Adaption and Validation of the Addenbrooke’s Cognitive Examination (ACE-III) as a Cognitive Screening Tool for Dementia for Older Adults with Comorbid Hearing Impairment

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I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

Name: Mary Heatley

Date: 19th June 2020
Overview

This three part thesis considers the relationship between age-related hearing loss and dementia, with a focus on the proposed explanatory pathways of this relationship and identification of cognitive impairment in individuals with hearing loss.

Part One: Conceptual Introduction - The conceptual introduction provides some context for the empirical paper by exploring the relationship between age-related hearing loss and cognitive decline and dementia. More specifically, the mechanisms that potentially underpin this association are outlined.

Part Two: Empirical Paper - The adaption and validation of the Addenbrooke’s Cognitive Examination (ACE-III) to screen for cognitive impairment in older adults with hearing impairment is detailed in the empirical paper. This was a joint project carried out with Courtney North (D ClinPsy, 2020) and Nattawan Utoomprurkporn (PhD, 2020). The contributions of each author are summarised in Appendix A.

Part Three: Critical Appraisal - The critical appraisal includes reflections on the entire research process, with specific contemplation of experiential challenges encountered and personal and professional learning taken forward. An in-depth appraisal of the empirical study is outlined in which quality is considered, including both strengths and limitations. Ethical concerns and potential barriers in relation to conducting research with individuals living with dementia are explored.
Impact Statement

The current study demonstrated the adaption and validation of a widely used cognitive screening tool for dementia, the Addenbrooke’s Cognitive Examination (ACE-III), in a population of older adults with age acquired hearing loss, termed the HI-ACE-III. There are a number of associated implications, both in terms of clinical utility for dementia screening, as well as advancement in the research field. Currently there are no adapted cognitive screening tools validated for clinical practice when the presence of hearing impairment has been established, potentially affecting the accuracy of cognitive performance estimates and interfering with the timely identification of cognitive impairment. While this study provides preliminary evidence, additional research may reveal further clinical benefit of the HI-ACE-III, including potential applications outside of the recruited population.

The reliance on verbally administered assessment tools has complicated the interpretation of research on the relationship between hearing impairment and dementia, as well as consideration of potential underlying mechanisms. Future research would be enhanced by standardisation of the assessment methods used to establish hearing acuity, cut-off points categorising hearing impairment and the inclusion of cognitive screening tools that are not affected by hearing acuity, such as the HI-ACE-III. The inclusion of a diverse population, with matched groups based on age and years of education as a minimum would improve interpretation and generalisability of the study findings. Finally, interventions for hearing impairment that may delay the onset of cognitive impairment and dementia should also be explored, with consideration of the poor uptake of current aural rehabilitation devices. Potential implications exist for both health care and public policy.
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<th>Description</th>
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<tbody>
<tr>
<td>3MS-R</td>
<td>Modified Mini-Mental Status Exam</td>
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<tr>
<td>ACE</td>
<td>Addenbrooke’s Cognitive Examination</td>
</tr>
<tr>
<td>ACE-R</td>
<td>Addenbrooke's Cognitive Examination Revised</td>
</tr>
<tr>
<td>ACE-III</td>
<td>Addenbrooke’s Cognitive Examination Version Three</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s Disease</td>
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<tr>
<td>AMNART</td>
<td>American Version of the Nelson Adult Reading Test</td>
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<tr>
<td>ARHL</td>
<td>Age Related Hearing Loss</td>
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<tr>
<td>APOE</td>
<td>Apolipoprotein E</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>COVID-19</td>
<td>Coronavirus disease 2019</td>
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<tr>
<td>dB</td>
<td>Decibels</td>
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<tr>
<td>D-HI</td>
<td>Dementia and Hearing Impaired Group</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>GNT</td>
<td>Graded Naming Test</td>
</tr>
<tr>
<td>GPCOG</td>
<td>General Practitioner Assessment of Cognition</td>
</tr>
<tr>
<td>HI</td>
<td>Hearing Impaired Group (Cognitively Intact)</td>
</tr>
<tr>
<td>HI-ACE-III</td>
<td>Hearing Impaired Addenbrooke’s Cognitive Examination third edition</td>
</tr>
<tr>
<td>HI-MoCA</td>
<td>Hearing impaired Montreal Cognitive Assessment</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems (10th ed.)</td>
</tr>
<tr>
<td>(m)AIAD</td>
<td>Modified Amsterdam Inventory for Auditory Disability and Handicap</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
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<tr>
<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
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<tr>
<td>MSQ</td>
<td>Mental Status Questionnaire</td>
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NHS       National Health Service
NICE      National Institute for Health and Care Excellence
PPI       Patient and Public Involvement
PTA       Pure Tone Audiometry
QSTAC     Queen Square Test of Auditory Cognition
QUADAS-2  Quality Assessment of Diagnostic Accuracy Studies Revised
RBANS     Repeatable Battery for the Assessment of Neuropsychological Status
RBANS-H   Hearing impaired Repeatable Battery for the Assessment of
           Neuropsychological Status
RHTNEH    Royal Throat Nose Ear Hospital
ROC       Receiver Operative Curve
ROCF      Rey-Osterrieth Complex Figure Copy
ROCF 3min Rey-Osterrieth Complex Figure 3 Minute Recall
ROCF 30min Rey-Osterrieth Complex Figure 30 Minute Recall
RUDAS     Rowland Universal Dementia Assessment Scale
SPSS      Statistical Package for the Social Sciences
SS        Spatial Span
SS DSF    Spatial Span Digit Span Forward
SS DSB    Spatial Span Digit Span Backward
SSQ       Speech, Spatial and Qualities of Hearing Scale
UCL       University College London
WAIS      Wechsler Adult Intelligence Scale
WHO       World Health Organisation
YoE       Years of Education
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Part One: Conceptual Introduction

Exploring Age-Related Hearing Loss as a Risk Factor for Dementia;
What are the Potential Mechanisms?
Abstract

An undeniable result of aging is age-related deteriorations in both cognition and hearing acuity. The emerging possibility of hearing loss as a precipitating factor in the onset and development of cognitive decline has led to increased interest and research efforts examining the relationship between the two conditions. Insight into the nature of the relationship between cognitive decline, dementia and age-related hearing loss is crucial in order to develop effective preventative and rehabilitative measures that could potentially reduce the considerable burdens associated with both conditions and contribute to hearing well, living well and aging well in later life.

This conceptual introduction firstly defines the concepts of dementia and age-related hearing loss. The empirical support for the association between reductions in hearing acuity and cognitive decline is critically examined. A number of potential mechanisms that may underpin this association are explored, along with the possibility that no single mechanism may be satisfactory to explain the longitudinal interplay between two such intricate phenomena. The clear need for a cognitive screening tool that is unaffected by hearing impairment is evident throughout the conceptual introduction; this will be explored further in the empirical paper.
1 Introduction

Dementia and Age-Related Hearing Loss (ARHL) are prevalent conditions in older adults, respectively affecting around 6.5% of individuals over 65 (Wu et al., 2017) and two thirds of individuals over 70 (Lin, Thorpe, Gordon-Salant & Ferrucci, 2011); the presence of each condition becomes increasingly likely as an individual ages (Deary et al., 2009; Liu & Yan, 2007). The number of people living with dementia (Prince et al. 2013) and ARHL (Shield, 2006) is anticipated to increase with the aging population. The individual and economic burdens associated with both conditions are considerable (Stucky, Wolf & Kuo, 2010; Xu, Zhang, Qiu & Cheng, 2017), and both can significantly affect wellbeing and quality of life (Banerjee et al., 2006; Strawbridge, Wallhagen, Shema, & Kaplan, 2000).

These conditions frequently co-occur, and a growing evidence base supports an association between ARHL and dementia (Thomson, Auduong, Miller & Gurgel, 2017), although it remains possible that hearing impairment exaggerates the apparent relationship (Deal et al., 2015: Lin et al., 2011b). More recently, ARHL has been cited as a risk factor for dementia (Livingston et al., 2017) and in the absence of disease-modifying treatment for dementia, there is an increased focus on risk reduction (Norton, Matthews, Barnes, Yaffe & Brayne, 2014).

The mechanisms underpinning the association between ARHL and dementia remain unclear (Wayne & Johnsrude, 2015); Three potential theories have been outlined. The first, known as the common cause theory, suggests common neurodegenerative processes underpin both conditions with no causal link between the two (Wayne & Johnsrude, 2015). Speculation on factors contributing to neurodegeneration include health status (Thomson et al., 2017) and genetic
predisposition (Kurniawan et al., 2012; Richard & Amouyel, 2001). Alternatively, ARHL may act as a risk factor for dementia by contributing to the acceleration of cognitive decline (Claes et al., 2016; Livingston et al., 2017). Termed the cascade hypothesis, hearing deficits are proposed to have a cascade effect on cognitive function, both directly, by way of impoverished sensory input, and indirectly, by way of psychosocial factors such as social isolation and lifestyle practices (Bernabei et al., 2014; Fratiglioni et al., 2000). Finally, the cognitive load hypothesis indicates a possible causal link with hearing loss affecting available cognitive resources, leading to cognitive underperformance by interfering with existing cognitive compensation strategies and taxing the brain (Panza et al., 2015; Tun, McCoy and Wingfield, 2009). It is possible that these theories are not mutually exclusive, with interaction between the pathways potentially contributing to the overall dementia risk (Thomson et al., 2017). All theories are considered to be underpinned by existing neurodegeneration, resulting in structural and functional brain changes (Thomson et al., 2017).

This conceptual introduction intends to explore the evidence for these potential mechanisms. Understanding the mechanisms may have important clinical implications for the diagnosis and management of both conditions, as well as contributing to more effective prevention and intervention for dementia (Stahl, 2017). Initial research exploring the impact of hearing rehabilitation on cognition and cognitive decline is outlined (Kalluri & Humes, 2012; Mulrow et al., 1990a; Mulrow et al., 1990b), although further research on the long-term protective effects is necessary (Lin & Albert, 2014; Moyer, 2012).
2 Dementia

Dementia is considered to be an umbrella term capturing a range of progressive neurological disorders often related to the cognitive decline of aging, with a number of associated causal contributors (Prince et al., 2013). The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) classifies dementia as mild or major neurocognitive disorders; differentiation is determined by the degree that cognitive decline interferes with independence of daily function.

2.1 Prevalence

A systematic review indicated an estimated 35.6 million individuals living with dementia worldwide in 2010 (Prince et al., 2013) revised to 47 million in 2015 (World Health Organisation; WHO, 2015). Estimate reliability is limited by heterogeneity of findings, difference in diagnostic procedures, poor study quality and poor research coverage in certain regions (Prince et al., 2013). The prevalence of dementia will increase with the aging population, with predictive estimates for 2030 at 65.7 million, increasing to 115.4 million in 2050 (Prince et al. 2013).

2.2 Pathophysiology of common dementia types

Alzheimer’s Disease (AD) accounts for around half of dementia cases (Lobo et al., 2000; Fratiglioni et al., 2000). The pathogenesis involves damage to neurons in the brain from the progressive accumulation of the protein tau in twisted strands, tangles, as well as the build-up of the protein fragment β-amyloid, termed plaques.
Vascular dementia is typically caused by blockage or damage to blood vessels providing blood to the brain, leading to bleeding or strokes (Rizzi, Rosset & Roriz-Cruz, 2014).

Dementia with Lewy bodies is identified by abnormal clumps of the protein α-synuclein in neurons within cortical and sub-cortical brain regions (Trojanowski & Lee, 1998). Mixed dementia, characterised by pathologies associated with multiple types of dementia, potentially affects around half of individuals with dementia (Schneider, Arvanitakis, Bang & Bennett, 2007).

2.3 Risk factors

It is likely that a unique interaction of risk factors contributes to dementia risk. Associated risk factors can broadly be categorised into a) age, b) genetic predisposition, c) social and environmental exposure and d) health status (Baumgart et al., 2015).

2.3.1 Age

Age is consistently indicated as a risk factor for dementia across different subtypes, as well as in different ethnic groups (Chen, Lin & Chen, 2009).

2.3.2 Genetic predisposition

Genetics may account for around 48% of the variation in susceptibility to AD (Gatz et al., 2005; Pedersen, Gatz, Berg & Johansson, 2004). In particular, the APOE genotype and carrying the APOE-ε4 allele has been implicated (Corder et al., 1993; Farrer et al., 1997; Richard & Amouyel, 2001).
Andersen and colleagues (1999) found women were at an increased risk of developing AD; educational differences, average life span and variations in manifestation of genotypes may underpin this sex differential.

2.3.3 Social and environmental exposure

Dietary and nutritional intake (Otsuka, Yamaguchi & Ueki, 2002; Solfrizzi et al., 2006) and environmental exposure to metals such as aluminium may influence susceptibility to dementia (Solfrizzi et al., 2006). Benzodiazepines are related to an increased risk of dementia (Lagnaoui et al., 2002). Conversely, statin use, which lowers cholesterol levels, was found to reduce the risk of dementia (Wolozin et al., 2007; Zandi et al., 2005;).

Length of time in education is negatively correlated with dementia risk, although not in AD (Cobb, Wolf, Au, White & D’agostion, 1995; Shadlen et al., 2006). This association is potentially influenced by socioeconomic status (Karp et al., 2004) and sex (Andersen et al., 1999). Less time in education may result in lower cognitive reserves, associated with earlier onset of dementia (Wilson et al., 2009).

2.3.4 Health status

Baumgart and colleagues (2015) ranked risk factors based on evidence strength, including a traumatic brain injury (Lye & Shores, 2000), followed by mid-life obesity (Beydoun, Beydoun & Wang, 2008), hypertension (Forette & Boller, 1991), strokes (Starkstein & Almeida, 2003), current smoking (Aggarwal et al., 2006; Merchant et al., 1999), diabetes (Craft, 2007), and a history of depression (Ownby, Crocco, Acevedo, John & Loewenstein, 2006).
Conversely, factors that reduce the risk of dementia (Baumgart et al., 2015) include physical activity (Barnes, Yaffe, Satariano & Tager, 2003; Lautenschlager et al., 2008) and moderate alcohol consumption (O’Keefe, Bybee & Lavie, 2007; Peters, Peters, Wamer, Beckett & Bulpitt, 2008), potentially through protective mechanisms including reducing inflammatory markers and vascular risk (Barnes, Whitmer & Yaffe, 2007; Heyn, Abreu & Ottenbacher, 2004). The protection offered may be moderated by APOE-ε4 status (Mukamal et al., 2003).

2.4 Impact and burden

Dementia impacts individuals and caregivers (Bourgeois & Hickey, 2009). Decreased quality of life for individuals with dementia has been related to decreased ability to perform daily activities, disinhibition and negative mood effects including depression and agitation (Banerjee et al., 2006; Logsdon, McCurry & Teri, 2008). Estimated costs related to dementia increased from $279.6 billion globally in 2000 to $948 billion in 2016 (Xu et al., 2017).

2.5 Interventions

Interventions registered for dementia aim to delay cognitive deterioration (van de Glind et al., 2013), and target behavioural and psychological symptoms (Kales, Gitlin & Lyketsos, 2015). Pharmacotherapy includes NMDA antagonists and acetylcholinesterase inhibitors, although a scoping review revealed mixed evidence (van de Glind et al., 2013). Non-pharmacological interventions include Cognitive Stimulation Therapy (CST) (Woods, Aguirre, Spector & Orrell, 2012), shown to have positive impacts for quality of life (Cooper et al., 2012).
3 Age-Related Hearing Loss (ARHL)

Age-related hearing loss (ARHL), or presbycusis, is a progressive sensory impairment affecting individuals in later life (Bowl & Dawson, 2019; Huang & Tang, 2010). ARHL is typically bilateral, with similar severity in both ears (Davis et al., 2016). It is characterised by reductions in hearing sensitivity and slowed processing of acoustic information (Gates & Mills, 2005). According to the WHO (1991; 2014), mild hearing loss ranges from an average hearing threshold of 26 dB in the better ear, rising to 41 dB for moderate, 61 dB for severe and over 81 dB for profound.

3.1 Prevalence

By age 70, estimates indicate 30% of European men and 20% of women have some degree of mild hearing loss (Roth, Hanebuth & Probst, 2011). By contrast, hearing loss that impairs communication has been described in two thirds of American adults over 70 (Lin et al., 2011a), increasing to 80.6% over 85. Comparison of prevalence figures is difficult due to different defined thresholds of hearing impairment and assessment methods (Cruickshanks, Zhan & Zhong, 2010), with audiometric testing more reliable than self-report (Nondahl et al., 1998; Dalton et al., 2003). Debate exists in prevalence trends (Crimmins & Saito, 2000; Desai, Pratt, Lentzner & Robinson, 2001), nevertheless the number of people affected is predicted to rise with an aging population, reaching around 1.2 billion by 2050 (Shield, 2006).
3.2 Pathophysiology of common presbycusis subtypes

Various pathophysiological processes are thought to result in ARHL as aging affects the central and peripheral auditory and central nervous systems (Mazelová et al., 2003). Six subtypes have been identified by surveying temporal bones and audiogram findings (Schuknecht, 1964; Schuknecht & Gacek, 1993): 1) sensory presbycusis involves loss of outer hair cells in the ear, 2) neural is related to loss of ganglion cells, 3) metabolic is attributed to atrophy of strial in the inner ear, 4) cochlear conductive is associated with changing physical characteristics of the cochlear duct, 5) mixed presbycusis, 6) indeterminate presbycusis where type is unclear.

3.3 Risk factors

A unique interaction of modifiable and non-modifiable risk factors must be considered for each case of ARHL (Huang & Tang, 2010; Yamasoba et al., 2013). While the relative contribution of non-modifiable genetic risk factors is higher than modifiable risk factors (Yamasoba et al., 2013), the effective management of modifiable risk factors may delay ARHL onset (Agrawal, Platz & Niparko, 2008). Similar to dementia, four general categories of risk factors associated with ARHL have been identified: a) age, b) genetic predisposition, c) environmental factors and d) health status (Helzner et al., 2005).

3.3.1 Age

Age is the most consistent risk factor; for every five-year age increase, prevalence of ARHL doubled (Helzner et al., 2005) after adjusting for variables including disease state.
3.3.2 Genetic predisposition

Genetic risk of developing ARHL has been demonstrated in a twin study (Karlsson, Harris & Svartengren, 1997) and a cohort study (Matthews, Finkelstein & Betensky, 2008). Specific genotypes may increase the risk; The Apolipoprotein E (APOE-ε4) genotype doubled the risk of hearing impairment in an older cohort (Kurniawan et al., 2012), although contradictory findings exist (O’Grady et al., 2007).

Links between sex and ARHL have been observed, with higher prevalence documented in men (Agrawal et al., 2008; Gopinath et al., 2009); Theories range from higher occupational noise exposure in men (Helzner et al., 2005) to hormonal differences (Sharashenidze, Schacht & Kevanishvili, 2007).

White elderly adults are more likely than black elderly adults to experience both ARHL (Helzner et al., 2005) and noise induced hearing loss (Jerger, Jerger, Pepe & Miller, 1986). Increased levels of skin pigmentation, melanin, in cochlear hair cells may be protective (Barrenäs & Lindgren, 1991).

