Table 2A), across time points, varied from 0.79 to 0.91, higher than the correlations between the SADAS-cog and the Q*mci*, which ranged between 0.73 and 0.83 (Table 2B).

Responsiveness of the SADAS-cog and Q*mci*, determined using the SRM, demonstrated that the mean change in SADAS-cog scores, between months 1 and 12, calculated for each patient, was 5 points, with an SD of 7.56. The estimated mean difference in scores, repeated for the Q*mci*, was 5.41 points, SD of 10.02. Paired-samples *t* test showed that there was no statistically significant difference in the SRMs for SADAS-cog and Q*mci* [$t(357) = -0.32$, $P = 0.75$]. This means that the changes in Q*mci* scores are very similar to changes in SADAS-cog scores, between months 1 to 12.

There was a statistically significant increase in SADAS-cog scores from a mean of 21.56, SD of 7.89 at month 1, to a mean of 26.56, SD of 12.01 at month 12 [$t(362) = 12.60$, $P < 0.001$]. There was also a statistically significant decrease in Q*mci* scores from month 1 (mean = 38.58, SD = 12.83) to month 12 (mean = 32.76, SD = 15.593; $t(359) = -10.23$, $P < 0.001$).

4. Discussion

This study compared the SADAS-cog with the Q*mci*, ADL, and CDR, by comparing observations at multiple time points, from data collected in the DARAD trial, over 1 year. The SADAS-cog correlated closely with the Q*mci*, irrespective of the method of analysis. Although individual values of the Q*mci* corresponded to a relatively wide range of values on the SADAS-cog, high correlation between the two tests (0.69–0.76) demonstrates that the information

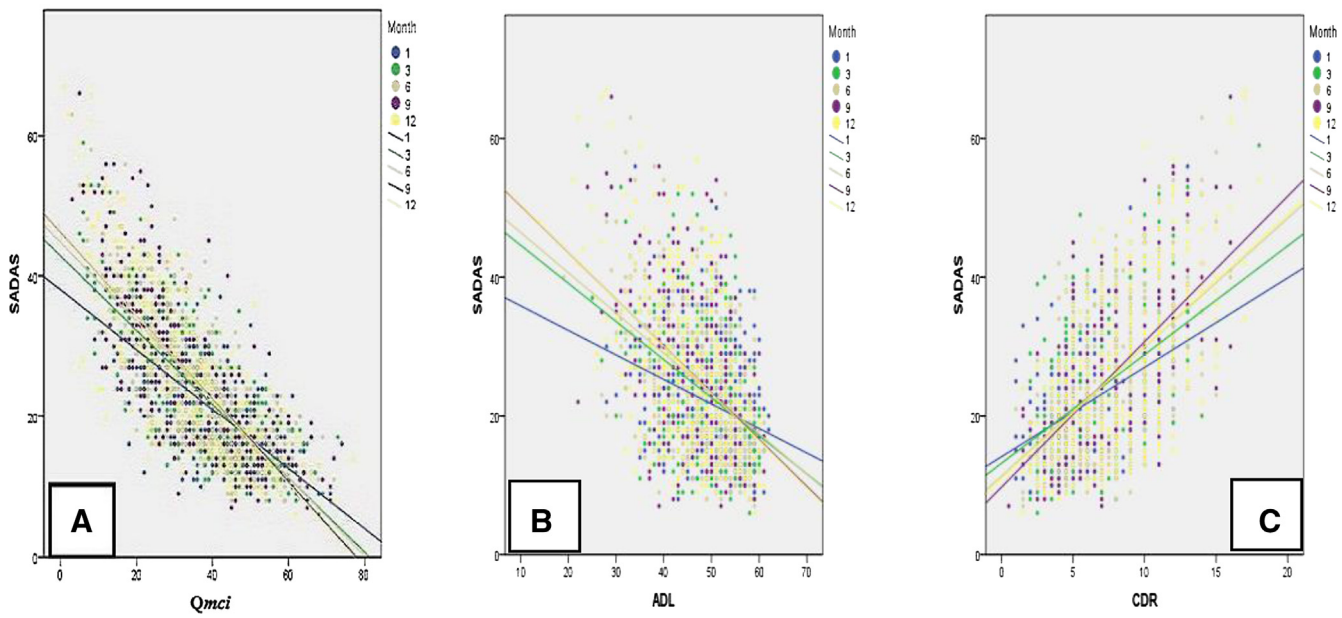


Fig. 1. Scatter plot depicting correlations between (A) SADAS-cog and Q*mci*, (B) SADAS-cog and Lawton–Brody activities of daily living (ADL) scale, and (C) SADAS-cog and CDR, at each time point (1, 3, 6, 9, and 12 months). SADAS-cog, Standardized Alzheimer's Disease Assessment Scale–cognitive section; Q*mci*, Quick Mild Cognitive Impairment; CDR, Clinical Dementia Rating.

Table 2. Correlation of (A) the SADAS-cog to itself and (B) the Q*mci* to itself, over each time point (1, 3, 6, 9, and 12 months)

A	(1)	(2)	(3)	(4)
(1) SADAS-cog at 1 mo	—			
(2) SADAS-cog at 3 mo	0.86[a]	—		
(3) SADAS-cog at 6 mo	0.86[a]	0.89[a]	—	
(4) SADAS-cog at 9 mo	0.83[a]	0.88[a]	0.90[a]	—
(5) SADAS-cog at 12 mo	0.79[a]	0.84[a]	0.87[a]	0.91[a]
B	**(1)**	**(2)**	**(3)**	**(4)**
(1) Q*mci* at 1 mo	—			
(2) Q*mci* at 3 mo	0.80[a]	—		
(3) Q*mci* at 6 mo	0.79[a]	0.83[a]	—	
(4) Q*mci* at 9 mo	0.77[a]	0.81[a]	0.83[a]	—
(5) Q*mci* at 12 mo	0.73[a]	0.76[a]	0.78[a]	0.82[a]

Abbreviations: SADAS-cog, Standardized Alzheimer's Disease Assessment Scale–cognitive section; Q*mci*, Quick Mild Cognitive Impairment screen.

[a] Correlation is significant at the 0.001 level.

obtained is sufficiently similar to justify substitution of the Q*mci*. Although the ratio of the mean change in Q*mci* scores between the first and final visits (5.41) to the SD of the change (10.02—ratio 0.54) is smaller than that for the SADAS-cog (5.0 and 7.56—ratio 0.68), both differences were significant at values of <0.001, and the apparent differences in SRMs are easily explained by chance ($P = 0.75$), suggesting that the Q*mci* and the SADAS-cog are equally sensitive to change and have similar responsiveness.

The SADAS-cog and Q*mci* also correlated with the ADL and CDR. The CI for correlation coefficient estimates for the Q*mci* and SADAS-cog and CI for correlations between the SADAS-cog and ADL or CDR did not overlap, indicating a significantly stronger relationship between the Q*mci* and SADAS-cog than between the ADL or CDR and SADAS-cog and Q*mci* scores. In other words, the Q*mci* and SADAS-cog are better predictors of each other than of the other two measures (ADL and CDR). This is expected given that the SADAS-cog and Q*mci* are discrete measures of cognitive function, which are distinct from ADLs [23]. Therefore, the magnitude of change in functional measures cannot be inferred from tests of cognitive function and requires direct measurement. This suggests that in addition to the use of cognitive testing, clinical trials in dementia should incorporate measures of ADLs.

The strength of this article lies in its methodology. Correlation between the SADAS-cog and each of the measures was demonstrated using different statistical methods. Each consistently confirmed strong correlation between the SADAS-cog and Q*mci* and moderate-to-strong correlation between the SADAS-cog and Q*mci*, ADL and CDR. The correlations demonstrated at each of the five time points were similar to the pooled correlation coefficients. Another strength, is that these data, a post hoc analysis of the DAR-AD trial database, represent the "real life" performance of the Q*mci*, compared with the accepted standard, in a previously conducted, multicenter, blinded, randomized controlled trial. Given that a four-point change, at 6 months, in the ADAS or SADAS-cog is widely recognized as a clinically significant difference [7,8], the similar responsiveness of the Q*mci* and SADAS-cog suggests that a comparable change in the Q*mci* is equivalent to a significant change in the SADAS-cog. Given that the Q*mci* is shorter and easier to score, these data support the use of the Q*mci* as an alternative to the SADAS-cog in clinical trials.