3.3.4 Environmental exposure

Significant noise exposure in the work environment was associated with a 55-90% increased risk of developing hearing loss (Gopinath et al., 2009). Ototoxic medications may cause inner ear damage and hearing loss (Brummett, 1980), although findings are mixed (Helzner et al., 2005).
3.3.5 Health status

Modifiable risk factors for ARHL include diabetes mellitus, heavy smoking, hypertension, high body mass index and cerebrovascular disease (Agrawal et al., 2008; Fransen et al., 2008; Gates, Cobb, D’Agostino & Wolf, 1993; Helzner et al., 2005). An inverse correlation with moderate alcohol consumption has been documented (Fransen et al., 2008; Helzner et al., 2005), possibly due to cardio-protective qualities (Fransen et al., 2008).

3.4 Impact and burden

ARHL is associated with an increased mortality risk (Hietanen, Era, Sorri & Heikkinen, 2004), and higher morbidity in terms of decreased physical and social functioning, reduced independence, increased frailty (Carabellose et al., 1993; Kamil et al., 2016), decreased wellbeing and increased risk of depressive symptoms (Strawbridge et al., 2000). A significant economic burden also accompanies ARHL, with estimated costs as high as $9.5 billion in the United States in 2002 (Stucky et al., 2010), projected to increase to $60 billion by 2030.

3.5 Interventions

The primary intervention for ARHL is clinical management through hearing aids (McCormack & Fortnum, 2012) or cochlear implantation (Sprinzl & Riechelmann, 2010). Treatment is associated with improvements in communication and increases in social, emotional and cognitive function (Mulrow et al., 1990a; 1990b).
4 Summary

As outlined, dementia and ARHL are both highly prevalent in the older population (Lin et al., 2011a; Roth et al., 2011; Prince et al., 2015). There is also evidence to suggest a higher prevalence of hearing loss in elderly individuals with cognitive impairment (Lopes et al., 2007); One sample indicated more than 90% of individuals with AD had some degree of hearing loss (Gold, Lightfoot & Hnath-Chisolm, 1996). When considering potential mechanisms for the association between ARHL and dementia, it is important to maintain awareness that prevalence findings do not represent complete incident dementia or hearing loss as many individuals remain undiagnosed (Brayne & Davis, 2012; Hands, 2000).

Accurate diagnosis of dementia subtype can be challenging, as clinical characteristics often overlap (Schott & Warren, 2012) and a post-mortem examination remains the only definitive diagnostic tool (Beach, Monsell, Phillips & Kukull, 2012; Harper et al., 2016). Meanwhile, the pathophysiological processes associated with ARHL are not fully understood (Huang & Tang, 2010). These factors potentially affect diagnostic accuracy and preclude access to appropriate treatment (Gaugler et al., 2013), and it is important to consider misdiagnosis rates when interpreting research considering potential mechanisms. As for associated risk factors for both ARHL and dementia, the potential for ecological fallacy in epidemiological research, when inferences are made about individuals based on group level data, must be kept in mind (Piantadosi, Byar & Green, 1988).
When considering interventions for dementia, engagement and adherence may be inconsistent due to a lack of insight into memory deficits, cognitive impairment and apathy or comorbid depression (Choi & Twamley, 2013). In terms of hearing loss, most individuals who would benefit from hearing aids do not use them (WHO, 2006) due to discomfort, low perceived benefit (McCormack & Fortnum, 2012) and stigma (Meister, Walger, Brehmer, von Wedel & von Wedel, 2008). These are important caveats when considering apparent support for potential mechanisms drawn from intervention research.
As dementia and ARHL frequently co-occur, there is considerable interest in the possibility of an association between the two phenomena (Thomson et al., 2017). An accelerated mean time for developing all-cause dementia has been demonstrated in adults over 65 with hearing loss at baseline (10.3 years), compared to individuals with intact hearing (11.9 years) (Gurgel et al., 2014). A review of early research reported a significant association in 11 of 15 included studies (Gennis, Garry, Haaland, Yeo & Goodwin, 1991), indicating hearing ability was related to cognitive status in individuals with dementia, but not in older adults without dementia. A systematic review considering more recent research found each of the 17 included studies indicated an association between hearing impairment and either incident all-cause dementia or cognitive decline (Thomson et al., 2017).

Both reviews were affected by considerable variability across included research in terms of study design, adjustment for potential confounding factors, recruited populations and methods to assess cognition and hearing ability, with some adopting measures with limited reliability such as the ability to hear finger friction. A further systematic review and meta-analysis only included observational, cross-sectional data and cohort studies where hearing loss was assessed using pure-tone audiometry, finding 36 studies (Loughrey, Kelly, Kelley, Brennan & Lawlor, 2018). ARHL was found to be significantly associated with an increased risk of both cognitive decline and incident dementia, as well as decline across all cognitive domains considered including executive function, processing speed, visuospatial ability and memory. Increased risks that did not reach statistical significance were observed for AD and vascular dementia.
However, while pure-tone audiometry is considered to determine hearing acuity by assessing the peripheral auditory system, it may fail to adequately measure central auditory processing (Cooper & Gates, 1992; Golding, Taylor, Cupples & Mitchell, 2006; Strouse & Burger, 1995). As it is likely cognitive functioning, central auditory processing and the peripheral auditory system are interrelated (Humes et al., 2012), it is possible pure-tone audiometry may not be the most effective tool to consider the relationship between hearing loss and cognitive decline (Thomson et al., 2017).

Studies incorporating the evaluation of central auditory processing also demonstrated a relationship between hearing impairment and AD (Gates et al., 2010; Quaranta et al., 2014). The presence of central auditory processing disorder related to both an increased odds ratio for developing AD (Quaranta et al., 2014) and performance decline on the Mini Mental State Examination (MMSE) (Gates et al., 2010). The relative risk for all-cause dementia was found to be inversely correlated with performance on a measure of central auditory processing (Gates et al., 1996). The risk more than doubled when both of a participant’s ears were affected compared to participants with reduced central auditory processing in a single ear.

Lin and colleagues (2011b) demonstrated hearing loss increases the risk of all-cause dementia; over a 10-year period mild hearing loss increased the risk two-fold, compared to three-fold in moderate hearing impairment and five-fold in severe. The risk of incident AD increased, although confidence intervals were wider, suggesting this conclusion is less certain. The severity of hearing loss was only established during baseline assessment, meaning it was not possible to draw conclusions regarding hearing loss trajectory. The authors analysed data from the
Baltimore Longitudinal Study of Aging, a volunteer cohort with high socioeconomic status, potentially limiting generalisability. Meanwhile in a population-based cohort of older adults, every 10 dB increase in hearing loss above 25 dB represented a 20% increase in the risk of developing all-cause dementia (Lin et al., 2013) and hearing impairment was independently associated with a 30-40% acceleration of cognitive decline.

The outlined systematic reviews and empirical studies appear to offer support for an association between dementia risk and ARHL, both when considering pure-tone audiometry and central auditory processing. However, there was often no information on attrition rates, both selective attrition and selective survival is known to affect research with older adults (Weuve et al., 2015). Considerable variability existed in assessment methods for hearing loss, the environmental conditions in which assessment took place, along with determined thresholds to establish hearing loss (Lin et al., 2013). Authors did not usually report whether aetiology of hearing loss was considered or controlled for (Loughrey et al., 2018), and often sample sizes were too small to allow for analysis based on dementia subtype. The generalisability of findings was frequently limited due to study population (Golub et al., 2017), particularly in terms of limited ethnic diversity. These factors raise important caveats when drawing conclusions about the relationship between dementia and hearing impairment and the associated mechanisms.

5.1 Could the relationship be an artefact of hearing impairment affecting the ability to accurately establish cognitive function?

Hearing impairment may result in exaggeration of apparent cognitive impairment when relying solely on screening measures requiring auditory perception
of material, partly through impaired understanding of assessment questions, leading to an overstatement of the relationship (Hodkinson, 1973; Herbst & Humphrey, 1980; Lin et al., 2011b; Deal et al., 2015; Dupuis et al., 2015). The strongest correlation between hearing acuity and performance was found for verbal subtests on the Wechsler Adult Intelligence Scale (WAIS) (Granick, Kleban & Weiss, 1976), the Mental Status Questionnaire (MSQ) (Ohta, Carlin & Harmon, 1981) and the MMSE (Gussekloo et al., 2005). It was also demonstrated that amplification (Weinstein & Amstel, 1986) and hearing augmentation (MacDonald, Joyson, Lee, Seymour & Soiza, 2012) during cognitive screening can improve performance. Hearing loss may also act to exacerbate behavioural symptoms related to dementia (Kreeger, Raulin, Grace & Priest, 1995; Palmer, Adams, Bourgeois, Durrant & Rossi, 1999).

By contrast, a number of researchers outlined procedures involving testing participants on an individual basis in a quiet environment, which is considered the optimum conditions to reduce the apparent impact of hearing impairment (Gordon-Salant, 2005). In these conditions, an independent association between hearing loss and incident all-cause dementia was demonstrated (Lin et al., 2011b), while moderate to severe hearing loss in late life was associated with faster decline in both global cognitive function and memory specifically (Deal et al., 2015), with the greatest estimated decline in individuals who did not wear hearing aids. The observed association between cognitive performance and hearing impairment has also been demonstrated on written versions of screening tests (Uhlmann, Teri, Rees, Mozlowski & Larson, 1989), and on non-auditory and non-verbal cognitive tests (Anstey, Hofer & Luszcz, 2003; Deal et al., 2015; Dupuis et al., 2015; Lin et al., 2013; Lin et al., 2017; Wong, Yu, Chan & Tong, 2014).
Cognitive decline was found to remain significant when hearing aids were applied (Wong et al., 2014), although it was found hearing aids did not fully compensate for auditory deprivation; Aided hearing thresholds were found to be 42 dB HL, indicating some weaker signals would not be audible. When artificial interference was used to reduce auditory function of middle-aged participants to approximate levels observed in older adults, cognitive performance was similar to control conditions without interference, suggesting miscommunication leading to underperformance does not underlie the association between ARHL and dementia (Lindenberger, Scherer & Baltes, 2001).

Overall, when contemplating potential mechanisms relating to the association between dementia and ARHL, it is important to keep in mind that hearing deficits may lead to overestimation of cognitive impairment if appropriate adjustments are not employed, for example controlling the environment in which the assessment takes place and ensuring prescribed hearing aids are utilised. Particular caution should be adopted in relation to studies relying solely on verbally administered assessment methods. An adapted and validated tool could support the estimation of cognitive abilities in the context of hearing impairment.

5.2 Could the relationship be an artefact of cognitive impairment affecting the ability to accurately establish hearing acuity?

Conversely, the presence of cognitive impairment may make it difficult to accurately assess an individual’s hearing status (Lin et al., 2011b). Common procedures for screening hearing like pure-tone audiometry may require cognitive abilities such as attention and working memory (Lemke, 2011). There is some evidence only a small proportion of individuals with dementia residing in nursing
homes were able to complete a complete audiometric assessment protocol (Burkhalter, Allen, Skaar, Crittenden & Burgio, 2009). Hearing deficits may go unrecognised in individuals with dementia as dementia related behavioural symptoms may mask hearing impairment (Palmer et al., 1999). In contrast, clinical practice and research has indicated that individuals at all stages of dementia can reliably participate in most standard audiometric procedures with some adaptations, such as home visits, although readings taken at later stages of dementia may constitute estimated thresholds (Allen et al., 2003; Lemke, 2011; Palmer et al., 1999; Weinstein & Amstel, 1986). While this is an important consideration when contemplating potential mechanisms, it seems unlikely that an artefact explanation accounts for the entirety of the relationship between dementia and ARHL, particularly when reasonable adjustments are utilised.
There are a number of proposed mechanisms potentially underlying the relationship between ARHL and cognitive decline and all-cause dementia (Fortunato et al., 2016; Lin & Albert, 2014; Stahl, 2017), including the common cause, cascade and cognitive load hypotheses.

### 6.1 The common cause hypothesis

The common cause hypothesis, first proposed by Baltes and Lindenberger (1994; 1997), indicates there is not a causal relationship between cognitive decline or all-cause dementia and hearing loss. Instead it is suggested the conditions may result from some common mechanism underlying the neurodegenerative process that manifest as age-related changes in both hearing and cognitive function (See Figure 1; Baltes & Lindenberger, 1997; Dawes et al., 2015a; Deal et al., 2015; Stahl 2017; Wayne & Johnsrude, 2015). As outlined, dementia and ARHL are multifactorial and a number of risk factors coexist.

**Common Cause Hypothesis**

- **Common Neurodegenerative Processes**
- **Shared Aetiology and Risk Factors** including Aging, Genetics and Cardiovascular Risk Factors

- **Structural and Functional Brain Changes**
- **Age-Related Hearing Impairment**
- **Cognitive Decline / Dementia**

*Figure 1. Conceptual model of the common cause hypothesis (adapted from Fortunato et al., 2016; Lin & Albert, 2014; Stahl, 2017; Uchida et al., 2019).*
The finding that the magnitude of the relationship was largely stable across levels of hearing impairment and degrees of cognitive function, with greater hearing loss associated with poorer cognitive function, was interpreted to support the common cause hypothesis (Lindenberger & Baltes, 1994; Lindenberger & Baltes, 1997). A relatively steady association between ARHL and cognitive impairment was observed across tests assessing different underlying cognitive constructs (Wayne & Johnsrude, 2015). Gates and colleagues (2010) suggested the presence of executive dysfunction in individuals with AD and those with central presbycusis without dementia offers evidence of the involvement of a common pathologic process.

Researchers have speculated this common factor could include age, vascular risk factors or genetic factors (Lin & Albert, 2014). Below evidence for potential factors as a common cause is briefly outlined.

6.1.1 Age

Herbst and Humphrey (1980) found a significant association between hearing impairment and all-cause dementia was lost when controlling for age, leading to speculation that the apparent association resulted from the fact both phenomena are functions of aging. However, a prospective study revealed cognitive decline was nearly twice as high in a group with hearing impairment than a group without, even when controlling for age and cognitive function at baseline (Uhlmann, Larson & Koepsell, 1986). Meanwhile, hearing impairment was found to significantly predict more rapid cognitive decline in individuals with AD but not for other subtypes of dementia, even with adjustment for age (Peters, Potter & Scholer, 1988). Ultimately age clearly contributes to both dementia and ARHL, but it appears the association is so strong it is not solely explained by age (Kay, Beamish & Roth, 1964).
6.1.2 Health status

Vascular risk factors including smoking, diabetes mellitus, hypertension, cardiovascular and cerebrovascular disease have an established impact on both cognition and hearing (Baumgart et al., 2015; Helzner et al., 2005; Livingston et al., 2017; Lourenco et al., 2018; Starkstein & Almeida, 2003). These factors may share a common contribution by way of inflammatory pathways (Chen et al., 2009). However, a number of researchers included adjustment for vascular risk factors including smoking status (Lin et al., 2011b; Thomson et al., 2017) potentially ruling these out as contributors to common neurodegenerative processes.

6.1.3 Genetic predisposition

Mutations in the DNA methyltransferase 1 (DNMT1) can cause hereditary sensory autonomic neuropathy, a form of neurodegeneration with peripheral and central involvement, associated with all-cause dementia and sensorineural hearing loss (Klein et al., 2011). Meanwhile, the APOE genotype has been linked with a number of conditions involving neurodegeneration, and it appears the presence of the APOE-ε4 allele may predispose susceptibility to both AD (Corder et al., 1993; Farrer et al., 1997; Pastor & Goate, 2004; Richard & Amouyel, 2001) and hearing loss (Kurniawan et al., 2012), although findings are inconsistent (Dawes et al., 2015b; Mener et al., 2016; O’Grady et al., 2007). However, it was established self-reported hearing loss at baseline was associated with 1.7 times the risk of incident all-cause dementia in a diverse cohort after adjusting for factors including the presence of the APOE-ε4 genotype (Golub et al., 2017).
The majority of evidence appearing to support the common cause hypothesis is correlational and further research is necessary to test this hypothesis further (Martini, Castiglione, Bovo, Vallesi & Gabelli, 2014). Prospective cohort studies may give further insight into the temporal order of any apparent casual effects. If the common cause hypothesis is accurate, treating common underling neurodegenerative processes has the potential to ameliorate both cognitive decline and hearing impairment (Stahl, 2017). However, no effective treatment has currently been identified for degeneration associated with either ARHL (Martini et al., 2014; Stahl, 2017) or dementia (Godyń, Jończyk, Panek & Malawska, 2016; Panza et al., 2016).

6.2 The cascade hypothesis

An alternative explanation for the association is a causal link between the two conditions, with hearing impairment contributing to the risk of cognitive decline and dementia through a number of interrelated mechanisms (Deal et al., 2015; Deal et al., 2017; Lin & Albert, 2014). The cascade hypothesis indicates extended auditory deprivation may cascade and affect cognition directly, through reductions in sensory input, and indirectly through decreased socialisation, isolation and low mood that is known to accompany hearing loss (See Figure 2; Dawes et al., 2015a; Stahl, 2017). While indirect evidence is outlined below, there is a lack of research directly investigating the cascade hypothesis as a potential mechanism in the context of the relationship between dementia and ARHL.
Figure 2. Conceptual model of the cascade hypothesis (adapted from Fortunato et al., 2016; Lin & Albert, 2014; Stahl, 2017; Uchida et al., 2019).

The direct cascade from hearing loss to cognitive impairment follows impoverished auditory input received, leading to a reduction of nerve activity in the auditory pathway (Uchida et al., 2019); the ‘Use-it-or-lose-it’ theory may apply in that a lack of use of auditory processing abilities may lead to further ability loss. Termed the ‘two-hit’ or ‘sequential hit model’, this decreased activity may contribute to structural brain changes and cerebral atrophy, which possibly acts as a ‘second hit’ alongside existing, latent brain pathology related to other causes, such as microvascular disease (Lin & Albert, 2014). Evidence from human and animal studies indicates reductions in stimulation and impoverished auditory signals as a result of an impaired cochlea can lead to changes in brain morphometry and cortical reorganisation (Peelle, Trojani, Grossman & Wingfield, 2011; Stahl, 2017).
Longitudinal and cross-sectional neuroimaging studies have indicated structural changes occur in the brain in older individuals with hearing impairment (Lin et al., 2014; Peelle et al., 2011), potentially contributing to cognitive decline. Individuals with hearing loss have accelerated rates of brain atrophy and grey matter volume loss in the primary auditory cortex (Eckert, Cute, Vaden, Kuchinsky & Dubno, 2012; Husain et al., 2011; Peelle et al., 2011). There are noticeable volume declines in the right temporal lobes including the superior, middle and inferior temporal gyri and the parahippocampus (Lin et al., 2014) along with microstructural changes (Chang et al., 2004; Lin et al., 2008). These regions are linked with integration of sensory information and semantic memory and these changes are implicated in early AD (Chételat et al., 2005; Kantarci & Jack, 2004; Mesulam, 1998; Tranel, Damasio & Damasio, 1997). The magnitude of differences in atrophy rates were comparable to differences observed when considering individuals who developed mild cognitive impairment and those who maintained normal cognition (Driscoll et al., 2009). Functional changes have also been observed in the form of neural activity changes (Peelle et al., 2011).

The indirect pathway is supported by findings that the risk of incident all-cause dementia in association with hearing loss became apparent at a threshold of more than 25 dB (Lin et al., 2011b; Lin et al., 2011c), considered the threshold at which verbal communication begins to be impaired (Dalton et al., 2003). Effective communication requires an intact auditory system for the perception of speech, but also cognitive function to track, integrate and remember utterances from different communicators and to retrieve existing knowledge and formulate a response (Schneider, Pichora-Fuller & Daneman, 2010).
The decline of hearing acuity can have a significant impact on interpersonal relationships by affecting communication ability and social functioning (Mick, Kawachi & Lin, 2014; Slawinski, Hartel & Kline, 1993; Strawbridge et al., 2000; Thomas & Herbst, 1980; Weinstein & Ventry, 1982). Hearing impairment has been associated with social isolation, social and emotional loneliness, depression and lower self-efficacy (Chia et al., 2007; Kramer, Kapteyn, Kuik & Deeg, 2002, Gates & Mills, 2005; Mick et al., 2014; Nachtegaal et al., 2009; Pronk et al., 2011). The relationship between hearing loss and reduced social functioning and an increased risk of endorsing depressive symptoms was found to follow a dose-response pattern as hearing impairment increased (Strawbridge et al., 2000).

An association between an increased risk of cognitive decline, AD and all-cause dementia, and social isolation and late-life depression has been demonstrated through neuroanatomical studies (Bennett, Schneider, Tang, Arnold & Wilson, 2006), epidemiologic studies (Barnes, de Leon, Wilson, Bienias & Evands, 2004; Fratiglioni, Wang, Ericsson, Maytan & Winblad, 2000; Gow, Pattie, Whiteman, Whalley & Deary, 2007; Tilvis et al., 2004; Wilson et al., 2007) and systematic reviews (Plassman, Williams, Burke, Holsinger & Benjamin, 2010). Being single and living alone with limited social connections was found to represent an increased risk for all-cause dementia and AD (Fratiglioni, Paillard-Borg & Winblad, 2004), further, social integration in later life was found to be protective against dementia and AD. Higher levels of social engagement as well as a larger social network were found to have an initial positive correlation with cognitive functioning and were also linked with a reduced rate of cognitive decline (Barnes et al., 2004).
A number of mechanisms may underlie the association between loneliness and isolation as a consequence of hearing impairment and reduced cognitive performance (Bernabei et al., 2014; Hawkley & Cacioppo, 2007); the impacts appear to accrue over time and contribute to acceleration of physiological aging and structural brain changes. Social isolation has been linked to increased inflammation from upregulation of pro-inflammatory genes (Cole et al., 2007; Cole, Hawkley, Arevalo & Cacioppo, 2011), as well as increases in systolic blood pressure (Hawkley & Cacioppo, 2010). A correlation has been found between social isolation and risk factors for hearing loss and cognitive impairment, including smoking, poor dietary choices and reduced exercise, as well as an increased likelihood of developing depressive symptoms and a reduced sense of self-esteem (Bernabei et al., 2014).

It would follow that reducing hearing handicap with hearing aids may reduce the direct and indirect cascade from hearing impairment to dementia (Stahl 2017). There is research demonstrating hearing aids improve wellbeing, reduce the likelihood of depression and increase social activity (Kochkin & Rogin, 2000). Shortly after application, a significant reduction in depressive symptoms and improvement in quality of life was observed (Boi et al., 2012), positive effect was also seen for general health, social functioning, emotional stability and reduced caregiver burden. Dawes and colleagues (2015a) found hearing aid use correlated with improvements in cognitive performance on visually presented cognitive tests, although this association was found to be independent of social isolation and depression. The authors suggested observed positive effects on cognition may have resulted from improved audibility or increases in self-efficacy associated with hearing aid use. Understanding about the longer-term protective effects for cognitive function is limited and further research is necessary (Moyer, 2012).
6.3 The cognitive load hypothesis

Cognitive load is considered to be the cognitive effort required to perform a task (Sweller, Ayres & Kalyuga, 2011), every individual has certain cognitive capacity that can be directed towards cognitive tasks. The cognitive load hypothesis posits that as hearing diminishes, cognitive resources are diverted from central cognitive processes, such as storage and retrieval, to perception of auditory information to compensate for degraded auditory signals and impaired encoding (Pichora-Fuller, Schneider & Daneman, 1995). Perceptual information from a damaged cochlea requires more processing before language content can be decoded (Lunner, Rudner & Rönnerb, 2009), requiring working memory capacity (Pichora-Fuller, 2007); This phenomenon is termed effortful listening and leads to depletion of cognitive reserves (Rabitt, 1968; Tun et al., 2009).

![Cognitive Load Hypothesis Diagram](image)

*Figure 3.* Conceptual model of the cognitive load hypothesis (adapted from Fortunato et al., 2016; Lin & Albert, 2014; Stahl, 2017; Uchida et al., 2019).
Similar to the cascade hypothesis, evidence supporting the cognitive load hypothesis is indirect and focused research efforts may increase understanding. There is evidence that increased listening effort during speech perception accompanies hearing impairment (McCoy et al., 2005; Pichora-Fuller et al., 1995), even when amplification was applied (Rakerd, Seitz & Whearty, 1996). However, existing studies are affected by insufficient statistical power, and a lack of standardisation and consistency (Ohlenforst et al., 2017).

Comparing speech perception and recall in younger and older participants supported the cognitive load hypothesis, as perceptual difficulties appeared to affect speech understanding directly and indirectly through reallocation of resources to effortful listening (Pichora-Fuller et al., 1995). It is proposed that increased processing load, either related to hearing impairment or induced experimentally when perceiving degraded speech, interferes with encoding and contributes to poorer recollection (Burkholder, Pisoni & Svirsky, 2005; McCoy et al., 2005; Murphy, Craik, Li & Schneider, 2000; Pichora-Fuller et al., 1995; Piquado, Cousins, Wingfield & Miller, 2010; Wingfield, Tun & McCoy, 2005) and places increased demands on working memory and executive function (Amichetti, Stanley, White & Wingfield, 2013; Wingfield & Tun, 2007).

Effortful listening was found to contribute to greater fatigue (Edwards, 2007), with negative consequences for recall accuracy and second task performance (Tun et al., 2009); A similar trend was observed when individuals perform ‘dual tasks’ and processing capacity is exceeded (Lavie, 1995; Lavie, 2005). It is suggested effortful listening constitutes a continual ‘dual task’ for individuals with hearing loss, as hearing and auditory processing are constantly active due to the evolutionary need to

It is also possible hearing loss amplifies existing cognitive impairment by depleting cognitive reserves and redirecting neural resources that were employed for cognitive compensation strategies, such as recruitment of compensatory brain regions (Panza et al., 2015; Stahl, 2017). Apparent cognitive decline from diversion of cognitive resources would potentially be temporary and reversible (Wayne & Johnsrude, 2015). However, prolonged cognitive load from hearing impairment may have a taxing effect on brain structures and contribute to acceleration of existing neurodegeneration, leading to permanent cognitive deterioration and the development of dementia (Stahl, 2017).

The relationship may be bidirectional and cognitive deterioration may also affect auditory performance; There is a long-standing suggestion that older adults have reduced cognitive resources compared to younger individuals, based on growing age differences in performance as cognitive tasks become increasingly demanding (Myerson et al., 1990). This has been supported by findings of over-activation in right prefrontal regions in older adults during the maintenance of a low working memory load, with the authors suggesting the over-activation represents functional compensation for reduced resources (Cappell et al., 2010). Conversely, under-activation and reduced accuracy was seen in older adults during high working memory load, interpreted to represent a threshold when task demands exceeded available cognitive resources.

It was shown elderly listeners were particularly vulnerable to rapid input of speech, although this was ameliorated by effective application of linguistic context to
aid comprehension (Wingfield, 1996). However, memory constraints in elderly subjects have been found to limit the ability to apply linguistic knowledge. The presence of simultaneous background noise was found to have a negative effect on a listening task and on the ability to perform cognitive activities, such as a complex visual task (Sarampalis, Kalluri, Edwards & Hafter, 2009). The application of a hearing aid with a digital noise reduction algorithm was found to improve performance on the cognitive task, indicating it reduced cognitive effort required and freed up cognitive resources. The concept of ‘cognition driven’ hearing aids, taking into account individual cognitive capacity and differences in working memory when designing and programming hearing aids, may be a future avenue to optimise signal processing and minimising the impact of sensory impairment on cognitive load (Lunner et al., 2009).

If a causal relationship did exist between hearing loss and cognitive decline then rehabilitation of hearing loss through hearing aids has the potential to lessen cognitive load (Stahl, 2017). A systematic review of hearing loss as a potential risk factor for all-cause dementia found that 9 of the 17 included studies considered the impact of hearing aid use on cognition, with 6 articles finding no correlation (Thomson et al., 2017). In the other three studies, hearing aid use was found to reduce the likelihood of cognitive decline (Amieva et al., 2015; Deal et al., 2015; Lin et al., 2011a) although hearing aid use was considered dichotomously, masking the complexity of user compliance (Thomson et al., 2017).

It was demonstrated that while hearing thresholds improved with the application of hearing aids, cognitive performance did not improve compared to controls without hearing aids (van Hooren et al, 2005). The authors interpreted this
to suggest that while hearing aids restore impairment in terms of the sensory organ, this does not extend to the central nervous system, although they recognised that benefits may emerge after the one-year study follow up period. In contrast, Mosnier and colleagues (2015) found that rehabilitation of hearing impairment through cochlear implantation had wide reaching improvements including cognitive abilities and also speech perception, social activity and quality of life. A significant improvement in cognitive function was identified after three months using a hearing aid for older individuals affected by ARHL (Acar, Yurekli, Babademez, Karabulut & Karasen, 2011) along with improvements in mood and social communication. These findings have not been replicated in individuals with all-cause dementia (Allen et al., 2003).

Anatomic studies of individuals who have undergone cochlear implantation revealed cortical reorganisation in both the primary and secondary auditory cortex (Cosetti et al., 2016; Lee et al., 2003; Petersen, Gjedde, Wallentin & Vuust, 2013) and an association has been observed between the amount of brain plasticity following implantation and the level of speech understanding. In terms of the impact on cognition, cochlear implantation has been associated with improvements in memory and verbal performance (Cosetti et al., 2016).

Research indicates that hearing aids initially increase working memory capacity (Lehrl, Funk & Seifert, 2005), however there is limited evidence in terms of the long-term impact (Kalluri & Hulmes, 2012). Further research is required on the longer term impact of hearing aids when considering cognitive load and reduction of the risk of cognitive decline or dementia (Lin & Albert, 2014).
Conclusion

There is mounting evidence to support hearing loss as an independent and modifiable risk factor precipitating the development of cognitive decline and dementia (Lin et al., 2011b; Lin & Albert, 2014), with the estimated attributable risk at 36%. The identification of the mechanism or mechanisms underlying this risk relationship may have considerable clinical relevance in developing effective intervention or management for ARHL and dementia. It is possible further research into prevention and rehabilitation of hearing loss may contribute to delays in dementia onset (Stahl, 2017); delays are especially valuable in the absence of more efficient pharmacotherapy. A randomised control trial with a large older adult cohort may help address the question of whether treating hearing loss reduces the risk of dementia, along with allowing exploration of outlined mechanistic pathways (Lin & Albert, 2014).

Current research is complicated by the fact that individuals who take up hearing aids are usually healthier and have higher socio-economic status (Stahl, 2017); While a randomised control trial would be the gold standard to investigate the impact of hearing aids on cognition and offer insight into potential mechanisms, this raises serious ethical concerns about restricting access to such a valuable intervention in a ‘watchful waiting’ condition.

While the beneficial effects of hearing aids to support cognitive function are potentially only modest (Uchida et al., 2019), the increasing burden of hearing loss and dementia in line with an aging population is justification for further investigation into the role hearing aids can play to support hearing well, living well and aging well in later life. While there has been an understandable focus on improving audibility
through hearing aid interventions (Kochkin, 2011), the more cognitive elements underpinning listening, including comprehending and communicating have been overlooked. ‘Cognition driven’ hearing aids may be a future avenue offering optimal benefit in supporting cognition (Lunner et al., 2009). A switch from a reactive to a proactive approach when considering hearing restoration would certainly do no harm in terms of cognition (Lin & Albert, 2014; Stahl, 2017), and treating hearing loss in individuals living with dementia has been shown to have benefits for the clinical management of associated ‘problem behaviours’ as reported by caregivers (Palmer et al., 1999).

Hearing loss often remains untreated (Popelka et al., 1998); The delayed uptake and poor adherence of hearing aids is an important consideration (Chien & Lin, 2012; van Hooren et al., 2005; Wong et al., 2014). Understanding influential factors affecting uptake, including degree of hearing loss, self-efficacy, ethnicity and the role of the clinician may offer insight into opportunities to increase buy in (Chien & Lin, 2012; Bainbridge & Ramachandran, 2014; Knudsen et al., 2010; Nieman, Marrone, Szanton, Thorpe & Lin, 2016).

When considering potential mechanisms of the association between ARHL and dementia, the majority of research is correlational, making it difficult to draw firm causal inferences to support either the cognitive load hypothesis or cascade hypothesis (Wayne & Johnsrude, 2015). While outlined research provides indirect evidence, there is a lack of direct investigative efforts to support each hypothetical mechanism and this represents an important future consideration. In terms of the common cause hypothesis, as with other observational epidemiological studies, it is
impossible to exclude an unmeasured common aetiology or aetiologies that may account for the association, for example certain genetic factors (Lin et al., 2011b).

Considerable variations across studies in terms of study population, methods employed to establish cognitive function and hearing ability, as well as consideration of potential confounders makes it difficult to compare findings and to provide conclusive support for a specific mechanism (Gennis et al., 1991; Thomson et al., 2017). Future research may benefit from standardisation in terms of research protocol, as well as including measures of central auditory processing in addition to pure-tone audiometry (Thomson et al., 2017). A further complicating factor when interpreting findings for potential mechanisms is the presence of different types of dementia and ARHL, small samples sizes usually limit potential to stratify analysis by type and it is possible type affects the association and corresponding mechanism.

In contradiction to the suggestion of ARHL as a risk factor for dementia, there is the possibility that ARHL may be considered an effect rather than a cause, with hearing loss representing an early symptom during the prodromal dementia phase (Gallacher et al., 2012; Martini et al., 2014). Difficulty understanding speech among noise may represent an early manifestation of neurodegenerative processes leading to dementia (Gates et al., 2010). While the neuropathology related to AD appears to be absent in the peripheral auditory pathways (Sinha, Hollen, Rodriguez & Miller, 1993), damage of the central auditory nuclei (Parvizi, van Hoesen & Damasio, 2001) and cortical areas (Kurylo, Corkin, Allard, Zatorre & Growdon, 1993) required for higher-order processing of language and auditory stimuli, may be related to neurodegeneration associated with AD.
Figure 4. Conceptual model of the potential integration of proposed pathways (adapted from Fortunato et al., 2016; Lin & Albert, 2014; Stahl, 2017; Uchida et al., 2019).

Ultimately, it is possible that some shared neurodegenerative process, increased cognitive load, direct impairment to sensory input and indirect psychosocial consequences may not be mutually exclusive, with each factor interacting and contributing to cognitive impairment and the likelihood of developing dementia (See Figure 4; Parham, Lin, Coelho, Sataloff & Gates, 2013).

Conceptually, this topic spans the fields of neurology, psychology and audiology at the least and this may have acted as a barrier to research advances. Interdisciplinary research efforts will be necessary to provide essential answers to the questions raised; What are the mechanisms underpinning the association between ARHL and dementia and does the treatment of hearing loss reduce the risk of cognitive decline and dementia.
References


Assessment of Neuropsychological Status for Hearing Impaired Individuals (RBANS-H) before and after cochlear implantation: a protocol for a prospective, longitudinal cohort study. *Frontiers in Neuroscience, 10*, 512.


Stahl, S. M. (2017). Does treating hearing loss prevent or slow the progress of dementia? Hearing is not all in the ears, but who’s listening?. *CNS Spectrums, 22*(3), 247-250.


Adaption and Validation of the Addenbrooke’s Cognitive Examination (ACE-III) as a Cognitive Screening Tool for Dementia for Older Adults with Comorbid Hearing Impairment
Abstract

**Background:** An association between dementia and age-related hearing loss has been consistently established, however current screening measures of cognitive performance may be affected by hearing loss. This potentially influences the accuracy of cognitive estimates.

**Aims:**

1. To develop an adapted version of the Addenbrooke’s Cognitive Examination (ACE-III) for older adults with hearing loss, the HI-ACE-III.
2. To test the ability of the HI-ACE-III to distinguish individuals with a diagnosis of dementia from those without and establish an optimum cut-off.
3. To test HI-ACE-III subscales for convergent and divergent validity against standardised cognitive measures of relevant domains.

**Method:** Adaption, carried out in consultation with experts and potential users, involved converting verbal instructions to visually presented instructions. Two groups of participants with hearing impairment over the age of 65 were recruited, the first were determined to be cognitively intact (HI group; n = 30), the second had an established dementia diagnosis (D-HI group; n = 16). The HI-ACE-III was administered along with additional visually presented cognitive tests; the Rey-Osterrieth Complex Figure (ROFC), Spatial Span (SS) and Graded Naming Test (GNT).

**Results:** The ROC analysis revealed an Area Under the Curve (AUC) value of .960 for the HI-ACE-III, with an optimum cut-off point of <87, achieving 93.8% sensitivity and 93.3% specificity and likelihood ratio of dementia of 14.06:1. Concurrent validity was demonstrated through correlations between HI-ACE-III domain scores and relevant standardised neuropsychological measures. Internal consistency of the HI-ACE-III was verified with Cronbach’s alpha (α = .925).

**Conclusions:** The HI-ACE-III showed good reliability, validity and diagnostic utility for dementia screening in older adults in a hearing impairment context. The adapted HI-ACE-III may offer an accurate and reliable indication of cognitive performance, supporting timely diagnosis of dementia and contributing to future research.
1 Introduction

Dementia is a progressive syndrome typically characterised by the presence of cognitive decline sufficient to interfere with the ability to independently manage activities of daily living (Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; American Psychiatric Association, 2013). Dementia affects around 6.5% of individuals over the age of 65 (Wu et al., 2017), although many individuals remain undiagnosed (Brayne & Davis, 2012). In line with the aging population worldwide, the prevalence of dementia is projected to nearly double every 20 years (Prince et al., 2013). Dementia has a considerable impact on both individual wellbeing and caregiver burden (Banerjee et al., 2006; Etters, Goodall & Harrison, 2008; Logsdon, McCurry & Teri, 2008; Bourgeois & Hickey, 2009). It is thought to be one of the foremost causes of disability globally (Ferri et al., 2005) and the associated global economic burden is substantial (Xu, Zhang, Qiu & Cheng, 2017). In 2015, The World Health Organisation (WHO) supported a research call for action to contribute to reducing the dementia burden. As a result, exploring potential risk factors associated with cognitive decline and dementia has received increased attention.