This article has several limitations. Although a four-point change in the SADAS-cog is traditionally accepted as significant, it is not an ideal test. Comparing the Q*mci* with the SADAS-cog only suggests that the Q*mci* has similar sensitivity and responsiveness, not that it is a "gold standard." Although useful, the Q*mci* is less comprehensive than the SADAS-cog and not all neuropsychological domains are accounted for. That said, in contrast to the SADAS-cog, the Q*mci* is shorter and easier to apply, covering many relevant cognitive domains including orientation, working memory, visuospatial, executive function, semantic memory, and episodic memory. In contrast, the SADAS-cog is overly long and heavily weighted toward language. The SADAS-cog, because of ceiling effects, is less responsive to detecting MCI [24], possibly limiting its usefulness. The Q*mci*, in contrast, is accurate at differentiating MCI from NC and dementia [12], suggesting that where this is the outcome measure of interest, the Q*mci* could be used in preference. Although the SADAS-cog requires substantial training [9], the Q*mci*, particularly the clock drawing subtest, also requires training. Explicit scoring and administration guidelines, including a clock-scoring template, are available to improve reliability. That said, clock drawing is a widely used screen for cognitive impairment [25], different scoring methods are consistent [26], and there is similar interrater reliability between trained and untrained raters [27]. It is also regarded as being the easiest and quickest stand-alone cognitive screen [25]. The ADL measure used in this study, the Lawton–Brody scale, has limitations. Although it has excellent interrater reliability [21] and measures both basic and instrumental ADLs, like most ADL measures it is self-reported, potentially over or underestimating functional impairment and is not a gold standard for measuring ADLs.

In summary, the ADAS-cog and its standardized form, the SADAS-cog, are valid, reliable, and widely used cognitive measures in clinical trials [17,20,28,29]. They have been validated internationally from Iceland [30] to Turkey [31] and Hong Kong [32] and despite flaws, remain the standard. These data demonstrate that the Q*mci* correlates strongly, significantly, and correspondingly over time to the SADAS-cog and that both are equally sensitive with similar responsiveness to deterioration over time. Although the correlation with each other was stronger, the SADAS-cog and Q*mci* had moderate to strong correlations with both functional (Lawton–Brody scale) and global assessments (CDR), confirming their utility in clinical practice and drug

trials. Although further validation will be required, this study provides a rationale for using the shorter Q*mci*, as a cognitive outcome measure in clinical drug trials, particularly where differentiating MCI from NC and dementia is important.

References

[1] Gifford DR, Cummings JL. Evaluating dementia screening tests: methodologic standards to rate their performance. Neurology 1999;52:224.

[2] Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386−91.

[3] Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356−64.

[4] O'Halloran JP, Kemp AS, Salmon DP, Tariot PN, Schneider LS. Psychometric comparison of standard and computerized administration of the Alzheimer's Disease Assessment Scale: Cognitive Subscale (ADAS-Cog). Curr Alzheimer Res 2011;8(3):323−8.

[5] Weyer G, Erzigkeit H, Kanowski S, Ihl R, Hadler D. Alzheimer's Disease Assessment Scale: reliability and validity in a multicenter clinical trial. Int Psychogeriatr 1997;9(2):123−38.

[6] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939−44.

[7] Matthews HP, Korbey J, Wilkinson DG, Rowden J. Donepezil in Alzheimer's disease: eighteen month results from Southampton Memory Clinic. Int J Geriatr Psychiatry 2000;5:713−20.

[8] Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al. Alzheimer's Disease Co- operative Study. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003;289:2819−26.

[9] Connor DJ, Sabbagh MN. Administration and scoring variance on the ADAS-Cog. J Alzheimers Dis 2008;15(3):461−4.

[10] Mohs RC, Knopman D, Petersen RC, Ferris SH, Ernesto C, Grundman M, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11(2):S13−21.

[11] Standish TI, Molloy DW, Bĕdard M, Layne EC, Murray EA, Strang D. Improved reliability of the standardized Alzheimer's Disease Assessment Scale (SADAS) compared with the Alzheimer's Disease Assessment Scale (ADAS). J Am Geriatr Soc 1996;44(6):712−6.

[12] O'Caoimh R, Gao Y, McGlade C, Healy L, Gallagher P, Timmons S, et al. Comparison of the quick mild cognitive impairment (Qmci) screen and the SMMSE in screening for mild cognitive impairment. Age Ageing 2012;41:624−9.

[13] Molloy DW, Standish TIM. A guide to the Standardized Mini-Mental State Examination. Int Psychogeriatr 1997;9(Suppl 1):87−94.

[14] Molloy DW, Standish TIM, Lewis DL. Screening for mild cognitive impairment: comparing the SMMSE and the ABCS. Can J Psychiatry 2005;50:52−8.

[15] O'Caoimh R, Gao Y, Gallagher P, Eustace J, McGlade C, Molloy DW. Which part of the Quick mild cognitive impairment screen (Q*mci*) discriminates between normal cognition, mild cognitive impairment and dementia? Age Ageing 2013;42:324−30.

[16] Loeb MB, Molloy DW, Smieja M, Standish T, Goldsmith CH, Mahony J, et al. A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. J Am Geriatr Soc 2004;52(3):381−7.

[17] Molloy DW, Standish TI, Zhou Q, Guyatt G. A multi-centre, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. Int J Geriatr Psychiatry 2013;28(5):463−70.

[18] Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412−4.

[19] Schafer KA, Tractenberg RE, Sano M, Mackell JA, Thomas RG, Gamst A, et al. Reliability of monitoring the Clinical Dementia Rating in multicenter clinical trials. Alzheimer Dis Assoc Disord 2004;18:219−22.

[20] Sano M, Bell KL, Galasko D, Galvin JE, Thomas RG, van Dyck CH, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. Neurology 2011;77:556−63.

[21] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179−86.

[22] SPSS Inc. SPSS for Windows 18.0. Chicago, IL: SPSS Inc; 2009.

[23] Reed BR, Jagust WJ, Seab JP. Mental status as a predictor of daily function in progressive dementia. Gerontologist 1989;29(6):804−7.

[24] Skinner J, Carvalho JO, Potter GG, Thames A, Zelinski E, Crane PK, et al. Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. Brain Imaging Behav 2012;6(4):489−501.

[25] Shulman KI, Herrman N, Brodaty H, Chiu H, Lawlor B, Ritchie K, et al. IPA survey of brief cognitive screening instruments. Int Psychogeriatr 2006;18:281−94.

[26] Juby A, Tench S, Baker V. The value of clock drawing in identifying executive cognitive dysfunction in people with a normal Mini-Mental State Examination score. CMAJ 2002;167(8):859−64.

[27] Lessig MC, Scanlan JM, Nazemi H, Borson S. Time that tells: critical clock-drawing errors for dementia screening. Int Psychogeriatr 2008;20(3):459−70.

[28] Rockwood K, Fay S, Song X, MacKnight C, Gorman M, Video-Imaging Synthesis of Treating Alzheimer's Disease (VISTA) Investigators. Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. CMAJ 2006;174(8):1099−105.

[29] Chen YH, Lin MS, Lee JK, Chao CL, Tang SC, Chao CC, et al. Carotid stenting improves cognitive function in asymptomatic cerebral ischemia. Int J Cardiol 2012;157:104−7.

[30] Hannesdóttir K, Snaedal J. A study of the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) in an Icelandic elderly population. Nord J Psychiatry 2002;56(3):201−6.

[31] Mavioglu H, Gedizlioglu M, Akyel S, Aslaner T, Eser E. The validity and reliability of the Turkish version of Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) in patients with mild and moderate Alzheimer's disease and normal subjects. Int J Geriatr Psychiatry 2006;21(3):259−65.

[32] Chu LW, Chiu KC, Hui SL, Yu GK, Tsui WJ, Lee PW. The reliability and validity of the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) among the elderly Chinese in Hong Kong. Ann Acad Med Singapore 2000;29(4):474−85.

C. The BMJ Open paper (*"Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia"*) Press Release List

Forbes

http://www.forbes.com/sites/larryhusten/2013/07/25/possible-cognitive-benefits-found-in-dementia-patients-taking-centrally-acting-ace-inhibitors/

NBC news

http://www.nbcnews.com/health/blood-pressure-drugs-may-help-alzheimers-study-suggests-6C10755394

The Times of London

http://www.thetimes.co.uk/tto/health/news/article3825493.ece

UK independent:

http://www.independent.co.uk/life-style/health-and-families/health-news/ace-inhibitor-drugs-offer-dementia-treatment-hope-8732915.html

World Health:

http://www.worldhealth.net/news/blood-pressure-drug-may-slow-cognitive-decline/

MNT (Medical News Today):

http://www.medicalnewstoday.com/articles/264008.php

NHS Choices, UK:

http://www.nhs.uk/news/2013/07july/Pages/Blood-pressure-drug-may-help-treat-dementia.aspx

Medpage Today:

http://www.medpagetoday.com/Cardiology/Dementia/40699

A3P:

http://en.a3p.org/index.php/fr/base-documentaire/breves/4673-alzheimer-une-%C3%A9tude-conforte-la-piste-des-m%C3%A9dicaments-contre-la-tension.html

Care Industry News

http://www.careindustrynews.co.uk/2013/07/use-of-blood-pressure-drugs-slows-cognitive-decline/

News in Australia

http://www.news.com.au/breaking-news/world/blood-pressure-drugs-slow-dementia/story-e6frfkui-1226686090462?from=public_rss

London Evening Standard

http://www.standard.co.uk/panewsfeeds/drug-offers-dementia-treatment-hope-8732874.html

NEJM Journal Watch

http://www.jwatch.org/fw107736/2013/07/26/centrally-acting-ace-inhibitors-seem-slow-cognitive

Pluse Today

http://www.pulsetoday.co.uk/clinical/therapy-areas/neurology/ace-inhibitors-slow-cognitive-decline-in-dementia/20003772.article#.UfKQ86Lz0Zc

Financial Press

http://financialpress.com/2013/07/26/possible-cognitive-benefits-found-in-dementia-patients-taking-centrally-acting-ace-inhibitors/

Heart Wire

http://www.theheart.org/article/1564673.do

Health Day:

http://consumer.healthday.com/cognitive-and-neurological-health-information-26/alzheimer-s-news-20/common-blood-pressure-drugs-may-help-slow-dementia-study-678636.html

Science Daily:

http://www.sciencedaily.com/releases/2013/07/130725202430.htm?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+sciencedaily%2Fmind_brain+(ScienceDaily%3A+Mind+%26+Brain+News)

Medscape:

http://www.medscape.com/viewarticle/808589

Healio Cardiology:

http://www.healio.com/cardiology/vascular-medicine/news/online/%7BF7A6B95A-114E-4689-B576-7FE89CA1C57D%7D/ACE-inhibitors-slowed-cognitive-decline-in-patients-with-dementia

Pri-med:

http://www.pri-med.com/pmo/MedicalNewsDetail.aspx?id=10240&topic=mc-topic::JJY7Y3J02

Dementia news:

http://dementianews.wordpress.com/2013/07/28/centrally-acting-ace-inhibitors-reduce-rate-of-cognitive-decline-in-dementia-bmj-open/

Alzheimer's Society:

http://www.alzheimers.org.uk/site/scripts/press_article.php?pressReleaseID=986

Science Index:

http://scienceindex.com/stories/3301916/Centrally_acting_ACE_inhibitors_in_dementia.html

Pharmacy Times:

http://www.pharmacytimes.com/news/Hypertension-Medications-Linked-to-Slower-Dementia-Progression

LAB Mate Online:

http://www.labmate-online.com/news/news-and-views/5/breaking_news/blood_pressure_medication_could_reduce_cognitive_decline_says_research/26282/

D. Key Instruments for this Research

Quick *Mild Cognitive Impairment* screen (Q*mci*)

Name: DOB: Years in Education: Date:

1. Orientation (one minute)

(Give 2 points for correct answer, 1 if attempted and incorrect, 0 if no attempt)

What country is this? _____

What year is this? _____

What month is this? _____

What is today's date? _____

What day of the week is this? _____

Score _____ / 10

2. Word Registration (30 seconds)

To begin say…
"I am going to say 5 words. After I have said these 5 words, repeat them back to me. Are you ready?" (Give 1 point per word repeated, in any order, no hints)

Dog	**rain**	**butter**	**love**	**door**

Score _____ / 5

Alternate word groups include…

cat	**dark**	**pepper**	**fear**	**bed**
rat	**heat**	**bread**	**round**	**chair**

© O'Caoimh R, Molloy D. W 2011.

3. Clock Drawing (one minute)

"Use the circle provided to draw a clock face, set the time to 'ten past eleven'."
(Give 1 mark for each number, 1 for each hand & 1 for the pivot correctly placed.
Loose 1 mark for each number duplicated or greater than 12, e.g, 15 or 45).

Score:	Numbers	Correct	+ _____/ 12
		Errors	- _____
	Hands		+ _____/ 2
	Pivot		+ _____/ 1
	Total		**+ _____/ 15**

4. Delayed Recall (30 seconds)

To begin say…
"A few minutes ago I named five words. Name as many of those words as you can remember." (Recall in any order, within 30 seconds, giving 4 points per word, no hints)

dog **rain** **butter** **love** **door**

Score _____ / 20

5. Verbal Fluency (one minute)

"Name as many *animals* as you can in one minute. Ready? Go."
(Give half a point per animal named; to a maximum of 40. Accept all 'creatures' including birds, fish, insects etc. Do NOT count suffixes twice, e.g. mouse/mice but allow points for similar names e.g. calf, cow, and bull. Alternative forms include *fruit & veg* or *towns & cities*).

Score _____ / 20

List here, in 'shorthand' if required:

© O'Caoimh R, Molloy D. W 2011.

6. Logical Memory (30 seconds)

"I am going to read you a short story. After I have finished reading I want you to tell me as much of the story as you can. OK?" [patient signifies agreement, then begin reading the paragraph at about 1 second for each word unit] **"The red… fox… ran across.....… the bushes."**
(Give 2 points per **highlighted** word, recalled exactly, immediately within 30 seconds, in any order, no hints.Two alternative stories are provided).

6. Logical Memory			
The **red**	The **brown**	The **white**	2 / 0
fox	**dog**	**hen**	2 / 0
ran across	**ran across**	**walked across**	2 / 0
the **ploughed**	the **metal**	the **concrete**	2 / 0
field.	**bridge**.	**road**.	2 / 0
It was **chased** by	It was **hunting**	It was **followed** by	2 / 0
a **brown**	a **white**	a **black**	2 / 0
dog.	**rabbit**.	**cat**.	2 / 0
It was a **hot**	It was a **cold**	It was a **warm**	2 / 0
May	**October**	**September**	2 / 0
morning.	**day**.	**afternoon**.	2 / 0
Fragrant	**Ripe**	**Dry**	2 / 0
blossoms	**apples**	**leaves**	2 / 0
were **forming** on	were **hanging** on	were **blowing** in	2 / 0
the **bushes**.	the **trees**.	the **wind**.	2 / 0

Score _____ / 30

Q*mci* Total Score _____ / 100

*Normal > 60
MCI=50-60
Dementia <50

Scored by _____Date / /

*adjust for age and education

© O'Caoimh R, Molloy D. W 2011.

Quick *Mild Cognitive Impairment* screen (Q*mci)*

Administration and Scoring Guidelines

1. Orientation



Scoring

2 points for the correct answer, 1 point for wrong answers, and 0 points for no answer or a conceptually unrelated answer (see details below).



Timing

Maximum of 10 seconds for each answer.

Instructions and Scoring Guide

Year	If the person gives the correct year score 2 points, the incorrect year score 1 point, and 0 points if no year is given.
Country	Score 2 points for correct country, 1 point for incorrect country, and 0 if no country is named.
Month	Score 2 points for the correct month or for the previous or following month if within two days of the change of the month (for example, if the date is September 30th, score the full 2 points if person answers October. Similarly, if the date is October 2nd, score 2 points if person says September). Score 1 point if the month is incorrect and 0 if no month is named.
Date	Score 2 points for exact date or ± one day, 1 point for any other date, 0 if no date is named.
Day of week	2 points for correct day, 1 point for incorrect day, 0 if no day named.

To begin say...

"I'd like to ask you some questions and give you some problems to solve. Would that be OK?"

What country is this? _____

What year is this? _____

What month is this? _____

What is today's date? _____

What day of the week is this? _____

Score _____ / 10

copyright D.W. Molloy 2004

2. Word Registration

Instructions and Scoring Guide



Scoring

Score 1 point for each word recalled after the first reading. If subject recalls all five, repeat the five items once and then go on to clock drawing. If subject does not repeat all 5, repeat the 5 items and ask the subject to repeat them. Do this until the subject correctly recalls all 5 items or for a maximum of 3 trials. Do not score for trials 2 and 3. These trials are to help the person learn in preparation for the delayed recall task.



Timing

Say the words very deliberately, one per second. Allow 10 seconds for the recall.

To begin say…

"I am going to say 5 words. After I have said these 5 words, repeat them back to me. Are you ready?"

Dog	**rain**	**butter**	**love**	**door**

Score _____ / 5

When finished, say… **"Remember these words because I'll ask you to recall them later."**

Alternate word groups include…

cat	**dark**	**pepper**	**fear**	**bed**
rat	**heat**	**bread**	**round**	**chair**

copyright D.W. Molloy 2004

3. Clock Drawing

Instructions and Scoring Guide



Scoring

Place the circle of the transparent scoring template over the circle of the patient's completed clock. Rotate the template circle so that the "12" s align. Score 1 point each if the 1, 2, 4, 5, 7, 8, 10, and 11 are in the correct quadrants. Score 1 point each if the 12, 3, 6, and 9 touch their quadrant lines. Subtract one point for each number repeated or for numbers above 12. (Should the patient not have drawn a "12" align the template with the 3, 6, or 9.)

Score the placement of hands according to the tips and pivot. Give 1 point for each hand between the dashed lines. Score 1 point for hands connecting at the pivot.



Timing

One minute.

To begin…

Give the sheet of paper with the pre-drawn circle and a pencil to the patient. Say **"Now put in the numbers like the face of a clock."** Then say **"Set the hands to show ten past eleven." Place the numbers and hands as carefully as you can."**

You may prompt at each stage…"**put in the numbers…. put the time as ten past eleven**".