Along with findings suggesting a higher prevalence of hearing loss in older adults with cognitive impairment (Lopes et al., 2007), there is mounting evidence to indicate age-related hearing loss as a risk factor for developing dementia (Livingston et al., 2017). A significant, independent correlation between higher severity of hearing loss and greater odds of having dementia was initially identified by Uhlmann and colleagues (1989). More recent research has offered further support for the association between cognitive decline, incident dementia and age-related hearing loss (ARHL) (Gennis, Garry, Haaland, Yeo & Goodwin, 1991; Lin et al., 2011a; 2013;
While most risk factors associated with dementia are not modifiable, including genetic predisposition and sex (Andersen et al., 1999; Pedersen, Gatz, Berg & Johansson, 2004), the impact of hearing loss can be improved through auditory rehabilitation (Castiglione et al., 2016). There is also evidence that decline in hearing has the highest relative risk out of all modifiable risk factors (Livingston et al., 2017). This presents interesting possibilities for interventions that may slow the progression of cognitive decline (Stahl, 2017). However, while a number of potential theories have been put forward, the mechanisms underlying the association between dementia and age acquired hearing impairment are poorly understood (Wayne & Johnsrude, 2015), as outlined in the conceptual introduction.

Cognitive screening tools are employed clinically to give a brief indication of cognitive abilities and to highlight individuals who might benefit from more comprehensive neuropsychological and neurological investigations when considering conditions such as dementia (Ismail, Rajji & Shulman, 2010). Current cognitive screening tools are reliant on verbal instructions, leading to speculation that hearing impairment exaggerates apparent cognitive impairment by affecting performance (Lin et al., 2011a; Deal et al., 2015). The aim of this research project is to adapt and validate an existing cognitive screening tool, the Addenbrooke’s Cognitive Examination (ACE-III) (Mathuranath, Nestor, Berrios, Rakowica and Hodges, 2000). The adapted version of the ACE-III is intended to appropriately assess for cognitive impairment in older adults with hearing loss, contributing to future research into the link between dementia and hearing loss, as well as timely identification of dementia and effective clinical management.
1.1 The association between age-related hearing loss and dementia

Hearing loss, considered from an average hearing threshold of 26 dB or higher (WHO, 1991; 2014), is estimated to affect around two thirds of adults aged 70 and over (Lin, Thorpe, Gordon-Salant & Ferrucci, 2011c). Lin and colleagues (2011a; 2011b) found a correlation between severity of hearing loss and risk of developing dementia. Older adults with mild hearing loss had a 1.9 fold increased risk, compared to 3.0 fold for moderate hearing loss and 4.9 fold for severe. These results remained significant after adjusting for potential confounders such as age, education and health status. A longitudinal cohort study revealed older adults with hearing impairment were found to develop dementia at a higher rate than hearing intact controls (Gurgel et al., 2014). Over a 17 year period, an association was demonstrated between auditory threshold, the minimum sound level an individual can detect, and dementia (Gallacher et al., 2012). Hearing impairment was also associated with more rapid decline in scores on the Modified Mini-Mental Status Exam (3MS-R; Tschanz et al., 2002). A direct association was found between a 1.2 dB reduction in hearing and 1 standard deviation (SD) decrease in executive function composite score (Gates et al., 2010). These findings were criticised for a lack of generalisability due to homogenous samples but have been replicated in an ethnically diverse sample (Golub et al., 2017).

Contradictory evidence comes from a cross-sectional study that revealed no association between impaired hearing and non-verbal tests of memory and cognitive speed, finding only a relationship with increasing visual impairment (Gussekloo et al., 2005). The authors suggested that findings indicating an association could result from the over-reliance on cognitive tests that require verbal administration. A
prospective study revealed that correlations between memory and hearing acuity were not significant after adjusting for gender and age (Gennis, Garry, Haaland, Yeo and Goodwin, 1991). Additionally, no correlation was found between hearing at baseline and cognitive functioning at 5 year follow up and hearing status was not predictive of change in cognitive screening test score. The comparability of findings both supporting and contradicting the association has been questioned due to varying criteria for establishing the presence of hearing impairment and for diagnosing mild cognitive impairment and dementia (Wei et al., 2017).

It is possible that auditory threshold can influence the cognitive assessment process and test performance (Gallacher et al., 2012). The authors found that hearing loss was more strongly associated with cognitive decline on tests administered verbally compared to those presented on the computer. When considering a sample of older adults with no known cognitive impairment living in the community, worse performance on the MoCA was observed in individuals with hearing impairment despite participants engaging with the verbal administration of the test (Dupuis et al., 2015). Meanwhile severe hearing impairment has been shown to impair test performance on neuropsychological assessment covering various cognitive domains (Hill-Briggs, Dial, Morere & Joyce, 2007).

Creating a validated version of a cognitive screening tool for cognitive impairment adapted for individuals with hearing loss would aid investigation into the association as it would minimise underperformance related to auditory threshold. A screening tool that is not reliant on audibility and is unaffected by hearing status would support longitudinal research into the etiological link between dementia and
hearing impairment, as well as research into potential interventions intended to delay the onset of dementia, such as the application of hearing aids.

While there is some suggestion that cognitive impairment may affect the accuracy of establishing hearing acuity (Lin et al., 2011) as screening measures such as pure-tone audiometry rely on certain cognitive abilities (Lemke, 2011), research indicates that reliable participation in most standard audiometric procedures can be achieved at all stages of dementia (Allen et al., 2003; Lemke, 2011). More specifically, the portable audiometer used in the current investigation has been successfully administered to individuals with cognitive impairment (Pletnikova et al., 2019).

1.2 The rationale for developing a screening tool that is not affected by hearing impairment

Cognitive screening tools are used to give an initial indication of cognitive functioning and highlight cases where further assessment, including neuroimaging and functional evaluation, is necessary to consider a possible dementia diagnosis (Ismail, Rajji & Shulman, 2010; Ngo & Holroyd-Leduc, 2014). At present, there are no cognitive screening tests that have been validated to assess for dementia in the context of hearing loss. Nearly all available screening tools are currently reliant on the verbal presentation of instructions. It has been suggested that problems with speech perception may interfere with performance on cognitive assessment (Gennis, Garry, Haaland, Yeo and Goodwin, 1991). Residents with significant hearing loss in a residential home were found to perform worse on the MMSE compared to individuals with mild hearing loss (Jupiter, 2012). This could potentially lead to an exaggeration of apparent cognitive impairment as a result of hearing loss. However,
it would not be appropriate to withhold intervention on the basis of hearing impairment as prompt diagnosis and treatment for dementia may result in better outcomes (Prince, Bryce & Ferri, 2011).

Consequently, in addition to the research utility, there is significant clinical utility in developing a validated cognitive screening tool that meets the needs of older adults with hearing impairment, along with establishing appropriate cut off scores. This screening tool could allow individuals with hearing impairment to gain appropriate and timely dementia diagnoses and access to clinical management by offering an accurate representation of their cognitive abilities.

1.3 Previous attempts to develop screening tests for individuals with hearing impairment

The MoCA is a sensitive and well validated, brief screening tool for mild cognitive impairment and dementia (Nasreddine et al., 2005). The MoCA was recently adapted for individuals with hearing loss, known as the HI-MoCA (Lin et al., 2017). Verbal instructions were presented visually on a PowerPoint, mirroring administration guidelines as closely as possible. The HI-MoCA was administered to over 100 participants aged over 60 with normal cognition; one group had hearing within the normal range while the other group had severe hearing loss. The authors found the HI-MoCA to be a reliable screening test and straightforward to administer to individuals with hearing impairment. The main limitation of this study is that no one with cognitive impairment or dementia was included, thus it is impossible to know the sensitivity and specificity of the HI-MoCA; In other words, how well it distinguishes between those with and without cognitive impairment and the efficacy by which it identifies individuals with dementia, the key function of a screening test.
Claes and colleagues (2016) intended to complete a prospective, longitudinal study adapting The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) for individuals with hearing impairment in order to explore the impact of cochlear implants on cognition. This research is in the early stages and the first step will be validating the use of the RBANS-H for older adults with hearing impairment.

1.4 The Addenbrooke’s Cognitive Examination

The Addenbrooke’s Cognitive Examination (ACE) was originally developed as an extension of the Mini-Mental State Exam (MMSE) due to limitations with the latter such as the inability to differentiate dementia type (Mathuranath, Nestor, Berrios, Rakowica and Hodges, 2000). While administration takes longer than the MMSE, it assesses a broader range of cognitive domains including memory, language, attention and visuospatial abilities (Hsieh et al., 2013). The third version, the ACE-III, included updates to improve sensitivity and reflect cross-cultural usage (Mioshi, Dawson, Mitchell, Arnold & Hodges, 2006; Hsieh et al., 2013).

The ACE-III has been shown to have high internal consistency and has been validated as a screening test for dementia (Hsieh et al., 2013; Matias-Guiu et al., 2017). It has been found to have high specificity and sensitivity at distinguishing dementia from normal cognition (Elamin, Holloway, Bak and Pal, 2016). The ACE-III was found to have the highest diagnostic accuracy in the screening of Alzheimer’s Disease (AD) in comparison to the MMSE, MoCA and Rowland Universal Dementia Assessment Scale (RUDAS) (Matías-Guiu et al., 2017). The ACE-III has never been adapted or validated as a screening tool for dementia for older adults with hearing
impairment. As the ACE-III is widely used, a hearing-impaired version would be useful for clinical and research settings.

1.5 Research Aims

The primary research objective is to develop and validate an adapted version of the Addenbrooke’s Cognitive Examination (ACE-III) for individuals with hearing loss, the HI-ACE-III.

The study has 3 aims:

1. To develop the HI-ACE-III by presenting any verbal instructions visually using a timed PowerPoint (Microsoft Corp.) presentation while maximising internal consistency with the original ACE-III.

2. (Primary aim) To test the ability of the HI-ACE-III to distinguish between a group of hearing-impaired individuals with and without dementia. This will include providing an optimum cut-off point that maximises sensitivity and specificity for this purpose.

3. To validate HI-ACE-III subscales against non-verbally presented measures of relevant cognitive abilities to establish convergent and divergent validity. The cognitive domains considered include visuospatial ability, incidental memory, spatial working memory and naming.
2. Method

2.1 Joint Project

This was a joint project with Nattawan Utoomprurkporn, PhD student and qualified audiologist, and Courtney North, Trainee Clinical Psychologist. The current study considered the adaption and validation of the HI-ACE-III for individuals with dementia. Utoomprurkporn (2020) focused on the validation of the HI-MoCA for individuals with Mild Cognitive Impairment (MCI). North (2020) was also involved in the adaption of the HI-ACE-III, considering the validation of the HI-ACE-III for participants with MCI. (See Appendix A for a detailed summary of the contribution of each researcher).

2.2 Ethics

Ethical approval for the study was granted by the University College London (UCL) and NHS Health Research Authority (HRA) and Research Ethics Committee (REC) (Reference: 18/LO/1225; Integrated Research Application System (IRAS) identification 247176; Appendix B). Local research and development approval was given in each NHS site through the North Central London Research Network (NoCLoR). The project was also registered on ClinicalTrials.gov, NCT number: NCT03648502. A risk assessment was completed and registered (Reference No. RA019358/1). The project was also covered by UCL Data Protection Registration (Reference No. Z6364106/2018/05/181 health research).

An information sheet about the study was provided to participants at least 24 hours prior to participation (Appendix C). Participants were also required to provide written informed consent regarding participation (Appendix D).
2.3 Sample Size and Power Calculation

A sample size calculation was performed using EasyROC, a web-tool for Receiver Operative Curve (ROC) analysis (Goksuluk, Korkmaz, Zararsiz and Karaagaoglu, 2016). Power was calculated for a ROC analysis to determine whether the adapted version of the ACE-III is significantly superior to chance at distinguishing participants with dementia from those who are cognitively intact.

Alpha for the calculation was set at 0.05, while beta was set at 0.8. The predicted effect size, which is equated to the area under the curve (AUC) in a ROC analysis, was set at 0.70. This is lower than the area under the curve figure of 0.897 for the ACE-III for non-hearing impaired controls and non-hearing impaired participants with mild AD (Matías-Guiu et al., 2017). This lower figure ensures a conservative estimate for the sample size due to the possibility that the hearing-impaired version of the screening tool is not as accurate at distinguishing cognitive impairment as the established version.

The sample size calculation indicated that a total of 24 participants would be required for each group. An initial recruitment target of 60 participants was set, 30 participants with hearing impairment and without cognitive impairment for the HI group and 30 participants with hearing impairment and a diagnosis of dementia for the D-HI group.

2.4 Participants

For the current study, there were two groups; The hearing impairment group without cognitive impairment (HI group) and dementia with hearing impairment group (D-HI group).
Inclusion criteria for both groups

1. Aged over 65 years old.
2. Had documented hearing loss, which was verified using a portable hearing screening device. Hearing loss was considered as an average threshold of 30dB or more.
3. Lived in the community and not a residential care setting.
4. Had capacity to consent to take part in the project.
5. Were able to communicate in English and could engage in the assessment without the support of an interpreter.

Additional inclusion criteria for the HI Group

1. Had a caregiver who consented to involvement in the study in order to act as an informant.
2. Were cognitively intact; this was verified using the General Practitioner Assessment of Cognition (GPCOG) (Brodaty et al., 2002).

Additional inclusion criteria for the D-HI Group

Exclusion criteria

1. Had hearing loss that is severe or profound (Pure Tone Audiometry (PTA) >70dBHL).
2. Had congenital or childhood-onset hearing loss.
3. Had uncorrected visual impairments or physical impairments which prevented them from participating in the written portion of the tests.
5. Had psychiatric comorbidity that may prevent participation or affect cognitive capabilities, for example the presence of hallucinations.

2.5 Setting

The HI group was recruited from patients with established hearing impairment without known cognitive impairment being treated at the adult audiology hearing aids clinic at the Royal Throat Nose Ear Hospital (RHTNEH). These participants were tested by Nattawan Utoomprurkpor, a qualified audiologist associated with the project. Data collection was supported by Professor Doris Bamiou, professor of neuroaudiology at University College London (UCL).

Participants for the dementia with hearing impairment group (D-HI group) were recruited from patients under the care of the Camden and Islington memory services. They had an existing diagnosis of dementia, along with established hearing impairment, confirmed through a hearing screening. Data collection was supported by Dr Sergi Costafreda Gonzalez, Consultant Psychiatrist in the memory service.

Testing either took place at the Royal National Throat Nose Ear Hospital, the Camden or Islington memory service, University College London or the participant’s
home address depending on the preference of the participant. Caregiver participation either took place in person or over the phone. Any travel expenses incurred as a result of participating were reimbursed to participants.

2.6 Recruitment process

At the Royal National Throat Nose Ear Hospital, potential participants for the HI group were approached by a clinician known to them in order to get their permission to be contacted by a researcher about the study (See Figure 1.).

In the memory service, participants were recruited by two means (See Figure 2.). A proportion of participants were informed about the study by a clinician known to them, if they were interested then a researcher contacted them about participating. The rest of the participants were identified through a research register. If there was uncertainty about eligibility, for example due to physical health comorbidities or queries about capacity, advice from the treating clinician was sought.

Once identified, the researchers met participants either at their home or at one of the hospital clinics in order to complete research screening and additional listed measures dependent on the group they were recruited into. If there were concerns about the individual’s capacity, a trained researcher assessed capacity to consent to participate in the research. In cases where the researcher was not able to establish capacity, the interview was discontinued and the participant was excluded from the study.
Figure 1. Flowchart outlining the recruitment process for the HI Group

Figure 2. Flowchart outlining the recruitment process for the D-HI Group

2.7 Data collection

All measures except those specified below were administered to both groups, HI and D-HI. The eligibility and hearing screening tests were carried out by the three researchers involved in the project. Training in the use of the audiogram and administration of the cognitive screening and assessment tools was completed by all researchers administering the tests. The approximate time for the administration of all the measures was two hours. Depending on the participant’s preference, this took place over one or two sessions.

Screening tests
Auditory tests

- Audiogram – Participants seen at the Royal National Throat Nose Ear Hospital had their hearing acuity established through a Pure Tone Audiogram carried out by a qualified audiologist in a soundproof room. A portable audiogram was used to confirm the presence of hearing impairment in participants not seen at the Royal National Throat Nose Ear Hospital.

Cognitive screening test (HI Group only)

- The GPCOG is a validated, brief screening tool for cognitive impairment that is recommended for use in primary care (Ismail, Rajji and Shulman, 2010). A score of 9 on the GPCOG patient section indicates that the individual is not cognitively impaired (Brodaty, Hemp & Low, 2004). If the individual scored between 5 and 8 on the patient section then the informant section was administered, if the GPCOG-informant score fell between 4 and 6 they were recruited into the study. In line with the study conducted by Lin and colleagues (2017), if a participant scored below cut off on the GPCOG they were excluded from the study; a score of 4 or below on the GPCOG-patient and 3 or below on the GPCOG-informant.

Hearing Impaired Addenbrooke’s Cognitive Examination III (HI-ACE-III)
The hearing impaired version of the original Addenbrooke’s Cognitive Examination-III (ACE-III) was developed as part of this study. The copyright owner of the ACE III, John Hodges, granted permission for the test to be adapted in this manner and also offered consultation. Further consultation during adaption took place with experts in neuropsychology from UCL, Dr Joshua Stott, Dr Narinder Kapur and Dr John King, as well as consultant psychiatrists working in the Camden and Islington memory clinics. Potential users of the adapted ACE-III were consulted in order to consider usability. A preliminary version of the HI-ACE-III was pilot tested with a group of older adults, caregivers for individuals living with dementia and clinicians working in a memory clinic. Feedback from the pilot testing was integrated into the final version of the HI-ACE-III.

The adapted version included read instructions presented on a computer using a PowerPoint (Microsoft Corp.) presentation instead of the verbal instructions used in the original test. The contrasting blue background and white characters were chosen based on guidelines regarding readability when using a computer screen (Hall & Hanna, 2004). To ensure standardisation in the administration of the HI-ACE-III, an administration manual was also developed (Appendix E). Administration took approximately 20 minutes.

An adapted version of the MoCA for individuals with hearing impairment (HI-MoCA) was also administered to participants as a part of an associated project (Utoomprurkporn, 2020). The HI-MoCA will not be discussed further in the current thesis. The administration of the HI-ACE-III and the HI-MoCA was counterbalanced to ensure that order effects did not impact performance.

*Non-verbal cognitive tests*
Additional cognitive measures were selected in order to evaluate the convergent and divergent validity of four of the HI-ACE-III subscales; visuospatial, attention, language (naming) and episodic memory. The instructions for these measures were also presented visually to ensure that performance was not affected by hearing acuity. The same guidelines regarding readability were followed (Hall & Hanna, 2004).

- The Rey-Osterrieth Complex Figure test (ROCF) (Rey, 1941) – This test is an established and validated measure of visuospatial abilities (Shin et al., 2006). The test requires the participant to copy an abstract figure. Administration took approximately 5 minutes, the time taken to complete the task was recorded.

- The ROCF Recall – This involves the immediate recall, following a 3 minutes delay, and delayed recall, after 30 minutes, of the abstract figure previously copied as outlined (Shin et al., 2006). This test assesses incidental memory as participants are not made aware of the recall trials. Administration took approximately 10 minutes.