Score:	Numbers	Correct	+ _____/ 12
		Errors	- _____
	Hands		+ _____/ 2
	Pivot		+ _____/ 1
	Total		**+ _____/ 15**

copyright D.W. Molloy 2004

4. Delayed Recall

Instructions and Scoring Guide



Scoring

Score 4 points for each word recalled. Subjects may recall words in any order.



Timing

10 seconds.

To begin say…

A few minutes ago I named five words. Name as many of those words as you can remember.

dog	**rain**	**butter**	**love**	**door**

Score _____ / 20

Alternate word groups include…

cat	**dark**	**pepper**	**fear**	**bed**
rat	**heat**	**bread**	**round**	**chair**

5. Verbal Fluency

Instructions and Scoring Guide



Scoring.

Give ½ point for each correct word recalled to a maximum of 40 words. Round up the final score. Do not count words with different suffixes twice (e.g. fish / fishes, mouse / mice, etc.). Accept alternate species (e.g. blue jay, robin, sparrow, duck, etc.). Alternate forms include fruits and vegetables, cities and towns.



Timing.

60 seconds. Write down each word the patient says. (You may need to develop some kind of "shorthand" for the speedier patients, such as writing the first 3 letters of each word and then completing them later.)

To begin say…

"Name as many *animals* as you can in one minute. Ready? Go."

Score _____ / 20

copyright D.W. Molloy 2004

6. Logical Memory

Instructions and Scoring Guide



Scoring.

Give 2 points for each correct word item recalled verbatim. All bolded words within each section must be recalled for score 2 points. Otherwise score 0. Recall may be in any order.



Timing.
30 seconds. Check off each word unit recalled.

To begin say…

"I am going to read you a short story. After I have finished reading I want you to tell me as much of the story as you can. OK?" [patient signifies agreement, then begin reading the paragraph at about 1 second for each word unit] **"The red… fox… ran across..... the bushes."**

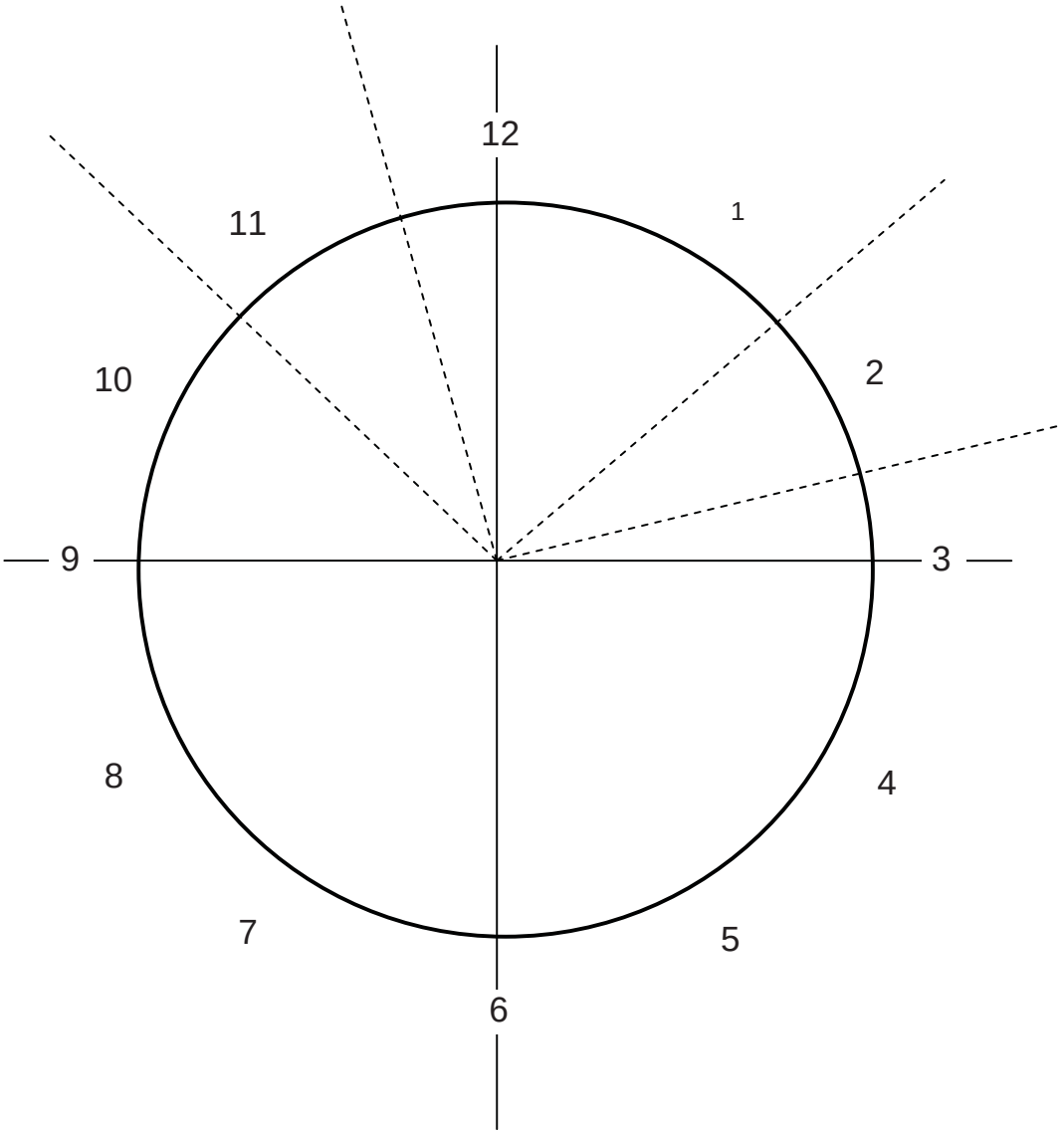
6. Logical Memory			
The **red**	The **brown**	The **white**	2 / 0
fox	**dog**	**hen**	2 / 0
ran across	**ran across**	**walked across**	2 / 0
the **ploughed**	the **metal**	the **concrete**	2 / 0
field.	**bridge**.	**road**.	2 / 0
It was **chased** by	It was **hunting**	It was **followed** by	2 / 0
a **brown**	a **white**	a **black**	2 / 0
dog.	**rabbit**.	**cat**.	2 / 0
It was a **hot**	It was a **cold**	It was a **warm**	2 / 0
May	**October**	**September**	2 / 0
morning.	**day**.	**afternoon**.	2 / 0
Fragrant	**Ripe**	**Dry**	2 / 0
blossoms	**apples**	**leaves**	2 / 0
were **forming** on	were **hanging** on	were **blowing** in	2 / 0
the **bushes**.	the **trees**.	the **wind**.	2 / 0

Score _____ / 30

Qmci Total Score _____ / 100

copyright D.W. Molloy 2004

The Clock Transparency Scoring Template



Scoring
Place this scoring template over the completed clock with the template's "12 o'clock" line placed over the subject's 12. Adjust the template to maximize the score for the numbers and hands. The total score is 15. Record scores on the score sheet as follows:

Numbers

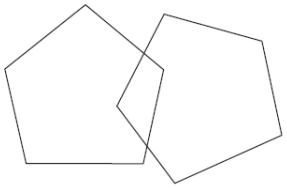
- For the numbers 12, 3, 6, and 9 score one (1) point if they touch their respective lines, zero (0) point if missed, and zero (0) if the number is omitted.
- For the numbers 1, 2, 4, 5, 7, 8, 10, and 11 score one (1) point for each number in the correct quadrant, zero (0) point if the number is outside the quadrant, and zero (0) if the number is omitted.
- **Subtract one point for each number repeated or more than 12.**

Hands

- Score the placement of the entire hand. If the hands are drawn within range, score one (1) point for each hand; if the hands are drawn outside the hatched line or are omitted score zero (0); Give one (1) point if the hands join at the pivot.

copyright D.W. Molloy 2004

STANDARDIZED MINI-MENTAL STATE EXAMINATION (SMMSE)

	QUESTION	TIME ALLOWED	SCORE
1	a. ***What year is this?***	10 seconds	/1
	b. ***Which season is this?***	10 seconds	/1
	c. ***What month is this?***	10 seconds	/1
	d. ***What is today's date?***	10 seconds	/1
	e. ***What day of the week is this?***	10 seconds	/1
2	a. ***What country are we in?***	10 seconds	/1
	b. ***What province are we in?***	10 seconds	/1
	c. ***What city/town are we in?***	10 seconds	/1
	d. ***IN HOME – What is the street address of this house?*** ***IN FACILITY – What is the name of this building?***	10 seconds	/1
	e. ***IN HOME – What room are we in? IN FACILITY – What floor are we on?***	10 seconds	/1
3	**SAY:** ***I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.*** Say the following words slowly at 1-second intervals - **ball/ car/ man**	20 seconds	/3
4	***Spell the word WORLD. Now spell it backwards.***	30 seconds	/5
5	***Now what were the three objects I asked you to remember?***	10 seconds	/3
6	**SHOW** wristwatch. **ASK:** ***What is this called?***	10 seconds	/1
7	**SHOW** pencil. **ASK**: ***What is this called?***	10 seconds	/1
8	**SAY:** ***I would like you to repeat this phrase after me: No ifs, ands or buts.***	10 seconds	/1
9	**SAY:** ***Read the words on the page and then do what it says.*** Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes	10 seconds	/1
10	**HAND** the person a pencil and paper. **SAY:** ***Write any complete sentence on that piece of paper.*** (Note: The sentence must make sense. Ignore spelling errors)	30 seconds	/1
11	**PLACE** design, eraser and pencil in front of the person. **SAY**: ***Copy this design please.***  Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.	1 minute	/1
12	**ASK** the person if he is right or left-handed. Take a piece of paper and hold it up in front of the person. **SAY**: ***Take this paper in your right/left hand*** (whichever is non-dominant), ***fold the paper in half once with both hands and put the paper down on the floor*** . Score 1 point for each instruction executed correctly. Takes paper correctly in hand Folds it in half Puts it on the floor	30 seconds	/1 /1 /1
	TOTAL TEST SCORE		**/30**

Note: This tool is provided for use in British Columbia with permission by Dr. William Molloy. This questionnaire should not be further modified or reproduced without the written consent of Dr. D. William Molloy.

ID: ☐☐☐☐☐ Date: / / (d d / m m / y y)

Baseline

Lawton – Activities of Daily Living (ADL) (caregiver)

Please circle the appropriate number.

1. **TOILETING** He/she:
   1. Soils or wets while awake more than once a week.
   2. Soils or wets while asleep more than once a week.
   3. Needs to be reminded or given help in cleaning self or has rare accidents (weekly at most).
   4. Cares for self at toilet completely with no incontinence.

2. **FEEDING** He/she:
   1. Does not feed self at all and resists efforts of others to feed them.
   2. Requires extensive assistance at all meals.
   3. Feeds self with moderate assistance and is untidy.
   4. Eats with minor assistance at meal times and/or with special preparation of food, or helps with cleaning up after meals.
   5. Eats without assistance.

3. **DRESSING** He/she:
   1. Is completely unable to dress self and resists efforts of others to help.
   2. Needs major assistance in dressing, but cooperates with efforts of others to help.
   3. Needs moderate assistance in dressing or selection of clothes.
   4. Dresses and undresses self with minor assistance.
   5. Dresses, undresses and selects clothing from own wardrobe.

4. **GROOMING**. He/she:
   1. Actively resists or negates all efforts of others to maintain grooming.
   2. Needs total grooming care, but can remain well groomed after help from others.
   3. Needs moderate and regular assistance or supervision in grooming.
   4. Grooms self adequately with occasional minor assistance e.g. shaving.
   5. Is always neatly dressed, well-groomed, without assistance.

5. **WALKING** He/she:
   1. Is bedridden more than half the time.
   2. Sits unsupported in a chair or wheelchair, but cannot propel self without help.
   3. Walks with assistance of another person; or railing, or cane, or walker; or wheelchair. Needs help in getting in and out of the house.
   4. Walks within residence or about one block distance.
   5. Goes about grounds or city.

6. **BATHING** He/she:
   1. Cannot or will not try to wash self, and resists efforts to keep him/her clean.
   2. Cannot or will not wash self, but is cooperative with those who bathe him/her.
   3. Washes face and hands only, needs help with rest of body.
   4. Bathes self with help getting in and out of tub.
   5. Bathes self (tab, shower, sponge bath) without help.

7. **USING THE PHONE** He/she:
   1. Does not use the phone at all.
   2. Answers the telephone, but does not dial.
   3. Dials a few well-known numbers.
   4. Operates the telephone on own initiative, looks up and dials numbers.

ID: ☐☐☐☐☐ Date: / /

Baseline (d d / m m / y y)

8. **SHOPPING** He/she:
   1. Is completely unable to shop.
   2. Needs to be accompanied on any shopping trip.
   3. Shops independently for small purchases.
   4. Takes care of all shopping needs independently.
   5. Does not apply - has never done this.

9. **FOOD PREPARATION** He/she:
   1. Needs to have meals prepared and served.
   2. Heats and serves prepared meals, or prepares meals but does not maintain adequate diet.
   3. Prepares adequate meals if supplied with ingredients.
   4. Plans, prepares and serves adequate meals independently.
   5. Does not apply - has never done this.

10. **HOUSEKEEPING** He/she:
    1. Does not participate in any housekeeping tasks.
    2. Needs help with all home maintenance tasks.
    3. Performs light daily tasks, but cannot maintain an acceptable level of cleanliness.
    4. Performs light daily tasks, such as dishwashing and bed making.
    5. Maintains the house alone, or with occasional assistance, e.g. "heavy work-domestic help."
    6. Does not apply - has never done this.

11. **LAUNDRY** He/she
    1. Needs all laundry to be done by others.
    2. Launders small items - rinses socks, stockings, etc.
    3. Does personal laundry completely.
    4. Does not apply - has never done this.

12. **TRANSPORTATION** He/she:
    1. Does not travel at all.
    2. Has travel limited to taxi or automobile with assistance of another.
    3. Travels on public transportation assisted or accompanied by another.
    4. Arranges own travel via taxi, but does not otherwise use public transportation.
    5. Travels independently on public transportation or drives own car.

13. **RESPONSIBILITY FOR MEDICATION** He/she:
    1. Is not capable of dispensing own medications.
    2. Takes responsibility if medication is prepared in advance in separate dosages.
    3. Is responsible for taking medication in correct dosages at correct time.

14. **ABILITY TO HANDLE FINANCES** He/she:
    1. Is not capable of handling money.
    2. Manages day-to-day purchases, but needs help with banking, major purchases etc.
    3. Manages financial matters independently, (budgets, writes cheques, pays rent and bills, goes to bank), collects and keeps track of income.

Quick Activities of Daily Living (Qadl) Score -- for caregiver

Tell us how the patient manages his / her “activities of daily living”. How does he / she function every day? Circle the number that best applies in the past week. If the person does not do this activity, e.g. another person does shopping, circle “N/A” for not applicable.

Type of activity	**What is the level of care required?**	**How much of a problem is this?**
In the past week how well was he/she able to…	na Not applicable-never did this 0 Performs spontaneously and independently 1 Needs prompting (verbal) 2 Needs set-up (physical) 3 Needs supervision (stand by) 4 Needs assistance (physical) 5 Complete care required	0 None 1 Little 2 Moderate 3 Great 4 Extreme
manage their own medications	na 0 1 2 3 4 5	0 1 2 3 4
handle money (pay bills, shop, etc.)	na 0 1 2 3 4 5	0 1 2 3 4
use the telephone	na 0 1 2 3 4 5	0 1 2 3 4
prepare food	na 0 1 2 3 4 5	0 1 2 3 4
groom (hair, shaving, nails, etc.)	na 0 1 2 3 4 5	0 1 2 3 4
bath (bath, shower)	na 0 1 2 3 4 5	0 1 2 3 4
walk	na 0 1 2 3 4 5	0 1 2 3 4
toilet (urine / feces)	na 0 1 2 3 4 5	0 1 2 3 4

transfer (e.g. bed to chair)	na	0	1	2	3	4	5		0	1	2	3	4
feed themselves (eat and drink)	na	0	1	2	3	4	5		0	1	2	3	4

Is this person mainly limited or impaired by physical problems?

Check off if any of the following reduced the person's ability to care for him / her self.

❑ Blindness ❑ Hearing ❑ Weakness ❑ Arthritis ❑ Memory and thinking

SADAS-cog

WORKBOOK

Wordset "A"

Patient Name : _____

Protocol: _____

Rater: _____

Date: _____/____/_____ (dd/mm/yy)

Time: _____

Version: 7/7/2006

Copyright © Molloy, Standish 1994

1. WORD RECALL TASK

Check each word recalled correctly.