- Spatial Span from the Wechsler Memory Scale, 3rd edition (WMS-III; Wechsler, 1997) – The Spatial Span subtest is viewed as an indicator of working memory, visuospatial processing and attention (Brown, 2016). The test involves the participant recreating a sequence of taps on numbered blocks performed by the test administrator. Administration took approximately 10 minutes.

- The Graded Naming Test (GNT) (McKenna & Warrington, 1980) – This test
is validated measure of word retrieval and identifies any naming difficulties (Warrington, 1997). Participants are required to name a number of visually presented images. Administration took approximately 20 mintes.

The following measures were only administered to participants tested at the Royal National Throat Nose Ear Hospital, as part of an associated project (Utoomprurkporn, 2020). These measures will not be reported on further in the current project.)

- Speech / word in background test (Emanuel, 2002) – a measure of auditory processing.
- Dichotic listening test (Moray, 1959) – a further auditory processing measure to investigate selective attention and lateralisation of brain function.
- The Queen Square Test of Auditory Cognition (QSTAC) (Johnson et al., 2019) – a test battery designed to assess central auditory function.

(The following measures were administered to all participants as part of an associated project (Utoomprurkporn, 2020). They will not be considered further in the current project.)

- The Speech, Spatial and Qualities of Hearing Scale (SSQ) (Gatehouse and Noble, 2004) – a measure that assesses hearing over a range of domains.
- Modified Amsterdam Inventory for Auditory Disability and Handicap ((m)AIAD) (Meijer et al., 2003) – a validated self-assessment of hearing disability in daily functioning.
2.8 Method of data analysis

The participants score for each of the tests outlined was included during the analysis. Statistical analysis was carried out with IBM Statistical Package for the Social Sciences (SPSS), Version 25.0 (2017). Significance levels were considered as $p < 0.05$.

Demographic data

Demographic data was analysed using descriptive statistics and frequency analysis, as well as independent samples t-tests and a chi-square test of independence. Further, subsidiary analysis was performed using Welch two-samples t-test to compare HI-Ace-III responses across the HI and D-HI groups. A performance comparison was undertaken between the HI-ACE-III and the original ACE-III using summary data from a published validation paper (Hsieh et al., 2013), as well as a diagnostic utility study (Matias-Guiu et al., 2017). As only summary data was available, a number of one-sample t-tests were conducted.

Convergent and divergent validity of the HI-ACE-III

Convergent and divergent validity of the HI-ACE-III composite for the following cognitive domains, attention, memory, fluency, language and visuospatial abilities, was considered through correlation with the outlined tests of cognitive function. Convergent validity is considered to be the degree to which measures yield broadly similar results to alternative measures intended to assess the same underlying construct (Campbell & Fiske, 1959), while divergent or discriminant validity determines whether measurements are independent of unrelated measures beyond the assessed construct. A Spearman’s rank-order correlations was performed in
accordance with the characteristics of the data. Conventions suggested by Cohen (1988) were used to interpret effect size, a correlation coefficient of .10 is considered to be a weak correlation, .30 moderate and .50 and larger is thought to be strong.

**ROC curve analysis of the HI-ACE-III**

An empirical Receiver Operating Characteristics (ROC) analysis was carried out to establish the area under the curve (AUC). The AUC is a measurement reflecting the overall performance of a screening tool in discriminating between individuals with and without a diagnosis. Specific to this study, the AUC was used to determine the diagnostic ability of the HI-ACE-III for correctly classifying participants with and without dementia. The dementia diagnosis was determined by a psychiatrist led memory clinic, while the GPCOG was used to establish that participants in the HI group were cognitively intact. An empirical ROC curve is non-parametric and as such, there are no assumptions about the underlying distributions of the data.

An AUC value of 1.0 is thought to represent a perfect test, whereas a value of .5 or smaller is believed to constitute chance findings. According to established guidelines for interpreting AUC values, an AUC value of 0.7–0.8 is considered acceptable, 0.8–0.9 is considered excellent and higher than 0.9 is outstanding (Hosmer & Lemeshow, 2000). The optimal cut-off score for maximising the detection of dementia was established based on the largest Youden index, also called Youden’s J statistic, a measure of diagnostic accuracy designed to maximise both sensitivity and specificity (Youden, 1950; Krzanowski & Hand, 2009). Conceptually, the Youden index is the point on the ROC curve that is the furthest vertical distance from the chance line. This method is considered to be superior to identifying the
point on the ROC curve that is nearest the top left-hand corner or closest to an AUC of 1.0, known as the K-index (Perkins & Schisterman, 2006). Positive and negative predictive values for the established cut-off were also considered in relation to the diagnostic accuracy. The likelihood ratio, reflecting the likelihood that a given score comes from a patient with dementia (Sackett, Haynes, Guyatt & Tugwell, 1991), was established for the cut-off score based on sensitivity and specificity values.

Hierarchical multiple regression

A hierarchical multiple regression was used to examine the unique contribution of cognitive status to variation in total HI-ACE-III score over and above demographic variables that differed between the groups and were associated with ACE-III score, including age and years of education. Cognitive status was the independent variable entered in the first block, while relevant demographics were entered as independent variables in the second block.

Internal consistency reliability of the HI-ACE-III

In order to check reliability, Cronbach’s alpha correlation coefficient was confirmed for each HI-ACE-III item. A value of .70 is considered the minimum acceptable value (Nunnally, 1994).
3. **Results**

3.1 **Demographic Characteristics**

Recruitment for the D-HI Group was suspended at 16 participants due to the outbreak of coronavirus (COVID-19) and the vulnerable characteristics of the recruited population. The D-HI sample was made up of 12 individuals with AD, two with vascular dementia, one with frontotemporal dementia and one with mixed dementia. The group was not categorised by dementia subtype during analysis due to the small sample size.

**Table 1**

*Demographic characteristics of participants according to group*

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Male</th>
<th>Female</th>
<th>YoE</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>HI</td>
<td>30</td>
<td>18 (60%)</td>
<td>12 (40%)</td>
<td>16.07</td>
<td>3.69</td>
</tr>
<tr>
<td>D-HI</td>
<td>16</td>
<td>12 (75%)</td>
<td>4 (25%)</td>
<td>10.53</td>
<td>3.87</td>
</tr>
</tbody>
</table>

*Note. YoE = Years of Education; M = Mean; SD = Standard Deviation*

Descriptive statistics were used to explore the demographic characteristics of participants in the Hearing Impaired (HI) group and Dementia Hearing Impaired (D-HI) group displayed in Table 1. The continuous demographic variables, age and Years of Education (YoE), were found to meet assumptions for parametric tests, including normality determined by the Shapiro-Wilk’s test and visual inspection of histograms and homogeneity of variance considered with Levene’s test for equality of variance.
An independent-samples t-test was conducted to compare years of education and age across the HI and D-HI groups. Participants in the D-HI were found to be significantly older ($t(44) = -2.64, p = .01$), with fewer years of education ($t(43) = 4.66, p < .01$). A chi-square test of independence was carried out, indicating that there was not a significant association between gender and cognitive status, $\chi^2 (1, N = 46) = 1.035, p = .309$

3.1.1 HI-ACE-III responses in the HI and D-HI groups

Table 2

Participant responses to the HI-ACE-III and HI-ACE-III composite domains across groups

<table>
<thead>
<tr>
<th>Group</th>
<th>HI-ACE-III Total</th>
<th>HI-ACE-III Attention</th>
<th>HI-ACE-III Memory</th>
<th>HI-ACE-III Fluency</th>
<th>HI-ACE-III Language</th>
<th>HI-ACE-III Visuospatial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>SD</td>
<td>$M$</td>
<td>SD</td>
<td>$M$</td>
<td>SD</td>
</tr>
<tr>
<td>HI</td>
<td>94.40***</td>
<td>4.95</td>
<td>17.53**</td>
<td>.73</td>
<td>24.40***</td>
<td>1.81</td>
</tr>
<tr>
<td>D-HI</td>
<td>62.62***</td>
<td>16.56</td>
<td>13.88**</td>
<td>3.74</td>
<td>13.13***</td>
<td>6.64</td>
</tr>
</tbody>
</table>

Note. HI group $n = 30, $ D-HI group $n = 16; M = $ Mean; $ SD = $ Standard Deviation; * $ p < .05, ** $ p < .01, *** $ p < .001

Participant performance on the HI-ACE-III is outlined in Table 2. A Welch two-samples t-test was used to adjust for unequal variance, indicating a significant mean difference in HI-ACE-III total scores across the two groups. Participants in the D-HI had significantly lower total HI-ACE-III total scores, $t(16.44) = 7.49, p < .001$. Further Welch two-samples t-tests revealed a significant mean difference between the HI and D-HI groups across all cognitive domain composite scale scores.
3.1.1 Subsidiary Analysis – Performance Comparison of the HI-ACE-III with the original ACE-III

A number of one-sample t-tests were run to determine if a significant mean difference existed between HI-ACE-III total score and composite domain scores from the current study and ACE-III total score and composite domain scores from a published validation (Hsieh et al., 2013) and diagnostic utility study (Matias-Guiu et al., 2017), demonstrated in Table 3. At a 95% confidence interval, no significant differences were observed between the HI-ACE-III scores and ACE-III scores from the original validation study across the HI and cognitively intact control groups. A similar pattern for the D-HI and AD group, with the exception of a significant mean difference observed for the HI-ACE-III visuospatial domain score, \( t(15) = -2.64, p = .018 \)

A significant mean difference for total ACE score compared with the findings of the diagnostic utility study was found between both the HI group and control condition \( t(29) = 5.49, p < .001 \) and the D-HI group and a group of included participants with mild AD \( t(15) = 2.82, p = .013 \), with participants in the current study scoring significantly higher. Further significant mean differences were observed across domain scores, with the exception of HI-ACE-III language domain score for both the HI and D-HI group, and HI-ACE-III visuospatial for the D-HI group.
Table 3

Comparison of the HI-ACE-III total and composite domain scores with published validation papers

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Attention</th>
<th>Memory</th>
<th>Fluency</th>
<th>Language</th>
<th>Visuospatial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>HI-ACE-III HI Group (n = 30)</td>
<td>94.40</td>
<td>4.95</td>
<td>17.53</td>
<td>.73</td>
<td>24.40</td>
<td>1.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.13</td>
<td>1.93</td>
<td>24.93</td>
<td>2.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15.40</td>
<td>.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsieh et al., 2013 ACE-III Control Group (n = 25)</td>
<td>95.4</td>
<td>3.3</td>
<td>17.4</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25.6</td>
<td>0.6</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Matías-Guiu et al., 2017 ACE-III Control Group (n = 25)</td>
<td>89.44***</td>
<td>8.66</td>
<td>16.48***</td>
<td>1.55</td>
<td>22.38***</td>
<td>3.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.48***</td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24.24</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.64***</td>
<td>1.22</td>
</tr>
<tr>
<td>HI-ACE-III D-HI Group (n = 16)</td>
<td>62.62</td>
<td>16.56</td>
<td>13.88</td>
<td>3.74</td>
<td>13.13</td>
<td>6.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.94</td>
<td>3.24</td>
<td>18.88</td>
<td>4.76</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10.81</td>
<td>2.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsieh et al., 2013 ACE-III AD Group (n = 28)</td>
<td>65</td>
<td>14.2</td>
<td>12.5</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>21.1</td>
<td>4.0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.7*</td>
<td>3.1</td>
</tr>
<tr>
<td>Matías-Guiu et al., 2017 ACE-III AD Group (n = 47)</td>
<td>50.94*</td>
<td>11.43</td>
<td>10.76**</td>
<td>3.14</td>
<td>8.63*</td>
<td>3.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.76***</td>
<td>2.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.38</td>
<td>5.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>2.85</td>
</tr>
</tbody>
</table>

Note. M = Mean; SD = Standard Deviation; * p < .05, ** p < .01, *** p < .001
### 3.2 Convergent and Divergent Validity

**Table 4**

Convergent and divergent validity of the HI-ACE-III composite domain scores in the HI Group

<table>
<thead>
<tr>
<th></th>
<th>HI-ACE-III Attention</th>
<th>HI-ACE-III Memory</th>
<th>HI-ACE-III Fluency</th>
<th>HI-ACE-III Language</th>
<th>HI-ACE-III Visuospatial</th>
<th>SS DSF</th>
<th>SS DSB</th>
<th>ROCF 3min</th>
<th>ROCF 30min</th>
<th>GNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI-ACE-III Attention</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HI-ACE-III Memory</td>
<td>.177</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HI-ACE-III Fluency</td>
<td>.075</td>
<td>.278</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HI-ACE-III Language</td>
<td>.353</td>
<td>.260</td>
<td>.106</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HI-ACE-III Visuospatial</td>
<td>.312</td>
<td>.272</td>
<td>-.103</td>
<td>.204</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SS DSF</td>
<td>.085</td>
<td>.109</td>
<td>.082</td>
<td>-.059</td>
<td>.054</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SS DSB</td>
<td>.373*</td>
<td>-.028</td>
<td>.116</td>
<td>.139</td>
<td>.194</td>
<td>.414*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ROCF</td>
<td>.344</td>
<td>.220</td>
<td>.175</td>
<td>.009</td>
<td>.243</td>
<td>.075</td>
<td>.262</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ROCF 3min</td>
<td>.097</td>
<td>.173</td>
<td>.371*</td>
<td>-.004</td>
<td>.398*</td>
<td>.181</td>
<td>.287</td>
<td>.480**</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ROCF 30min</td>
<td>.031</td>
<td>.080</td>
<td>.289</td>
<td>-.190</td>
<td>.328</td>
<td>.075</td>
<td>.278</td>
<td>.452*</td>
<td>.898***</td>
<td>-</td>
</tr>
<tr>
<td>GNT</td>
<td>.164</td>
<td>.371*</td>
<td>.108</td>
<td>.373*</td>
<td>.356</td>
<td>.034</td>
<td>.285</td>
<td>.273</td>
<td>.535**</td>
<td>.522**</td>
</tr>
</tbody>
</table>

*Note.* HI group $n = 30$; SS DSF = Spatial Span Digit Span Forward; SS DSB = Spatial Span Digit Span Backward; ROCF = Rey-Osterrieth Complex Figure Copy; ROCF 3min = Rey-Osterrieth Complex Figure 3 Minute Recall; ROCF 30min = Rey-Osterrieth Complex Figure 30 Minute Recall; GNT = Graded Naming Test; * $p < .05$, ** $p < .01$, *** $p < .001$
Table 5

Convergent and divergent validity of the HI-ACE-III composite domain scores in the D-HI Group

<table>
<thead>
<tr>
<th></th>
<th>HI-ACE-III Attention</th>
<th>HI-ACE-III Memory</th>
<th>HI-ACE-III Fluency</th>
<th>HI-ACE-III Language</th>
<th>HI-ACE-III Visuospatial</th>
<th>SS DSF</th>
<th>SS DSB</th>
<th>ROCF 3min</th>
<th>ROCF 30min</th>
<th>ROCF 30min</th>
<th>GNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI-ACE-III Attention</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-ACE-III Memory</td>
<td>.712**</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-ACE-III Fluency</td>
<td>.487</td>
<td>.369</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-ACE-III Language</td>
<td>.448</td>
<td>.374</td>
<td>.294</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-ACE-III Visuospatial</td>
<td>.358</td>
<td>.652**</td>
<td>.500*</td>
<td>.484</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS DSF</td>
<td>.175</td>
<td>.236</td>
<td>.476</td>
<td>-.057</td>
<td>.420</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS DSB</td>
<td>.664**</td>
<td>.611*</td>
<td>.300</td>
<td>.154</td>
<td>.252</td>
<td>.497</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCF 3min</td>
<td>.394</td>
<td>.217</td>
<td>.680**</td>
<td>.168</td>
<td>.367</td>
<td>.434</td>
<td>.415</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCF 30min</td>
<td>.427</td>
<td>.498</td>
<td>.181</td>
<td>-.094</td>
<td>.181</td>
<td>.101</td>
<td>.395</td>
<td>.345</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNT</td>
<td>.297</td>
<td>.542*</td>
<td>.408</td>
<td>.807***</td>
<td>.679**</td>
<td>-.043</td>
<td>.073</td>
<td>.113</td>
<td>-.143</td>
<td>.157</td>
<td></td>
</tr>
</tbody>
</table>

Note. D-HI group n = 16; SS DSF = Spatial Span Digit Span Forward; SS DSB = Spatial Span Digit Span Backward; ROCF = Rey-Osterrieth Complex Figure Copy; ROCF 3min = Rey-Osterrieth Complex Figure 3 Minute Recall; ROCF 30min = Rey-Osterrieth Complex Figure 30 Minute Recall; GNT = Graded Naming Test; * p < .05, ** p < .01, *** p < .001
Testing for outliers and visual inspection of scatterplots was first undertaken. Normality was assessed using the Shapiro-Wilk test, indicating that while data for some HI-ACE-III composite scores and cognitive assessments in relevant domains approximately followed a normal distribution ($p > .05$), the majority did not. Variables that deviated from normality in the HI group included HI-ACE-III Attention, HI-ACE-III Memory, HI-ACE-III Fluency, HI-ACE-III Language, HI-ACE-III Visuospatial and Rey-Osterrieth Complex Figure copy (ROCF). While Spatial Span Digit Span Backwards (SS DSB), Rey-Osterrieth Complex Figure copy (ROCF), the ROCF 3 minute recall (ROCF 3min) and the ROCF 30 minute recall (ROCF 30min) deviated from normality in the D-HI group. As a result, a Spearman’s rank-order correlation was run to assess the association between subscale composite scores on the HI-ACE-III and additional non-verbal cognitive assessment measures in both the HI and D-HI Group. The correlation matrix for the HI group is detailed in Table 4, while the correlation matrix for the D-HI group is outlined in Table 5.

In the HI-Group, statistically significant, moderate, positive correlations were found between the HI-ACE-III Attention composite and Spatial Span Digit Span Forward (SS DSF), $r_s(28) = .373, p = .042$, HI-ACE-III Memory and Graded Naming Test (GNT), $r_s(28) = .371, p = .044$, HI-ACE-III Fluency and ROCF 3min, $r_s(28) = .371, p = .043$, HI-ACE-III Language and GNT, $r_s(28) = .373, p = .042$, and HI-ACE-III Visuospatial and ROCF, $r_s(28) = .398, p = .029$. While in the D-HI group, a moderate, positive association was found between HI-ACE-III Memory and GNT, $r_s(14) = .542, p = .030$. Strong positive correlations were observed between HI-ACE-III Attention and SS DSB, $r_s(14) = .664, p = .005$, HI-ACE-III Memory and SS DSB, $r_s(14) = .611, p = .012$, HI-ACE-III Fluency and ROCF, $r_s(14) = .68$, $p =$
.005, and HI-ACE-III Visuospatial and GNT, \( r_s(14) = .679, p = .004 \). Finally, a strong positive association was shown between HI-ACE-III Language and GNT, \( r_s(14) = .679, p = .004 \).
3.3 ROC Curve Analysis of the HI-ACE-III

Table 6

Summary of ROC analysis for predicting dementia

<table>
<thead>
<tr>
<th>AUC</th>
<th>SE</th>
<th>95% CI</th>
<th>Cut-off Score</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>YI</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.960</td>
<td>0.035</td>
<td>0.893 – 1.000</td>
<td>&lt;80</td>
<td>87.5%</td>
<td>96.7%</td>
<td>93.3%</td>
<td>93.5%</td>
<td>0.842</td>
<td>26.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;84</td>
<td>87.5%</td>
<td>93.3%</td>
<td>87.5%</td>
<td>93.3%</td>
<td>0.808</td>
<td>13.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;86.5*</td>
<td>93.8%*</td>
<td>93.3%*</td>
<td>88.2%*</td>
<td>96.6%*</td>
<td>0.871*</td>
<td>14.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;88.5</td>
<td>93.8%</td>
<td>90%</td>
<td>83.3%</td>
<td>96.4%</td>
<td>0.838</td>
<td>9.38</td>
</tr>
</tbody>
</table>

Note. AUC – Area Under the Curve; SE – Standard Error; CI – Confidence Interval; PPV – Positive Predictive Value; NPV – Negative Predictive Value; YI – Youden Index; LR – Likelihood Ratio; * - Highest Youden Index

As outlined in Table 6 and Figure 3, ROC analysis was carried out to determine the performance of the HI-ACE-III at discriminating individuals with dementia from cognitively intact control participants. Figure 1 shows the ROC curve. The AUC value was .960, 95% CI [0.893, 1.000]. At an optimum cut-off score of <87, the largest Youden index of 0.871 was achieved, with sensitivity of 93.8% and specificity value 93.3% (See Appendix F for entire sensitivity and specificity values). According to positive and negative predictive values, at this cut-off point, the HI-ACE-III correctly classifies 88.2% of dementia cases or 15 individuals with dementia and 96.6% of cases without dementia or 28 individuals without dementia. The likelihood ratio of dementia was 14.06:1 at a cut-off of <86.5. As half marks are not awarded on the ACE-III, the clinical cut off should be considered to be scores of 87 or less.
Figure 3. ROC curve for discriminating hearing-impaired individuals with dementia using the HI-ACE-III
3.4 Hierarchical Multiple Regression

Table 7

Hierarchical Regression Analysis predicting total HI-ACE-III score

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Step 1</th>
<th></th>
<th>Step 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>SE (b)</td>
<td>b</td>
<td>SE (b)</td>
</tr>
<tr>
<td>Constant</td>
<td>94.40</td>
<td>1.679</td>
<td>110.838</td>
<td>16.021</td>
</tr>
<tr>
<td>Cognitive Status</td>
<td>-17.0***</td>
<td>1.454</td>
<td>-13.407***</td>
<td>1.579</td>
</tr>
<tr>
<td>Age</td>
<td>-.408*</td>
<td>.183</td>
<td>-.160</td>
<td></td>
</tr>
<tr>
<td>YoE</td>
<td>.890*</td>
<td>.335</td>
<td>.218</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted $R^2$.755                      .815
$F$ 136.756***                  65.432***
$\Delta R^2$.761                      .066
$\Delta F$ 136.756***                  7.882***

Note. N = 46; YoE = Years of Education; $\Delta R^2 = R^2$ Change; $\Delta F = F$ Change * $p < .05$, ** $p < .01$ *** $p < .001$

A hierarchical multiple regression analysis was conducted to examine the unique contribution of cognitive status to HI-ACE-III total score, detailed in Table 7. The relevant assumptions of the hierarchical multiple regression were tested before it was conducted. Independence of residuals was demonstrated by the Durbin-Watson statistic, as the value obtained was close to 2 (Durbin-Watson = 2.42). Analysis of collinearity statistics revealed no evidence of multicollinearity, as VIF scores were well below 10 and tolerance values were greater than 0.1 (Hair, Black, Babin & Anderson, 2010). Outliers for each regression model were investigated. While one studentised deleted residual was greater than ±3 standard deviations (-3.43), no leverage value exceeded 0.2 (Huber, 1981) and the values for Cook’s Distance were all under 1, suggesting that the model was not unduly influenced by any individual case. Visual inspection of the Q-Q Plot and P-P Plot for the model indicated that the assumption of normal distribution of the residuals was met.
Linearity was determined through examination of a partial regression plot and a plot or studentised residuals and predicted values. There were no obvious signs of funnelling from visual inspection of a plot of studentised residuals and unstandardised predicted values. This suggests that the assumption of homoscedasticity has been met. The sample size of 46 meets the desirable general rule that the ratio of observations to independent variables falls between 15 to 20 observations for each independent variable (15.33:1) (Hair, Black, Babin & Anderson, 2010).

Cognitive status was included as a variable in the first block (Step 1) and contributed significantly to the regression model, $F(1,43) = 136.76, p < .001$. The adjusted $R^2$ was .755, indicating cognitive status accounted for approximately 75.5% of variation in total HI-ACE-III score. In the final block (Step 2), the addition of participant age and Years of Education (YoE) along with cognitive status to predict total HI-ACE-III score was statistically significant, $F(3,41) = 65.43, p < .001$. The addition of age and YoE explained an additional 6.6% of variation in total HI-ACE-III score, accounting for approximately 81.5% of variation in total HI-ACE-III score, according to the adjusted $R^2$ of .815. The increase was statistically significant, $F(2,41) = 7.88, p = .001$. Cognitive status, $t(41) = -8.493, p < .001$, age, $t(41) = -.160, p = .031$ and YoE, $t(41) = 2.659, p = .011$, were all significant predictors of total HI-ACE-III score, with cognitive status representing by far the largest contributor.

3.5 Internal Consistency of the HI-ACE-III

The internal consistency of the HI-ACE-III, as measured by Cronbach’s coefficient, was very good ($\alpha = .925$).
4 Discussion

The need for brief and effective cognitive screening tools for older adults with hearing impairments is clear given the high prevalence of progressive hearing loss with age (Hill-Briggs et al., 2007), as well as the association between hearing impairment and cognitive deterioration. The intention of this study was to develop and validate a visually presented, computer-based version of the ACE-III to screen older adults with hearing impairment for dementia. The results indicate that the HI-ACE-III is a highly sensitive and specific screening tool for dementia for older adults with hearing impairment in the tested population, however there are some important caveats.

The discrimination between cognitively intact hearing-impaired individuals and hearing-impaired individuals with dementia was very satisfactory (Hosmer & Lemeshow, 2000); the generated ROC Curve was significant, with a large area under the curve (0.96) and encouraging sensitivity (93.8%) and specificity (93.3%) levels for the established cut-off point (<87). This falls between the previously recommended cut-off points for identifying dementia in the original ACE-III validation for dementia study (Hsieh et al., 2013), points that were found to have high sensitivity and specificity, (88: sensitivity 100%, specificity 96%; 82: sensitivity 93%, specificity 100%). The inclusion of a subgroup of individuals with primary progressive aphasia may have increased discrimination capacity and explain the high levels of specificity found in the validation study, as the original ACE-III is weighted towards language tasks. There has been variation in the identified cut-off point across studies in different contexts (Habib & Stott, 2019), this potentially relates to differences in age and education of included participants (Jubb & Evans, 2015).
It is important to note that it is not possible to diagnose dementia on the basis of screening tools alone, however they can be used to identify cognitive decline that may warrant further investigation (Ismail, Rajji & Shulman, 2010; Ngo & Holroyd-Leduc, 2014). Therefore, a highly desirable property of cognitive screening tools such as the ACE-III is sensitivity to cognitive deficits associated with aging and dementia (Ritchie, Terrera & Quinn, 2015). The identification of true positive cases, individuals scoring below the identified cut-off that do have dementia, is crucial in clinical practice for the timely identification of cases that require further investigation. However as further assessment can be costly and time-consuming, specificity is also important. Specificity involves the exclusion of true negative cases, individuals who are cognitively intact who are accurately identified as such. As such, the HI-ACE-III cut-off was selected to balance these two factors.

In an original investigation into the ACE, the dementia likelihood ratio was found to rise from 8.4:1 at 88 to 100:1 at 82 (Mioshi et al., 2006). A more moderate dementia likelihood ratio of 14.06:1 was achieved with the HI-ACE-III at a cut-off of 87, rising to 26.25:1 when considering a cut-off of 80. This lower likelihood ratio at the 87 cut-off may represent the identification of mild cases of dementia (Mioshi et al., 2006); While mild dementia is harder to diagnose as boundaries between mild dementia and normal aging and MCI are vague (Jekel et al., 2015; Petersen et al., 2014), there are considerable added benefits of identifying dementia in the mild stage, including proactive intervention (Prince, et al., 2011). Internal consistency for the HI-ACE-III, as determined by Cronbach’s alpha, was high (α = .925), which was higher than a previous validation study with the ACE-III (α = .88; Hsieh et al., 2013).
The performance of the HI and D-HI group were broadly in line with the original ACE-III validation papers (Hsieh et al., 2013), although the memory and fluency subscale scores were not included. There were small variations between the D-HI group and the group with AD included in the study by Hsieh and colleagues (2013). This may be due to the fact that the current study considered dementia of various types rather than AD specifically. Both the HI and D-HI groups had largely higher subscale mean scores than an investigation into the diagnostic utility of the ACE-III for MCI and dementia (Matías-Guiu et al., 2017), with the exception of fluency. This is in line with previous findings that both Letter Fluency and performance on the American Version of the Nelson Adult Reading Test (AMNART) declined linearly as levels of hearing loss increased in cognitively intact, older individuals (Lin et al., 2011b). Hearing impairment and lower levels of education have also been found to affect phonological verbal fluency in particular (Santos, Chiossi, Soares, Oliveira & Chiari, 2014).

When considering concurrent validity, some of the anticipated correlations were observed between HI-ACE-III composite domain scores and performance on standardised neuropsychological measures, including HI-ACE-III attention and Spatial Span Digit Span Forward (SS DSF) and Backward (SS DSB), HI-ACE-III memory and SS DSB both considered to be measures of working memory (Kessels et al., 2000), HI-ACE-III language and Graded Naming Test (GNT) and HI-ACE-III visuospatial and the Rey-Osterrieth Complex Figure 3 Minute Recall (ROCF 3min). Providing objective validation of the HI-ACE-III as a measure of these domains.

The correlation between HI-ACE-III memory and the GNT may result from the retrieval component involved in language processing in the GNT (Martin et al.,
There is also overlap in that the memory domain includes the ability to recall the name of well-known individuals as well as the recall of a name and address. The significant associations observed between HI-ACE-III fluency and the ROCF and ROCF 3min and the HI-ACE-III visuospatial and GNT were not anticipated. There is a potential association between semantic and phonemic fluency and executive functioning (Whiteside et al., 2016). Loss of vestibular function associated with aging, which often accompanies hearing impairment, was found to be associated with lower visuospatial performance (Bigelow et al., 2015), and impaired visuospatial skills are often one of the first indicators of dementia and AD. Along with the outlined association between hearing loss and reduced fluency (Lin et al., 2011b), this may offer some explanation for these correlations by accounting for poor performance by participants in both of these domains.

4.1 Limitations and potential future directions

The current study has certain limitations. While power was probably adequate given the high AUC, the reduced number of participants in the D-HI group due to early discontinuation of recruitment related to the COVID-19 outbreak affected the ability to determine the diagnostic utility of the HI-ACE-III in differentiating between cognitively intact hearing-impaired individuals and hearing-impaired individuals with dementia. The low number of participants may also make it more difficult to establish a reliable cut-off point and limit the precision of sensitivity and specificity estimates. A larger sample size would be necessary to confirm the findings. Due to the small sample size, participants with dementia were not divided into subgroups such as AD and vascular dementia. Previous research has indicated that the ACE-III can discriminate between different dementia subtypes.
(Alexopoulos et al., 2010; Kwak, Yang & Kim, 2010; Hsieh et al., 2013) and the ability of the HI-ACE-III to support differential diagnosis may be an interesting follow-up investigation. However, it is also useful to note that the HI-ACE-III can identify dementia of any type.

As outlined by Lin and colleagues (2017), converting verbal instructions to visually presented instructions is likely to involve different neural pathways in the brain (Bernstein & Liebenthal, 2014), however further research is necessary to fully understand these pathways (Muhle-Karbe, Duncan, De Baene, Mitchell & Brass, 2017). Adaptation of the HI-ACE-III was kept to a minimum in order to mirror the original ACE-III as closely as possible and correlational findings generally indicate good construct validity, although more in-depth investigation into the psychometric properties of the HI-ACE-III may offer further insight.

Like the original, the HI-ACE-III is heavily weighted towards verbal tests with a number of language items included and it fails to explicitly test judgement and reasoning (Cullen, O’Neill, Evans, Coen & Lawlor, 2007). It could have been beneficial to include a more comprehensive battery of neuropsychological assessment to determine concurrent validity of the HI-ACE-III, however, the length of the current assessment battery reached two hours and adding further tests may have affected performance due to participant’s capacity to engage in lengthy assessment. It would also be important to investigate the utility of the HI-ACE-III when administered in a clinical setting, such as a memory clinic.

The HI and D-HI group varied considerably in terms of age and years of education, both factors that are associated with dementia risk and cognitive performance (Jubb & Evans, 2015). Both age and years of education were found to significantly
contribute to the regression model in the current study, accounting for an additional 6.6% of variation in total HI-ACE-III score. Although the sample size falls short of the 74 that would be suggested by Green (1991) \((N > 50 + 8m, \text{where } m \text{ is the number of independent variables included})\), indicating that the regression model may be underpowered. It would be beneficial for future researchers to adopt a matched subjects design based on age and years of education to reduce any potential impact of these factors, or separate participants into groups based on years of education and considering optimal cut-offs for each group, as outlined by Jubb and Evans (2015).

While there have been some advances in terms of adapting existing screening tools, including the HI-MoCA (Lin et al., 2017), it remains unclear how alterations affect test validity (Pye, Charalambous, Leroi, Thodi & Dawes, 2017). A wider battery of validated, adapted measures would allow clinical decision making in terms of selected measures based on factors such as length and clinician familiarity.

5 Conclusion

Regardless of certain limitations, the HI-ACE-III has been found to be an accurate screening instrument in the detection of dementia in individuals with hearing impairment. This is thought to be one of the first attempts to seek validation of a screening tool in this context. The HI-ACE-III will be particularly relevant for prompt identification of individuals with hearing impairment who require more extensive neuropsychological and neurological investigation. The HI-ACE-III is easy to administer and may be useful in both future research and in clinical practice.
References


Jubb, M. T., & Evans, J. J. (2015). An investigation of the utility of the
Addenbrooke's cognitive examination III in the early detection of dementia in
memory clinic patients aged over 75 years. *Dementia and Geriatric Cognitive
Disorders, 40*(3-4), 222-232.

residents. *Journal of the American Medical Directors Association, 13*, 744-
747.

Neuropsychology, 7*(4), 252-258.

Press.

Examination Revised (K-ACER) for differential diagnosis of Alzheimer's
disease and subcortical ischemic vascular dementia. *Geriatrics &


Stahl, S. M. (2017). Does treating hearing loss prevent or slow the progress of dementia? Hearing is not all in the ears, but who’s listening?. *CNS Spectrums, 22*(3), 247-250.


Part Three: Critical Appraisal
1 Introduction

This project gave me the opportunity to explore the value of adapting cognitive screening tools for specific populations, in this case older adults with hearing impairment. I was able to engage in cognitive testing in a research setting and I gained insight into the potential contributions that research can offer in the field of clinical psychology. The process also helped me to consider my future balancing dual roles as a clinician with the valuable opportunity to support research.

This critical appraisal will begin with some consideration of the personal and professional contexts that drew me to join a research project in the field of cognitive impairment and dementia, as well as to focus on adapting a cognitive screening tool. I also consider the impact of the outbreak of Coronavirus disease 2019 (COVID-19) part way through the research project. I will then reflect upon some of the methodological benefits, as well as the practical and theoretical challenges of this particular research design within the context of a doctoral research project. This will be considered in the frame of the Quality Assessment of Diagnostic Accuracy Studies tool (Whiting et al., 2011). This includes difficulties with recruitment and ethical dilemmas that arose, along with some of the knowledge I have gained by engaging with each stage of the research project. While limitations were raised in the empirical paper, this appraisal will focus more on the experiential aspects of these challenges. I will conclude by considering my development as a clinical psychologist within a research context.
2 Personal and professional contexts

Prior to joining the doctoral training course, I had experience of working in both a memory clinic and a neurorehabilitation service. This fostered my interest in the clinical value of cognitive assessments and the valuable contributions that can be made to formulations from quantitative and qualitative interpretations of neuropsychological assessment findings. The scope of neuropsychological assessments is wide-ranging, allowing differential diagnosis and supporting functional recovery (Harvey, 2012).

While neuropsychological assessment is a powerful tool, it is important to consider that the process of undergoing an assessment can be incredibly impactful. I have found that engaging with a cognitive assessment can be highly emotive both for the individual, their relatives and also myself as the clinician. Beyond the anxiety about performance, engaging in the assessment can be incredibly confronting, highlighting abilities that may have been lost or difficulties that the individual was not previously aware of. My experiences have helped me to try to achieve a balance between empathic reassurance while maintaining standardisation during testing. This proved to be an important awareness and a valuable approach during recruitment and testing sessions as part of this project.

I also found that working with older adults, both in a clinical setting and in a research context, presented a really unique opportunity to offer a positive experience of psychology for a population that may have never considered accessing psychology services or may even have pre-existing negative appraisals of mental health services. It felt important to maintain awareness of generational perspectives when
considering the field of psychology and the undeniable history of persecution during
the development of the profession.

Visiting individuals at home to carry out the screening and assessment
sessions and speaking with them and their caregivers gave me an insight into the
lived experiences of people living with dementia. Generally, both the individual and
their caregivers welcomed having someone visit and interact with them and I believe
that the social contact was actually a benefit to the individuals taking part.

When deciding on the project I wanted to engage with, I was struck by the
fact that dementia is a topic that is often overlooked by other trainees and even other
professionals in the psychology field. Despite an aging population, older adults are
underrepresented in clinical research (Mody et al., 2008). Individuals with cognitive
impairment in particular are often excluded from research (Taylor, DeMers, Vig &
Borson, 2012). Being an older adult who is living with dementia is almost doubly
stigmatising both in the research field as well as in daily life (Graham et al., 2003;
Sartorius, 2003).

Historically, it was thought that people with dementia had lost their ‘sense of
self’ so they were unable to make meaningful communications and contributions
(Cohen & Eisdorfer, 1986). The added value of conducting research with individuals
living with dementia rather than about individuals living with dementia was
introduced in literature in the 1990s (Cotrell & Schulz, 1993). This led to a
conceptual shift to a focus on how to give voice to the experiences of individuals
living with dementia and to explore opportunities for meaning making (Hubbard,
Downs & Tester, 2003). When writing up the project I noticed that the majority of
the research is still focused on the impact of dementia on relatives and caregivers
rather than the impact on the individuals living with dementia themselves, despite considerable efforts to readdress this balance (Harris, 2002; Whit latch, 2001). The need for more research on dementia in a primary care setting is well established (Woods et al., 2003), particularly when considering effective diagnostic tools for early detection. This supported my decision to join the project as I felt that the research would offer a valuable contribution.