Trial 1	✓
Bird	
Market	
Water	
Circle	
House	
Slave	
Dollar	
Sky	
Factory	
Picture	

Trial 2	✓
Bird	
Circle	
Sky	
Factory	
Picture	
House	
Slave	
Water	
Market	
Dollar	

Trial 3	✓
Picture	
Circle	
Sky	
Market	
House	
Slave	
Water	
Dollar	
Factory	
Bird	

Calculation of Word Recall score: Maximum possible correct 30

Minus Actual Correct - ____

Equals Total Incorrect = ____

Divided by 3 ÷ 3

Equals = ⌊⌋⌊⌋.⌊⌋

[Conduct open-ended interview (tell me about: jobs, family, born/raised)]

2. Naming Fingers and Objects

☒	☑		☒	☑		☒	☑	
☐	☐	Thumb	☐	☐	Flower	☐	☐	Scissors
☐	☐	Little	☐	☐	Bed	☐	☐	Comb
☐	☐	Index	☐	☐	Whistle	☐	☐	Wallet
☐	☐	Middle	☐	☐	Pencil	☐	☐	Harmonica
☐	☐	Ring	☐	☐	Rattle	☐	☐	Stethoscope
			☐	☐	Mask	☐	☐	Tongs

Circle total incorrect ☒

	{0 1 2}	{3 4 5}	{6 7 8}	{9 10 11}	{12 13 14}	{15 16 17}
	↓	↓	↓	↓	↓	↓
Score ⇒	0	1	2	3	4	5

3. Commands

☒	☑	
☐	☐	Make a fist.
☐	☐	Point to the ceiling, then to the floor
☐	☐	Put the pencil on top of the card, then put it back
☐	☐	Put the watch on the other side of the pencil and turn over the card
☐	☐	Tap each shoulder twice with two fingers keeping your eyes shut

Total Incorrect ☒ = Score . (Range 0-5) ☐

4. Constructional Praxis

☒	☑		☒	☑	
☐	☐	Circle	☐	☐	Rhombus
☐	☐	Two overlapping rectangles	☐	☐	Cube

Total Incorrect ☒ = Score (Range 0-5) ☐

if no figures drawn; or if scribbles, or if parts of forms or words instead of forms drawn Scrore 5

5. Ideational Praxis

☒	☑	
☐	☐	Fold a letter
☐	☐	Put letter in envelope
☐	☐	Seal envelope
☐	☐	Address envelope
☐	☐	Indicate location of stamp

Total Incorrect ☒ = Score. (Range 0-5) ☐

6. Orientation

☒	☑		☒	☑	
☐	☐	Full name	☐	☐	Day of week
☐	☐	Month	☐	☐	Season
☐	☐	Date	☐	☐	Place
☐	☐	Year	☐	☐	Time

Total Incorrect ☒ = Score. (Range 0-8) ☐

7. Word Recognition Task

Original words are shaded. Unshaded words are new . In the column headed ".☒☑," words are noted as correctly identified or not. The column headed "R" is used to record instances where the subject needed to be **reminded** according to the Remembering Test Instructions task (Item 12).

Trial 1	R	☒☑
Friend		
Excuse		
Officer		
Thought		
Lad		
Camp		
Fate		
Custom		
Banker		
Golf		
Permission		
Ability		
Blister		
Dirt		
Figment		
Icebox		
Concept		
Pianist		
Nonsense		
Tripod		
Fallacy		
Gender		
Bullet		
Intellect		

Trial 2	R	☒☑
Friend		
Excuse		
Plant		
Lad		
Custom		
Amount		
Industry		
Banker		
Ability		
Dirt		
Occasion		
Cradle		
Figment		
Icebox		
Banality		
Singer		
Hypothesis		
Nonsense		
Noose		
Distinction		
Tank		
Tripod		
Decree		
Fallacy		

Trial 3	R	☒☑
Seal		
Friend		
Excuse		
Lad		
Method		
Engine		
Custom		
Soul		
Banker		
Jelly		
Ability		
Origin		
Dirt		
Fireplace		
Figment		
Jeopardy		
Alligator		
Icebox		
Surtax		
Volcano		
Adage		
Nonsense		
Tripod		
Fallacy		

Calculation of Word Recognition score:

Maximum possible errors is		72
Minus actual correct	-	____
Equals total incorrect	=	____
Divided by 3	÷	3
Equals final score	=	␣␣.␣

(Note: Scoring cutoff. Max. =12)

Version: 7/25/2006

8. Spoken Language Ability		
Score	Rating	Description
0	NONE	no instances of lack of understandability
1	VERY MILD	one instance of lack of understandability
2	MILD	subject has difficulty less than 25% of time
3	MODERATE	subject has difficulty 25-50% of time
4	MODERATELY SEVERE	subject has difficulty more than 50% of time
5	SEVERE	1- or 2-word utterances; fluent, but empty speech; mute

9. Comprehension		
Score	Rating	Description
0	NONE	no instances of misunderstanding
1	VERY MILD	1 instance of misunderstanding
2	MILD	3-5 instances of misunderstanding
3	MODERATE	requires several repetitions and rephrasing
4	MODERATELY SEVERE	patient only occasionally responds correctly; eg. yes-no questions
5	SEVERE	patient rarely responds to questions appropuiately, not due to poverty of speech

10. Word-finding difficulty in spontaneous speech Note: do not include Finger and Object Naming in this rating.		
Score	Rating	Description
0	NONE	no instances of word-finding difficulty
1	VERY MILD	1 or 2 instances, not clinically significant
2	MILD	noticeable circumlocution or synonym substitution
3	MODERATE	loss of words without compensation on occasion
4	MODERATELY SEVERE	frequent loss of words without compensation
5	SEVERE	nearly total loss of content words; speech sounds empty; 1-2 word utterances

11. Remembering Test Instructions		
Score	Rating	Description
0	NONE	did not need reminding
1	VERY MILD	needed reminding 1 time
2	MILD	needed reminding 2 times
3	MODERATE	needed reminding 3 or 4 times
4	MODERATELY SEVERE	needed reminding 5 or 6 times
5	SEVERE	needed reminding 7 or more times

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's CDR. Please note information from additional questions.

Memory Questions for Informant:

1. Does he/she have a problem with his/her memory or thinking? ☐ Yes ☐ No
1a. If yes, is this a consistent problem (as opposed to inconsistent)? ☐ Yes ☐ No
2. Can he/she recall recent events? ☐ Yes ☐ No
3. Can he/she remember a short list of items (shopping)? ☐ Yes ☐ No
4. Has there been some decline in memory during the past year? ☐ Yes ☐ No
5. Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (collateral source's opinion) ☐ Yes ☐ No
6. Does he/she completely forget a major event (e.g. a trip, a party, a family wedding) within a few weeks of the event? ☐ Yes ☐ No
7. Does he/she forget pertinent details about the major event? ☐ Yes ☐ No
8. Does he/she completely forget important information of the distant past (e.g. date of birth, wedding date, place of employment)? ☐ Yes ☐ No
9. Tell me about some recent event in his/her life she should remember. (For later testing, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the patient or other participants got there)
   Within 1 week: _____
   _____
   _____
   Within 1 month: _____
   _____
   _____
10. When was he/she born? _____
11. Where was he/she born? _____
12. What was the last school he/she attended? _____
    Name _____
    Place _____
    Grade _____
13. What was his/her main occupation/job (or spouse's job if patient was not employed)? _____
    _____
14. What was his/her major job (or spouse's job if patient was not employed)? _____
    _____
15. When did he/she (or spouse) retire and why? _____
    _____

Orientation Questions for Informant:

How often does he/she know the exact:

1. Date of the Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

2. Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

3. Year?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

4. Day of the Week?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Can he/she find his/her way around familiar streets?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighbourhood?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

8. How often can he/she find his/her way around indoors?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

Judgement and Problem Solving Questions for Informant:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them:

☐ As good as they have ever been
☐ Good, but not as good as before
☐ Fair
☐ Poor
☐ No ability at all

2. Rate his/her ability to cope with small sums of money (e.g. calculate change, leave a small tip):

☐ No loss
☐ Some loss
☐ Severe loss

3. Rate his/her ability to handle complicated financial or business transactions (e.g. balance cheque book, pay bills):

☐ No loss
☐ Some loss
☐ Severe loss

4. Can he/she handle a household emergency (e.g. plumbing leak, small fire)?

☐ As well as before
☐ Worse than before because of trouble thinking
☐ Worse than before, another reason (why) _____

_____

5. Can he/she understand situations or explanations?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Does he/she behave* appropriately (i.e. in his/her usual (premorbid) manner) in social situations and interactions with other people?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

_____
* This item rates behaviour, not appearance

Community Affairs Questions for Informant

Occupational ☐ Yes ☐ No ☐ N/A

1. Is the patient still working?
   If not applicable, proceed to item 4
   If yes, proceed to item 3
   If no, proceed to item 2

2. Did memory or thinking problems contribute to the patient's decision to retire? (Question 4 is next) ☐ Yes ☐ No ☐ D/K

3. Does the patient have significant difficulty in his/her job because of problems with memory or thinking?

   ☐ Rarely or Never ☐ Sometimes ☐ Usually ☐ Don't Know

4. Did he/she ever drive a car? ☐ Yes ☐ No
   Does the patient drive a car now? ☐ Yes ☐ No
   If no, is this because of memory or thinking problems? ☐ Yes ☐ No

5. If he/she is still driving, are there problems or risks because of poor thinking? ☐ Yes ☐ No

6. *Is he/she able to independently shop for needs?

   ☐ Rarely or Never (Needs to be accompanied on any shopping trip) ☐ Sometimes (Shops for limited number of items: buys duplicate items or forgets needed items) ☐ Usually ☐ Don't Know

7. Is he/she able to carry out activities independently outside the home?
   ☐ Rarely or Never (Generally unable to perform Activities without help) ☐ Sometimes (Limited and/or routine e.g. superficial participation In church or meetings; trips to beauty salons) ☐ Usually (Meaningful participation in activities e.g. voting) ☐ Don't Know

8. Is he/she taken to social functions outside the family home? ☐ Yes ☐ No
If no, why not _____

9. Would a casual observer of the patient's behaviour think the patient was ill? ☐ Yes ☐ No

10. If in a nursing home, does he/she participate well in social functions (thinking)? ☐ Yes ☐ No

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in community affairs?
If not, please probe further.