3 The value of validation research

While a full neuropsychological assessment battery offers a comprehensive indication of an individual’s cognitive abilities, it is not always possible to carry out a full battery with every individual in both clinical and research settings. This results from the time-consuming nature of carrying out the battery, interpreting the findings, writing the report and providing feedback to clients and professionals; The mean time to administer, score and interpret a full battery was found to be more than three and a half hours (Camara, Nathan & Puente, 2000). There is also a shortage of clinicians trained to either undertake the assessment or to offer supervision. Brief screening tools can be routinely administered and are shown to be adequate in the detection of dementia (Lin et al., 2013), they can also offer a ‘baseline’ of cognitive abilities that allows clinicians to track more subtle changes over time. Routine screening can contribute to early detection of dementia, leading to proactive rather than reactive management and intervention (Borson et al., 2013), and it is suggested that the perceived benefits of routine cognitive screening in older adults outweigh any potential harm. Wider application of routine cognitive screening may also help to close the so-called dementia diagnostic gap, referring to the underdiagnosis of dementia and cognitive impairment (Larner, 2013).
In order to provide clinical value, brief cognitive screening tools must be reliable, broadly producing the same results if administered repeatedly or by different clinicians, and the test must be valid, indicating that the test measures what it purports to measure. The third version of Addenbrooke’s Cognitive Examination (ACE-III) has been shown to be a reliable and valid screening tool, with excellent diagnostic utility for identifying cognitive impairment and detecting dementia (Hsieh, Schubert, Hoon, Mioshi & Hodges, 2013; Jubb & Evans, 2015; Matias-Guiu et al., 2017). While the ACE-III is widely used, a specific version for individuals with hearing impairment had not been developed or validated prior to the current study. This knowledge supported my decision to take the project on.

4 Conducting research in the context of COVID-19

COVID-19 is a contagious virus with a high rate of serious physical health complications and deaths that emerged in China and spread to countries across the world. The virus first started to spread in December 2019 and to me it was just a story featured in the news until the rate of infections in Europe began to escalate through February and March 2020.

While the official lockdown in the United Kingdom was introduced on Monday 23rd March 2020, we had come to the decision as a research team to suspend recruitment in early March. The COVID-19 outbreak had been characterised by the circulation of inconsistent and incorrect information as researcher, medical professionals and the public tried to understand the virus. However, a reliable message early on was the fact that the elderly were particularly vulnerable. The individuals I was recruiting for the dementia and hearing impairment group were in the high-risk group both due to their age and also as a result of physical health
comorbidities. My parallel placement in a hospital also contributed to the risk of me spreading the virus.

Once the lockdown began, I was suddenly trying to complete my research project in an unprecedented time without access to some of my usual stress-relieving strategies, like spending time with friends. My final placement also looked very different as I was unable to join the community neurorehabilitation team and stroke ward as planned. While there were some unexpected benefits, for example less time spent commuting and more time to devote towards project write up, I wonder if in the future I will reflect on the project as feeling unfinished due to the interruption of the outbreak. Outside of suspending recruitment, the virus outbreak also prevented some of the rituals that usually mark the end of a research project, for example not being able to say goodbye or thank you to the clinicians and other members of the staff team who offered so much support throughout the research journey.

The virus plunged everyone into uncertainty that was a poignant mirror of the uncertainty that must come with living with dementia. I was also struck by the added challenges facing the individuals with dementia that we were recruiting, including retaining an understanding of why they are suddenly unable to maintain their regular routine, including not being able to leave the house and not being visited by relatives. The sudden shift to internet-based communication likely left older adults feeling particularly uncomfortable and isolated.
5 Quality assessment

The following sections will consider the strengths and limitations of the project in terms of the domains suggested in the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting et al., 2011).

5.1 Patient selection and recruitment

While we employed a random sampling approach which is a preferred method, this may have actually introduced bias in terms of disparity in years of education, and age across the cognitively intact and dementia groups. A matched subjects design based on years of education and age may be more appropriate for future research on the diagnostic accuracy of cognitive screening tools.

I had anticipated that recruitment for the dementia with hearing impairment group (D-HI group) would be more challenging than the cognitively intact group, with research consistently showing that recruitment of a sufficient sample size can be difficult in the field of dementia research (Wilcock et al., 2007), with under-recruitment commonly seen in clinical trials involving older adults (McMurdo et al., 2011). I believed that the initial target of 30 would be feasible with support from clinicians based in two large memory clinics in London and three researchers carrying out recruitment.

I encountered a number of both common and novel challenges when recruitment began beyond the global pandemic. This included the fact that initial contact with potential participants took place by telephone in order to arrange a screening assessment, practical barriers included individuals not being able to hear well on the telephone due to hearing-impairment and this combining with cognitive
impaired making it difficult for them to understand the purpose of the research and what would be expected of them in terms of participation. While I could see the necessity to include certain information in the study information sheet on an ethical basis, we found the resulting length and density to be a deterrent for older adults living with dementia. Future studies may want to consider how this information can be communicated without overwhelming the individual. I also encountered the phenomenon of ‘gatekeepers’ or ‘proxies’, where caregivers of individuals with dementia make the decision about whether the individual participates in a research study without consulting the individual (Bartlett & Martin, 2002). While we respected the decisions of caregivers, this also introduces potential bias in terms of the individuals who are consulted about participating and might be related to individual characteristics of caregivers or family dynamics. This might also offer insight into the family view of the ‘sick role’ of the individual living with dementia.

Physical health comorbidities and physical health appointments made it difficult to schedule in the screening and testing sessions. The presence of multiple comorbid conditions is known to affect recruitment of older adults (MacFarlane et al., 2016). These additional appointments likely increased the perceived burden and inconvenience of participating in the research project, which is known to act as a deterrent to participating in dementia research (Dunn, Hoop, Misra, Fisher & Roberts, 2011). This potentially introduced further bias in terms of sampling, as the individuals who opted to participate were likely physically healthier with fewer health comorbidities than the people who declined.

Consent to be contacted about research was discussed during the initial assessment at the memory clinic, the elapsed time between this assessment and when
we began screening to identify potential participants varied considerably. Several potential participants we identified had experienced considerable deterioration both in terms of their cognitive function and their physical health, making them either not eligible or not able to take part.

We found that recruitment was more successful when individuals were referred by clinicians, however we experienced difficulties maintaining awareness within the team of recruitment for the project outside of the clinician who was directly associated. We recognised that clinicians were already managing high workloads with additional pressures such as reducing waiting times. In addition, a number of studies were recruiting from the same memory clinic, potentially contributing to research fatigue.

A number of potential participants did not retain full awareness of their dementia diagnosis and often their caregivers expressed a preference that the term dementia was not used during the screening or testing sessions. This raised an interesting question about the ability to achieve informed consent to participate in the research study in these cases (Bartlett & Martin, 2002). There are different schools of thought in the field when it comes to this topic, some suggest using the term ‘memory problems’ unless the word dementia is explicitly used by either by the individual with dementia or their caregivers (Hellström, Nolan, Nordenfelt & Lundh, 2007). Bartlett and Martin (2002) contradict this view, believing that only using the words ‘memory problems’ when conducting research could be considered deceptive, whilst also recognising that informing individuals that they have dementia may result in harm and distress. Ultimately, we followed advice by Reid and colleagues (2001); they suggested meeting with potential participants on their own terms and not
denying individuals the opportunity to participate in research or insist that they admit to having dementia.

It is also recommended to be increasingly flexible when conducting research with individual’s with dementia, and to adapt the research process to suit the individual as far possible in order to privilege the voice of the person living with dementia. Despite the use of telephone reminders, a number of potential participants forgot about the arranged sessions and were either unable to take part in the session or were unavailable. Where possible, relatives and caregivers were recruited to support with arranged sessions. In the future, I would consider further potential adaptations in order to ensure participation once an individual has expressed an interest in taking part.

Ultimately, all these difficulties with recruitment resulted in a sample size that was smaller than desired in terms of power calculations, indicating that the study was underpowered. Where possible, we tried to avoid inappropriate exclusions, although future researchers may want to explore the feasibility of including individuals living with dementia who are residing in care homes, although this can raise further concerns in terms of capacity to consent to participate.

5.2 Test development, administration and interpretation

Overall, I feel that the process of developing the version of the third version of the Addenbrooke’s Cognitive Examination (ACE-III; Hsieh et al., 2013) for individuals with hearing impairment (HI-ACE-III) was a strong element of the project. I believe that a huge positive of the original ACE-III is the open access for the test to be used in research and clinical settings. While I can understand the
motivation to monetise cognitive screening tools, this limits access due to the overstretched budget of the National Health Service, acting as a barrier to the potential benefits on a service and client level. Experts in the field of neuropsychology were also very generous with their time, offering consultation and insight during development.

While Patient and Public Involvement (PPI) is a relatively modern consideration when conducting research (Bagley et al., 2016), I could really see the added value of involving older adults to ensure that the testing sessions were ‘participant friendly’. Their involvement also offered reassurance that the study was relevant and ethically sound.

We were not blind to participant group when administering and scoring the tests. The cognitively intact individuals were tested by Nattawan Utoomprurkporn (PhD, 2020) to allow her to complete a comprehensive audiometric assessment in a soundproof booth. It was most appropriate for Nattawan to complete this testing as a qualified audiologist. I completed the testing sessions for participants with dementia, along with Courtney North (DClinPsy, 2020). Again, it felt most appropriate for us to test these participants as we both had previous experiences working with individuals living with dementia.

Scoring and interpretation of the test results was also not blind to participant group, instead this was done using the ACE-III administration and scoring guide and a joint decision by all researchers was made in situations where there was uncertainty, for example with the more subjective items like the clock draw. While the lack of blinding could have potentially introduced bias, blinding in future research would take considerable planning as screening and initial contact would
have to be carried out by different researchers and our availability for screening and testing was already limited due to clinical and academic doctorate commitments.

5.3 Reference standard

The reference standard in the current study are the methods used to establish the presence or absence of dementia, it is crucial to select the most accurate reference standard as possible as the diagnostic accuracy of the HI-ACE-III was considered based on classifications determined by the reference standard. It is also assumed that any discrepancy between the reference standard and the HI-ACE-III score is a result of incorrect classification by the HI-ACE-III. While the term ‘gold standard’ is debated in the field of psychiatry due to the lack of confirmatory biomarkers (Faraone & Tsuang, 1994), the current study employed the most accurate methods for identifying the presence of dementia while an individual is alive. Participants received a diagnosis following clinical assessment, including both cognitive and physical examinations, under the care of a multidisciplinary, psychiatry led memory service (Pink, O’Brien, Robinson & Longsdon, 2018).

When determining that individuals were cognitively intact, we needed to use a measure that would not mirror the tools of interest, the ACE-III and the Montreal Cognitive Assessment (MoCA), too closely. If there was too much overlap between the measure used during the screening assessment, it may have affected participant performance during the testing session. The General Practitioner’s Assessment of Cognition (GPCOG) has been shown to be an effective tool to screen for cognitive impairment, it has the added benefit of brief administration and includes an informant section, which has been shown to be unaffected by the assessed individual’s age, years of education and the presence of depression (Brodaty et al.,
Every individual received the same reference standard according to the group that they were recruited to.

5.4 Flow and timing

One potential issue in timing relates to variation in the time elapsed between administration of the reference standard, in this case the investigation to determine whether the individual has a dementia diagnosis, and the administration of the index test, the HI-ACE-III. However, while cognitive capabilities can vary over time, there is currently no potential for recovery of cognitive capacity to the point where an individual no longer has a dementia diagnosis. The screening session for the cognitively intact participants took place either on the same day as the assessment session, or very shortly afterwards. This prevented the possibility of deterioration of cognitive abilities prior to the administration of the HI-ACE-III, outside of an abrupt change such as delirium, which would have been recognised by the researcher of the caregiver or relative who was acting as an informant.

6.0 Conclusion

This space to reflect on my research journey has allowed me to increase my confidence as a scientist-practitioner, particularly in my ability to creatively react to some of the unexpected situations that emerged. Despite all the necessary planning and preparation, it is never possible to anticipate all the challenges that may emerge during the research process. Managing competing deadlines while working collaboratively with others has proved to be another important skill. While I had some prior experience of working with individuals with dementia, my knowledge
and understanding has increased considerably through the process of completing the conceptual introduction and empirical research.

Considering the QUADAS domains, it is clear that the study had some considerable strengths but also some areas where there is the potential to make improvements. Despite some of the challenges and associated limitations outlined, it is clearly essential and also rewarding to include older adults with cognitive impairments in clinical research. A delicate balance between inclusivity and safeguarding needs to be achieved. I hope that some of the reflections will be valuable to anyone who considers conducting research with people with dementia in the future. The process of conducting the project has given me more insight into the necessary hurdles to produce research that is good quality. The challenges of recruitment in an NHS setting highlighted the importance of developing good relationships with treating clinicians and maintaining a consistent presence in order to facilitate the recruitment process. Finally, the process highlighted the importance of considering some of the specific complexities of recruiting individuals with dementia, such as the need to consider the role of ‘gatekeepers’.
References


assessment of diagnostic accuracy studies. *Annals of Internal Medicine, 155*(8), 529-536.


Appendices

Appendix A

*Contributions to the Joint Research Project*

The design of the research study and ethics application had begun when the trainees, Courtney North and Mary Heatley, joined the project, and they were able to make contributions to this process. The development of the project materials including adapting and piloting the HI-ACE-III, as well as the patient and public involvement in the research was undertaken jointly by the two trainees and the PhD student, Nattawan Utoomprukporn.

Nattawan Utoomprukporn was responsible for training Courtney North and Mary Heatley in the administration of the portable audiogram. Courtney North and Mary Heatley supported Nattawan Utoomprukporn in the administration of the cognitive screening and assessments. Recruitment and testing of cognitively intact individuals in the HI group was undertaken by Nattawan Utoomprukporn, including liaising with informants. Recruitment and testing of participants with MCI and dementia was undertaken jointly. Scoring and inputting of data from all three groups was shared equally. Analysis of the results, as well as writing up the final theses was carried out individually.
Appendix B

Ethical Approval Letters

1. **NHS HRA Approval Letter**

2. **NHS REC Approval Letter**

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### NHS HRA Approval Letter

Professor Doris Bamiou

School of Health (ear institute)

332 Grays Inn Rd, Kings Cross, London

WC1X 8EE

14 September 2018

Dear Professor Bamiou

Study title: Validation of the “Montreal Cognitive Assessment (MoCA) and Addenbrooke’s Cognitive Examination III (ACE-III)” as cognitive screening tools for the hearing impaired.

IRAS project ID: 247176

Protocol number: 18/0306

REC reference: 18/LO/1225

Sponsor: University College London

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

**How should I continue to work with participating NHS organisations in England and Wales?** You should now provide a copy of this letter to

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all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "**summary of assessment**" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a ‘green light’ email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed [here](#).

**How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?**

HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see [IRAS Help](#) for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

**How should I work with participating non-NHS organisations?**

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to **obtain local agreement** in accordance with their procedures.

**What are my notification responsibilities during the study?**

The document “**After Ethical Review – guidance for sponsors and investigators**”, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
• Notifying amendments
• Notifying the end of the study

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Ms Jessica Broni-Tabi
E-mail randd@uclh.nhs.uk
Telephone 02034472122

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is 247176. Please quote this on all correspondence.

Yours sincerely

Catherine Adams
Senior Assessor
Email: hra.approval@nhs.net

Copy to: Ms Jessica Broni-Tabi, Sponsor’s Representative
         Mr Joe Marley, University College London Hospital NHS Trust
List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering letter on headed paper [Cover letter : revision documents]</td>
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<td>02 August 2018</td>
</tr>
<tr>
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<td>05 July 2018</td>
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<tr>
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<td></td>
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<tr>
<td>Non-validated questionnaire [ACE-III written for hearing impaired]</td>
<td>1.0</td>
<td>29 June 2018</td>
</tr>
<tr>
<td>Participant consent form [consent]</td>
<td>1.1</td>
<td>31 July 2018</td>
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<tr>
<td>Participant information sheet (PIS) [PIS_normal cognition]</td>
<td>v1.2</td>
<td>29 August 2018</td>
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<tr>
<td>Participant information sheet (PIS) [PIS_communication partner]</td>
<td>v1.1</td>
<td>29 August 2018</td>
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<tr>
<td>Participant information sheet (PIS) [PIS_MCI]</td>
<td>v1.2</td>
<td>29 August 2018</td>
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<tr>
<td>Participant information sheet (PIS) [PIS_dementia]</td>
<td>v1.2</td>
<td>29 August 2018</td>
</tr>
<tr>
<td>Research protocol or project proposal [Project protocol]</td>
<td>1.1</td>
<td>31 July 2018</td>
</tr>
<tr>
<td>Summary CV for Chief Investigator (CI) [CI summary CV]</td>
<td>v1.0</td>
<td>05 June 2018</td>
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<tr>
<td>Summary CV for student [student CV]</td>
<td>v1.0</td>
<td>15 May 2018</td>
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<tr>
<td>Summary CV for supervisor (student research) [first supervisor CV]</td>
<td>v1.0</td>
<td>05 June 2018</td>
</tr>
<tr>
<td>Summary CV for supervisor (student research) [second supervisor CV]</td>
<td>v1.0</td>
<td>05 June 2018</td>
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<tr>
<td>Validated questionnaire [MOCA for hearing impaired]</td>
<td>1.0</td>
<td>29 June 2018</td>
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<td>Validated questionnaire [MOCA original]</td>
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<td>01 July 2017</td>
</tr>
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<td>Validated questionnaire [ACE-III]</td>
<td>1.0</td>
<td>20 December 2012</td>
</tr>
<tr>
<td>Validated questionnaire [SSQ questionnaires]</td>
<td>v1.0</td>
<td>25 November 2012</td>
</tr>
<tr>
<td>Validated questionnaire [m-AIAD questionnaires]</td>
<td>v1.0</td>
<td>01 June 2013</td>
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</table>

Information for Sponsors and Participating NHS Organisations

The below provides all parties with information to support the arranging of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter. As part of the application process, details may change prior to a Letter of HRA and HCRW Approval being issued. NHS organisations should be assured that we will continue to work with the sponsor on any assessment criteria which are ‘pending’, and this should not impact on the arranging or capacity and capability.
## Assessment criteria

<table>
<thead>
<tr>
<th>Section</th>
<th>Assessment Criteria</th>
<th>Compliant with Standards?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>IRAS application completed correctly</td>
<td>Yes</td>
<td>No comments</td>
</tr>
<tr>
<td>2.1</td>
<td>Participant information/consent documents and consent process</td>
<td>Yes</td>
<td>The information sheets have been updated to comply with GDPR wording</td>
</tr>
<tr>
<td>3.1</td>
<td>Protocol assessment</td>
<td>Yes</td>
<td>No comments</td>
</tr>
<tr>
<td>4.1</td>
<td>Allocation of responsibilities and rights are agreed and documented</td>
<td>Yes</td>
<td>A statement of activities will act as agreement of an NHS organisation to participate. The sponsor is not requesting and does not expect any other site agreement.</td>
</tr>
<tr>
<td>4.2</td>
<td>Insurance/indemnity arrangements assessed</td>
<td>Yes</td>
<td>Valid insurance certificate supplied</td>
</tr>
<tr>
<td>4.3</td>
<td>Financial arrangements assessed</td>
<td>Yes</td>
<td>No comments</td>
</tr>
<tr>
<td>5.1</td>
<td>Compliance with the Data Protection Act and data security issues assessed</td>
<td>Yes</td>
<td>No comments</td>
</tr>
<tr>
<td>5.2</td>
<td>CTIMPS – Arrangements for compliance with the Clinical</td>
<td>Not Applicable</td>
<td>No comments</td>
</tr>
</tbody>
</table>
Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

All organisations will be undertaking the same activity (i.e. there is only one ‘site-type’) as detailed in the protocol and supporting documentation.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS or on the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net, or HCRW at Research-permissions@wales.nhs.uk.

We will work with these organisations to achieve a consistent approach to information provision.

<table>
<thead>
<tr>
<th>Section</th>
<th>Assessment Criteria</th>
<th>Compliant with Standards?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3</td>
<td>Compliance with any applicable laws or regulations</td>
<td>Yes</td>
<td>No comments</td>
</tr>
<tr>
<td>6.1</td>
<td>NHS Research Ethics Committee favourable opinion received for applicable studies</td>
<td>Yes</td>
<td>No comments</td>
</tr>
<tr>
<td>6.2</td>
<td>CTIMPS – Clinical Trials Authorisation (CTA) letter received</td>
<td>Not Applicable</td>
<td>No comments</td>
</tr>
<tr>
<td>6.3</td>
<td>Devices – MHRA notice of no objection received</td>
<td>Not Applicable</td>
<td>No comments</td>
</tr>
<tr>
<td>6.4</td>
<td>Other regulatory approvals and authorisations received</td>
<td>Not Applicable</td>
<td>No comments</td>
</tr>
</tbody>
</table>
## Principal Investigator Suitability

<table>
<thead>
<tr>
<th>This confirms whether the sponsor’s position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Principal Investigator is expected at participating organisations. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.</td>
</tr>
</tbody>
</table>

## HR Good Practice Resource Pack Expectations

<table>
<thead>
<tr>
<th>This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. Where arrangements are not already in place, for research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.</td>
</tr>
</tbody>
</table>

## Other Information to Aid Study Set-up

<table>
<thead>
<tr>
<th>This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.</td>
</tr>
</tbody>
</table>
Dear Professor Bamiou

Study title: Validation of the “Montreal Cognitive Assessment (MoCA) and Addenbrooke’s Cognitive Examination III (ACE-III) ” as cognitive screening tools for the hearing impaired.

REC reference: 18/LO/1225
Protocol number: 18/0306
IRAS project ID: 247176

Thank you for your letter of 31 August 2018, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on
the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where an NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at
the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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<td>IRAS Application Form XML file [IRAS_Form_02072018]</td>
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<td>IRAS Checklist XML [Checklist_30082018]</td>
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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study
The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

18/LO/1225 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project.

Yours sincerely

Sir Adrian Baillie
Chair

Email:nrescommittee.london-surreyborders@nhs.net

Enclosures: “After ethical review – guidance for researchers"

Copy to: Ms Jessica Broni-Tabi
Mr Joe Marley, University College London Hospital NHS Trust
Appendix C
Participant Information Sheet

Participant information sheet
YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of trial: Validation of “Montreal Cognitive Assessment (MoCA) and Addenbrooke’s Cognitive Examination III (ACE-III)” as a cognitive screening tools for the hearing impaired.

Department: Ear institute, Faculty of Brain science

Name and contact details of the Trial Manager:
Nattawan Utoomprurkporn
Email : n.utoomprurkporn.12@ucl.ac.uk
Tel : 020 34567870
Ear institute, Faculty of Brain science, University College London

We would like to invite you to take part in a research project

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve for you.
- Please take the time to read the following information carefully. Discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part.
- Ask us if there is anything that is not clear or if you would like more information.
- Thank you for reading this information sheet.
1. Why are we doing this trial?

Hearing problems are very common in older adults, but we don’t have good quality pencil and paper tests to identify whether people with hearing loss might have dementia or not. The purpose of this trial is to develop such tests.

Early and appropriate detection of dementia among older adults with hearing loss is very important. Early detection of dementia can help these older adults, who are at risk, to get timely intervention needed for them.

2. Why am I being asked to take part?

We have invited you to take part in this trial because you have a diagnosis of hearing loss and are aged 65 or over. 30 participants who have hearing loss with dementia will be recruited from a total of 90 participants in this trial.

We need people with dementia to take part in this trial because we need to know how easy they find our new tests in comparison to people without dementia.

3. Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw at any time without giving a reason and without it affecting any benefits that you are entitled to.

If you do withdraw, any identifiable/personal information we have collected about you will be destroyed. Data which is not identifiable may be retained.

4. What will happen to me if I take part?
If you decide you would like to take part in the trial, a researcher will arrange a convenient time to meet with you to carry out a ‘screening’ visit. This initial visit will assess whether you are eligible to take part in the study. This assessment will involve doing a hearing test and answering some questions.

If the tests show that you are eligible to take part in the study then they will ask you to fill in some questionnaires and short tests of your memory, language and thinking abilities.

If you have a communication partner (someone you see on a near daily basis) they will also be invited to take part if you are happy for them to do so. If they do not formally want to take part, they do not have to.

The whole session will last about 2 hours, but you can take a break or do this over several visits if that suits you.

Then we will ask for your permission to contact your key worker in the memory clinic about your results at your next routine annual follow up. This is to examine whether there has been any change in your memory, cognitive or language abilities over the course of the year.

5. What are the possible benefits of taking part?

We believe participants could potentially benefit from the dementia tests and hearing tests, since they may pick up issues which were not previously known about and, which we may then be able to help.

More broadly, the information we get may lead to good quality dementia tests for people with hearing loss, which could help to improve things for people with hearing loss in the future.

6. What are the possible disadvantages and risks of taking part?

We do not feel there are significant risks associated with this project.
You will spend about 2 hours completing the assessment. As mentioned, previously if you are tired, or wish to take a break for any reason you can do that before completing the rest of the study.

All the tests and questionnaires are routinely used in the NHS and are not known to cause upset or harm. However, if you feel upset or distressed by the assessments you can speak to the researcher. You can also withdraw from the trial at any point, without giving a reason.

---

7. What if something goes wrong?

If you have concerns about any aspect of this trial you should ask to speak to the researcher or you can contact the Chief Investigator, Nattawan Utoomprurkprukporn (email n.utoomprurkporn.12@ucl.ac.uk).

If you feel your complaint has not been handled satisfactorily, please contact the Patient and Liaison Service (PALS) at your NHS Trust. PALS can provide information on Trust policies and put you in touch with the relevant people to help your resolve your concerns. PALS can also assist people in making formal complaints if necessary. You can find your nearest PALS office on the NHS choices website or ask your GP surgery or hospital for the details (or phone NHS on 111).

---

8. Will my taking part in this project be kept confidential?

A copy of this information sheet and your signed consent form will be placed in your medical notes so that any health care professionals involved in your care are aware of your participation in the trial.

All the information that we collect about you during the course of the research will be stored at University College London and kept strictly confidential and only accessed by authorised members of the research team. All data collected about you will be anonymised by using participant ID numbers which will uniquely identify each individual and be stored in a locked filing cabinet. The anonymised data will also be stored electronically on password protected computers. Identifiable
information is only kept for a short period where it is necessary for the conduct of the trial. You will not be able to be identified in any ensuing reports or publications. The research team will occasionally need to allow monitors from Regulatory Authorities to inspect the study paperwork, in order to meet legal, ethical and safety requirements. All individuals who have access to data will be bound by strict data protection and confidentiality rules.

**Limits to confidentiality**

If during the interview or assessments you tell the researcher something that makes them concerned for your safety, or the safety of others, they will have to share this information as appropriate with the safeguarding team.

9. **What will happen to the results of this trial?**

We intend to publish the results of this study in scientific journals and public platform. All results will have your personal information removed so you cannot be identified in any published articles.

10. **Data Protection Privacy Notice**

As a university (UCL), we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of
society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner’s Office (ICO).

The data controller for this project will be University College London (UCL). The UCL Data Protection Office provides oversight of UCL activities involving the processing of personal data and can be contacted at data-protection@ucl.ac.uk. UCL’s Data Protection Officer is Lee Shailer and he can also be contacted at data-protection@ucl.ac.uk.

Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this and will endeavour to minimise the processing of personal data wherever possible.

University College London (UCL) is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. UCL will destroy all identifiable information about you immediately after the study has finished (The duration of this study is 3 years, your identifiable data will be kept only until 2021).

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information, if you are concerned about how your personal data is being processed, please contact UCL in the first instance at data-protection@ucl.ac.uk. If you remain unsatisfied, you may wish to contact the Information
Commissioner’s Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

UCLH/Camden and Islington NHS foundation trust will collect information from you and/or your medical records for this research study in accordance with our instructions.

UCLH/Camden and Islington NHS foundation trust will keep your name, NHS number and contact details confidential and will not pass this information to our sponsor UCL. UCLH/Camden and Islington NHS foundation trust will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from UCL and regulatory organisations may look at your medical and research records to check the accuracy of the research study. UCL will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

UCLH/Camden and Islington NHS foundation trust will destroy identifiable information about you from this study immediately after the study has finished (This study is intended to be for 3 years until 2021).

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.
11. Who is organising and funding the trial?

This trial is sponsor and organised by University College London (UCL).

The funding of the trial is from “The national Brain Appeal” (Funding advances in neurology and neurology).

12. Who has reviewed the trial?

This trial has been reviewed by an independent group of people, called the Research Ethics Committee, to protect your safety, rights, well-being and dignity. The trial has been given a favourable opinion by (London - Surrey Borders Research Ethics Committee) Research Ethics Committee.

13. Contact for further information

Nattawan Utoomprurkporn
Ear institute, Faculty of Brain science, University College London
332 Grays inn road, Kings cross, London WC1X 8EE
Tel: 020 34567870
Email: n.utoomprurkporn.12@ucl.ac.uk

Professor Doris Eva Bamiou (Chief investigator of the trial)
Ear institute, Faculty of Brain science, University College London
332 Grays Inn road, Kings cross, London WC1X 8EE
Tel: 020 34567870

Thank you for reading this information sheet and for considering taking part in this research trial.

Validation of cognitive screenings for the hearing impaired
Dementia : v1.2 (29/08/2018) IRAS 247176
Appendix D

Participant Consent Form

IRAS ID: 247176

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Validation of “Montreal Cognitive Assessment (MoCA) and the Addenbrooke’s Cognitive Examination III (ACE-III)” as a cognitive screening tool for the hearing impaired.

Name of Researcher:

1. I confirm that I have read the information sheet dated....................
   (version............) for the above study. I have had the opportunity to
   consider the information, ask questions and have had these answered
   satisfactorily.

2. I understand that my participation is voluntary and that I am free to
   withdraw at any time without giving any reason, without my medical
   care or legal rights being affected.

3. (If appropriate) I understand that relevant sections of my medical
   notes and data collected during the study may be looked at by
   individuals from [company name], from regulatory authorities or
   from the NHS Trust, where it is relevant to my taking part in this
   research. I give permission for these individuals to have access to my
   records.

4. (If appropriate) I understand that the information collected about me
   will be used to support other research in the future and may be shared
   anonymously with other researchers.

5. (If appropriate) I agree to my General Practitioner being informed
   of my participation in the study. / I agree to my General Practitioner
   being involved in the study, including any necessary exchange of
   information about me between my GP and the research team.
6. (If appropriate) I understand that the information held and maintained by the Health and Social Care Information Centre (or amend as appropriate) and other central UK NHS bodies may be used to help contact me or provide information about my health status.

7. I agree to take part in the above study.

_________________________  ______________________  ______________________
Name of Participant          Date                        Signature

_________________________  ______________________  ______________________
Name of Person               Date                        Signature
taking consent
Appendix E

HI-ACE-III Administration Manual

HI-ACE-III Administration Instructions

Materials needed for administration: answer / score sheet, pen, pencil with eraser, blank sheet of paper and timer

The PowerPoint works when it is viewed as a slideshow. Please ensure that you are viewing the PowerPoint on a device that is big enough, in particular when displaying the pictures. Before administering the HI-ACE-III, the tester should be trained in administration and read the administration instructions.

Instruction Screen – The participant should read the displayed instructions, they appear in two parts. Blank slides will appear between most test slides. Once the participant has informed you that they are ready to begin, move to the blank slide. This is to prevent the participant from referring back to instructions several times.

Attention - Orientation
The questions on the next two slides will appear one at a time with a blank screen in between. Please press the enter key to continue once the client has given their answer and record the answer on the answer sheet.

If the participant says the month in numbers e.g. 14th of the 8th then prompt for the name of the month. If the participant is at home, ask for the name of the place e.g. apartment complex/retirement village and for the floor, you might ask for the name of the room (e.g. living room). If it is a single story health setting, you could ask about a local landmark. When the season is changing (e.g., at the end of August) and the participant says, “Autumn” then ask, “could it be another season?” If the answer is “Summer”, give 1 point since the two seasons are in transition. Do not give 1 point if the answer is “Winter” or “Spring”. Conditional prompts – what can we do with these?

Attention - Registration of 3 items

Three words are going to flash up on the screen and I would like you to say them after you have seen all three of them.

Lemon
Key
Ball

Try to remember them because I’m going to ask you later

This slide is timed, once lemon has appeared the words will each be displayed for 2 seconds in an attempt to represent the length of time the word would be presented verbally. You can repeat this slide up to 3 times if they are unable to remember all three on the first trial by pressing backspace and enter. Only the first trial is scored, record the number of trials it takes to learn all 3 words and record any incorrect items.

Attention - Serial 7 Subtraction

Could you take 7 away from 100?
I would like you to keep taking away 7 from each new number until you see the word STOP on the screen

Only show the second part of the instruction once the client has provided their answer to ‘Could you take 7 away from 100?’. The blank screen should be displayed while the client provides their answers. Record all responses and do not stop the client if they make a mistake. Stop the client after 5 subtractions
by clicking from the blank screen to stop screen, check subsequent answers for scoring.

Memory – Recall of 3 Items

Which 3 words did I ask you to repeat and remember earlier?

The blank screen should be presented while the participant provides their answers. Record responses verbatim and score 1 point for each correct item. Do not prompt the participants for the items.

Verbal Fluency – Letter and Category

I am going to give you a letter of the alphabet and I would like you to generate as many words as you can beginning with that letter but not names of people or places.

Do you understand? Are you ready?

P

For example, if I give you the letter C you could give me words like Cat, Cry, Clock. But you can’t give me words like Catherine, Canada.

This slide is timed, the P will appear for 3 seconds before a blank screen will be displayed. It will automatically move to the stop screen after a minute has passed. Any answers given after the minute has passed should not be counted. Record each word that the participant generates on the answer sheet in 15 second intervals. Do not include any answers given after stop has appeared.
This slide is also timed, the blank slide will appear for 1 minute after you have one minute has appeared for 3 seconds. *If the participant misunderstands the instructions and perseverates by naming animals beginning with “p” then reiterate to the participant that they should name animals beginning with any letter.* Record each word the participant generates on the answer sheet in 15 second intervals. Do not include any answers given after stop has appeared.

Memory – Anterograde Memory – Name and Address

The address slide is timed (8 seconds) and will appear 3 times in order to represent the 3 learning trials. *If the participant starts reciting it before it has disappeared, ask them to wait until it has disappeared.* Record responses for each trial but only responses in the third trial contribute to the ACE-III score.

Memory – Retrograde Memory – Famous People

Record responses verbatim. *Ask for a surname if only the first name is given. If there has been a recent change in leaders, probe for the name of the outgoing politician.*
Language – Comprehension

Please place a pencil and piece of paper side by side in front of the client before presenting these slides.

Pick up the pencil and then the paper

This is a practice trial. If this is incorrectly performed, score 0 and do not continue any further with this item by pressing return 8 times. The slides with instructions are timed (8 seconds). Before beginning each trial, always place the pencil and piece of paper side by side in front of the participant.

Place the paper on top of the pencil  Pick up the pencil but not the paper  Pass me the pencil after touching the paper

Language – Sentence Writing

Please write two (or more) complete sentences about your last weekend. Write on the paper provided, in complete sentences and do not use abbreviations.

Please provide the participant with the answer sheet and a pen once they have read the instructions. The blank screen should be displayed while the participant completes the task.

Language – Single Word Repetition

Please say each word after it has disappeared from the screen

Caterpillar  Eccentricity
All these slides are timed with each word appearing for 2.5 seconds with 2.5 seconds for the participant to say the word. There is no need to press enter until the blank screen appears after statistician. If the participant tries to say the word before it has disappeared, please prompt them to wait for it to disappear.

Language – Proverb Repetition

Please repeat after it has disappeared from the screen

All that glitters is not gold

A stitch in time saves nine

These slides are timed once the proverb has appeared (3 seconds). The blank screen during which the participant provides their response is not timed and you will need to manually press enter to move to the next proverb.

Language – Object Naming

Please name the following pictures

These slides are not timed. The participant should be allowed enough time to name or attempt to name all the pictures in any order. Record responses verbatim.

Language – Comprehension

Point to the one which is associated with the monarchy

Point to the one which is a marsupial
These slides are not timed and you should proceed to the pictures once the client has read the question. The client should point to the picture on the screen. Please do not provide any feedback regarding the word meaning. Self-corrections are allowed.

Language – Reading

Please read the following words

Sew
Pint
Soot
Dough
Height

These words will appear one at a time as you press the return key. Keep the words on the screen while the client reads them. If possible, record the mistakes using the phonetic alphabet.

Visuospatial Ability – Intersecting Infinity Loops

Please give the client the answer sheet in order for them to complete the next three items. Please ensure that the answer sheet is folded so that the participant cannot see the perceptual abilities or memory recall sections.

For the clock draw, switch to the blank slide once the client has begun drawing the clock. If the client does not like their first drawing and would like to do it again, you can allow for that and score the second clock. Clients may correct their mistakes by erasing it while drawing.

Please take the answer sheet back from the client.
Perceptual Abilities – Counting Dots

The instructions will disappear before the dots are presented. Please ensure that the clients are not pointing to the dots on the screen in order to count them. The dot counting slides are not timed.

Perceptual Abilities – Identifying Letters

The instructions will disappear before the letters are presented. The participant is allowed to point. These slides are also not timed.
Memory – Recall of Name and Address

Now tell me what you remember about that name and address you were repeating at the beginning

Only proceed if subject has not been able to recall one or more details from the name or address, otherwise administration of the test is complete. The blank screen should be displayed while the participant provides their answer. This is not timed.

Let me give you some hints

Hint: Was the name
Jerry Barnes
Harry Barnes
Harry Bradford

Hint: Was the number
37
73
76

Hint: Was the road name
Orchard Place
Oak Close
Orchard Close

Hint: Was the town
Oakhampton
Kingsbridge
Dartington

Hint: Was the county
Devon
Dorset
Somerset

This gives the participant a chance to recognise items they could not recall. First, tick the correctly remembered items on the shaded column and then proceed with the prompts. The hints will appear one category at a time.

The End
Appendix F

ROC Curve for HI-ACE-III Predicting Dementia – Diagnostic Accuracy Data for all Potential HI-ACE-III Cut-Off Scores

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