Community Affairs: Such as going to church, visiting friends or family, political activities, professional organisations such as bar association, other professional groups, social clubs, service organisations, educational programs.

***Please add notes if needed to clarify patient's level of functioning in this area**
Home and Hobbies Questions for Informant:

1a. What changes have occurred in his/her abilities to perform household tasks? _____

_____

1b. What can he/she still do well? _____

_____

2a. What changes have occurred in his/her abilities to perform hobbies? _____

_____

2b. What can he/she still do well? _____

_____

3. If in a nursing home, what can he/she no longer do well (Home and Hobbies)? _____

_____

Everyday Activities (The Dementia Scale of Blessed):

	No Loss		Severe Loss
4. Ability to perform household tasks	0	0.5	1

Please describe _____

_____

_____

5. Is he/she able to perform household tasks at the level of:
(Pick one. The informant does not need to be asked directly)

☐ No meaningful function
(Performs simple activities, such as making a bed, only with much supervision)

☐ Functions in limited activities only
(With some supervision, washed dishes with acceptable cleanliness; sets table)

☐ Functions independently in some activities
(Operates appliances, such as a vacuum cleaner; prepares simple meals)

☐ Functions in usual activities but not at usual level

☐ Normal function in usual activities

IMPORTANT:
Is there enough information available to rate the patient's level of impairment in HOME & HOBBIES?
If not, please probe further.

Household Tasks**:** such as cooking, laundry, cleaning, grocery shopping, taking out garbage, front and backyard work, simple care maintenance and basic home repair**.**

Hobbies: Sewing, painting, handicrafts, reading, entertaining, photography gardening, going to theatre or concert, woodworking, participating in sports

Personal Care Questions for Informant:

*What is your estimate of his/her mental ability in the following areas:

	Unaided	Occasionally misplaced buttons etc.	Wrong sequence commonly forgotten items	Unable to dress
A. Dressing (The Dementia Scale of Blessed)	0	1	2	3
	Unaided	Needs prompting	Sometimes needs help	Always or nearly always needs help
B. Washing, grooming	0	1	2	3
	Cleanly; proper utensils	Messily; spoon	Simple solids	Has to be fed completely
C. Eating habits	0	1	2	3
	Normal complete control	Occasionally wets bed	Frequently wets bed	Doubly incontinent
D. Sphincter control (The Dementia Scale of Blessed)	0	1	2	3

*A box-score of 1 can be considered if the patient's person care is impaired from a previous level, even if they do not receive prompting.

Memory Questions for Patient

1. Do you have problems with memory or thinking? ☐ Yes ☐ No

2. A few moments ago your (spouse etc) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details if needed, such as location of the event, time of day, participants, how long the event was, when it ended and how the patient or other participants got there.)

Within 1 week
1.0 – Largely correct _____
0.5 _____
0.0 – Largely incorrect _____

Within 1 month
1.0 – Largely correct _____
0.5 _____
0.0 – Largely incorrect _____

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three attempts)

Elements	1	2	3	4	5
	John	Brown	42	Market St	Sydney
	John	Brown	42	Market St	Sydney
	John	Brown	42	Market St	Sydney

(Underline elements repeated correctly in each attempt)

4. When were you born? _____

5. Where were you born? _____

6. What was the last school you attended?
Name _____
Place _____ Grade _____

7. What was your main occupation/job (or spouse's if not employed)? _____

8. What was your last major job (or spouse's if not employed)? _____

9. When did you (or your spouse) retire and why? _____

10. Repeat the name and address I asked you to remember:

Elements	1	2	3	4	5
	John	Brown	42	Market St	Sydney

(Underline elements repeated correctly.)

Orientation Questions for Patient:

Record the patient's answer verbatim for each question

1. What is the date today?	☐ Correct ☐ Incorrect
2. What day of the week is it?	☐ Correct ☐ Incorrect
3. What is the month?	☐ Correct ☐ Incorrect
4. What is the year?	☐ Correct ☐ Incorrect
5. What is the name of this place?	☐ Correct ☐ Incorrect
6. What town or city are we in?	☐ Correct ☐ Incorrect
7. What time is it?	☐ Correct ☐ Incorrect
8. Does the patient who the informant is (in your judgement)?	☐ Correct ☐ Incorrect

Judgement and Problem Solving Questions for the Patient:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the patient's best understanding of the problem. Circle the nearest response.

Similarities:

Example: "How are a pencil and pen alike?" (writing instruments)
"How are these things alike?" Patient's Response

1. turnip.....cauliflower _____
   (0 = vegetables)
   (1 = edible foods, living things, can be cooked, etc)
   (2 = answers not pertinent; differences; buy them)

2. desk.....bookcase _____
   (0 = furniture, office furniture; both hold books)
   (1 = wooden, legs)
   (2 = not pertinent, differences)

Differences:

Example: "What is the difference between sugar and vinegar?" (sweet vs. sour)
"What is the difference between these things?" Patient's Response

3. lie.....mistake _____
   (0 = one deliberate, one unintentional)
   (1 = one bad, the other good – or explains only one)
   (2 = anything else, similarities)

4. river.....canal _____
   (0 = natural – artificial)
   (2 = anything else)

Calculations:

5. How many five cent pieces in a dollar? ☐ Correct ☐ Incorrect

6. How many 20 cent pieces in $5.40? ☐ Correct ☐ Incorrect

7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down. ☐ Correct ☐ Incorrect

Judgement:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?

(0 = try the telephone book, city directory, go to the courthouse for a directory; call a mutual friend)
(1 = call the police, call the operator (usually will not give address)
(2 = no clear response)

9. Patient's assessment of disability and station in life and understanding of why he/she is present at the examination (may have covered, but rate here):

☐ Good Insight ☐ Partial Insight ☐ Little Insight

CLINICAL DEMENTIA RATING (CDR) Patient's Initials_____

CLINICAL DEMENTIA RATING (CDR)	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented to place of examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgement & Problem Solving	Solves everyday problems and handles business and financial affairs well; judgement good in relation to past performances	Slight impairment in solving problems, similarities and differences	Moderate difficulty in handling problems, similarities and differences; social judgement usually maintained	Severely impaired in handling problems, similarities and differences; social judgement usually impaired	Unable to make judgements or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretence of independent function outside home Appears well enough to be taken to functions outside the family home independent function	Appears too ill to be taken to functions outside the family home
Home & Hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies and intellectual interest slightly impaired	Mild but definite impairment of function at home more difficult tasks abandoned; more complicated hobbies and interests abandoned	Only simple tasks preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Full capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

NAME _____ AGE_____ SEX_____ DATE _____

Cornell Scale for Depression in Dementia

Ratings should be based on symptoms and signs occurring during the week before interview. No score should be given if symptoms result from physical disability or illness.

SCORING SYSTEM

a = Unable to evaluate 0 = Absent
1 = Mild to Intermittent 2 = Severe

Score greater than 12 = Probable Depression

	a	0	1	2
A. MOOD-RELATED SIGNS				
1. Anxiety; anxious expression, rumination, worrying				
2. Sadness; sad expression, sad voice, tearfulness				
3. Lack of reaction to pleasant events				
4. Irritability; annoyed, short tempered				
B. BEHAVIORAL DISTURBANCE	a	0	1	2
5. Agitation; restlessness, hand wringing, hair pulling				
6. Retardation; slow movements, slow speech, slow reactions				
7. Multiple physical complaints *(score 0 if gastrointestinal symptoms only)*				
8. Loss of interest; less involved in usual activities *(score 0 only if change occurred acutely, i.e., in less than one month)*				
C. PHYSICAL SIGNS	a	0	1	2
9. Appetite loss; eating less than usual				
10. Weight loss *(score 2 if greater than 5 pounds in one month)*				
11. Lack of energy; fatigues easily, unable to sustain activities				
D. CYCLIC FUNCTIONS	a	0	1	2
12. Diurnal variation of mood; symptoms worse in the morning				
13. Difficulty falling asleep; later than usual for this individual				
14. Multiple awakenings during sleep				
15. Early morning awakening; earlier than usual for this individual				
E. IDEATIONAL DISTURBANCE	a	0	1	2
16. Suicidal; feels life is not worth living				
17. Poor self-esteem; self-blame, self-depreciation, feelings of failure				
18. Pessimism; anticipation of the worst				
19. Mood congruent delusions; delusions of poverty, illness or loss				

NOTES/CURRENT MEDICATIONS:

ASSESSOR:

Score

Instruction for use: (Cornell Dementia Depression Assessment Tool)

1. The same CNA (certified nursing assistant) should conduct the interviewed each time to assure consistency in the response.
2. The assessment should be based on the patient's normal weekly routine.
3. If uncertain of answers, questioning other caregivers may further define the answer.
4. Answer all questions by placing a check in the column under the appropriately numbered answer. (a=unable to evaluate, 0=absent, 1=mild to intermittent, 2=severe).
5. Add the total score for all numbers checked for each question.
6. Place the total score in the "SCORE" box and record any subjective observation notes in the "Notes/Current Medications" section.
7. Scores totaling twelve (12) points or more indicate probable depression.

ID: ☐☐☐☐☐ Date: / /

Baseline (d d / m m / y y)

Dysfunctional Behavior Rating Instrument (DBRI) (caregiver)

These questions are about your relative. How often has your relative had any of the following behaviours in the last few weeks:

CIRCLE THE NUMBER THAT BEST APPLIES:	IF YES, HOW OFTEN DOES THIS OCCUR?	HOW MUCH OF A PROBLEM IS THIS?
	0 Never	0 No problem
	1 About every two weeks	1 Very little problem
	2 About once a week	2 Little problem
	3. More than once a week	3 Somewhat of a problem
	4 At least once daily	4 Moderate problem
	5. More than five times a day	5 Great deal of problem

1.	Asks same questions over and over	0 1 2 3 4 5	0 1 2 3 4 5
2.	Repeats stories over and over	0 1 2 3 4 5	0 1 2 3 4 5
3.	Became angry	0 1 2 3 4 5	0 1 2 3 4 5
4	Was withdrawn (did not speak or do anything unless he/she was asked)	0 1 2 3 4 5	0 1 2 3 4 5
5.	Was demanding	0 1 2 3 4 5	0 1 2 3 4 5
6.	Was afraid to be left alone	0 1 2 3 4 5	0 1 2 3 4 5
7.	Was aggressive	0 1 2 3 4 5	0 1 2 3 4 5
8.	Was hiding things	0 1 2 3 4 5	0 1 2 3 4 5
9.	Was suspicious	0 1 2 3 4 5	0 1 2 3 4 5
10.	Had temper outbursts	0 1 2 3 4 5	0 1 2 3 4 5
11.	Had delusions i.e. thoughts that:		
	Spouse was "Not my husband/wife"	0 1 2 3 4 5	0 1 2 3 4 5
	Home was "Not my home"	0 1 2 3 4 5	0 1 2 3 4 5
	There were "People in the house"	0 1 2 3 4 5	0 1 2 3 4 5
	That "People were stealing things"	0 1 2 3 4 5	0 1 2 3 4 5
	Other: _____	0 1 2 3 4 5	0 1 2 3 4 5
12.	Hallucinations:		
	Saw things that were not there:	0 1 2 3 4 5	0 1 2 3 4 5
	Heard things or people that were not there:	0 1 2 3 4 5	0 1 2 3 4 5
	Other:_____	0 1 2 3 4 5	0 1 2 3 4 5
13.	Was agitated e.g. pacing:	0 1 2 3 4 5	0 1 2 3 4 5
14.	Was crying:	0 1 2 3 4 5	0 1 2 3 4 5
15	Was frustrated:	0 1 2 3 4 5	0 1 2 3 4 5
16	Wandered, got lost in house, on property, or elsewhere:	0 1 2 3 4 5	0 1 2 3 4 5
17	Was up at night:	0 1 2 3 4 5	0 1 2 3 4 5
18.	Wanted to leave:	0 1 2 3 4 5	0 1 2 3 4 5
19.	Kept changing mind:	0 1 2 3 4 5	0 1 2 3 4 5
20.	Are there any other behaviours not mentioned above that your relative had?	0 1 2 3 4 5	0 1 2 3 4 5
21.	Refused to cooperate:	0 1 2 3 4 5	0 1 2 3 4 5
22.	Embarrassing behaviour in public:	0 1 2 3 4 5	0 1 2 3 4 5

Geriatric Depression Scale (Short Form)

Patient's Name: _____ Date: _____

Instructions: Choose the best answer for how you felt over the past week. Note: when asking the patient to complete the form, provide the self-rated form (included on the following page).

No.	Question	Answer	Score
1.	Are you basically satisfied with your life?	YES / ***NO***	
2.	Have you dropped many of your activities and interests?	***YES*** / NO	
3.	Do you feel that your life is empty?	***YES*** / NO	
4.	Do you often get bored?	***YES*** / NO	
5.	Are you in good spirits most of the time?	YES / ***NO***	
6.	Are you afraid that something bad is going to happen to you?	***YES*** / NO	
7.	Do you feel happy most of the time?	YES / ***NO***	
8.	Do you often feel helpless?	***YES*** / NO	
9.	Do you prefer to stay at home, rather than going out and doing new things?	***YES*** / NO	
10.	Do you feel you have more problems with memory than most people?	***YES*** / NO	
11.	Do you think it is wonderful to be alive?	YES / ***NO***	
12.	Do you feel pretty worthless the way you are now?	***YES*** / NO	
13.	Do you feel full of energy?	YES / ***NO***	
14.	Do you feel that your situation is hopeless?	***YES*** / NO	
15.	Do you think that most people are better off than you are?	***YES*** / NO	
		TOTAL	

(Sheikh & Yesavage, 1986)

Scoring:

Answers indicating depression are in bold and italicized; score one point for each one selected. A score of 0 to 5 is normal. A score greater than 5 suggests depression.

Sources:

- Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol*. 1986 June;5(1/2):165-173.
- Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull*. 1988;24(4):709-711.
- Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982-83;17(1):37-49.

Geriatric Depression Scale (Short Form)
Self-Rated Version

Patient's Name: _____ Date: _____

***Instructions*: Choose the best answer for how you felt over the past week.**

No.	Question	Answer	Score
1.	Are you basically satisfied with your life?	YES / NO	
2.	Have you dropped many of your activities and interests?	YES / NO	
3.	Do you feel that your life is empty?	YES / NO	
4.	Do you often get bored?	YES / NO	
5.	Are you in good spirits most of the time?	YES / NO	
6.	Are you afraid that something bad is going to happen to you?	YES / NO	
7.	Do you feel happy most of the time?	YES / NO	
8.	Do you often feel helpless?	YES / NO	
9.	Do you prefer to stay at home, rather than going out and doing new things?	YES / NO	
10.	Do you feel you have more problems with memory than most people?	YES / NO	
11.	Do you think it is wonderful to be alive?	YES / NO	
12.	Do you feel pretty worthless the way you are now?	YES / NO	
13.	Do you feel full of energy?	YES / NO	
14.	Do you feel that your situation is hopeless?	YES / NO	
15.	Do you think that most people are better off than you are?	YES / NO	
		TOTAL	

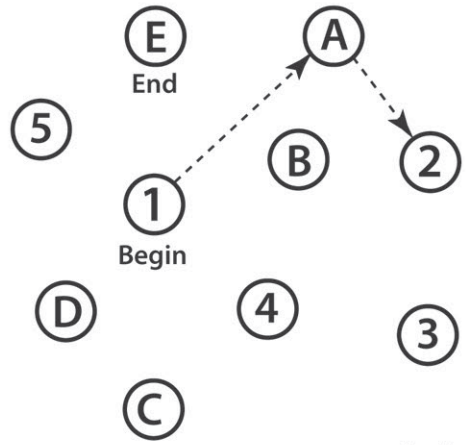
(Sheikh & Yesavage, 1986)

MONTREAL COGNITIVE ASSESSMENT (MOCA)

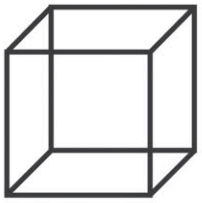
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



[ ]



Copy cube

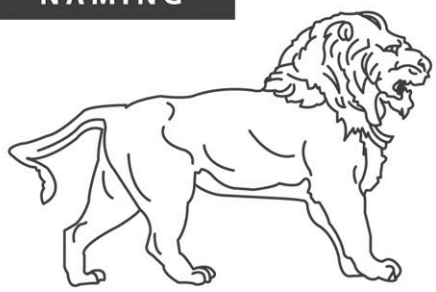
[ ]

Draw CLOCK (Ten past eleven)
(3 points)

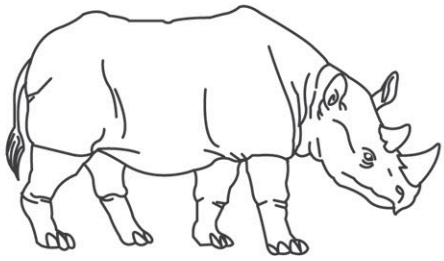
[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

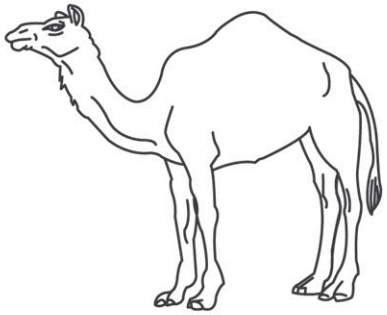
NAMING



[ ]



[ ]



[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]
Optional	Category cue					
	Multiple choice cue					

Points for UNCUED recall only

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

© Z.Nasreddine MD

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____