Is Anxiety a Risk Factor in Cognitive Ageing?

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Declaration

Except where otherwise acknowledged, this thesis is my own original work and has not been submitted for a higher degree at any other university or institution. I developed the research questions and analytical strategies. This thesis draws on secondary data of the Personality And Total Health Through Life (PATH) study, commenced in 1999. For the PATH study, I participated in data collection for the 2014/2015 sub-study on informant reports but was otherwise uninvolved in data collection. I conducted and interpreted all statistical analyses presented in this document.

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Abstract

Background: The modifiability of anxiety, combined with the extraordinary worldwide growth in the prevalence of dementia, have motivated previous research which suggests anxiety may be a predictor of cognitive ageing. The aim of this PhD investigation is to extend the published research with new data, pool results with a fresh meta-analysis, and examine methods with a view to recommending strategies for future research.

Method: The two, primary research questions, are: (1) Is anxiety a risk factor for the rate of age-associated, cognitive decline; and, (2) Is anxiety a risk factor for age-associated, incident, cognitive impairment? From published evidence on neuropsychological mechanisms, I developed "The Diathesis-Anxiety Heuristic of Cognitive Ageing". This model suggested a causal relationship between long-term anxiety and cognitive ageing and introduced the possibility of neuropsychological feedback loops which may serve as a control mechanism. My systematic review and meta-analysis updated previously published, pooled results. This statistical investigation was extended by drawing on new data from the Personality And Total Health (PATH) Through Life, dataset. PATH is an Australian, population based, prospective cohort study over four waves of data, at four-yearly intervals. Participants were aged 60 to 64 years at baseline, with sample size of 2,390. Analyses included multilevel modelling with stratifications and alternative temporal treatments, and testing for current and delayed effects of anxiety.

Results: For anxiety as primary predictor, the only significant, meta-analysis result was for dementia as outcome, based on five studies: relative risk ratio (RR) = 1.81 (95% confidence Interval (CI): 1.22–2.70), $p = 0.003$, dispersion (I^2) = 78.6%. From PATH, the only fully adjusted association found was for participants who consumed anxiolytics at baseline (n = 126). Anxiety symptoms were associated with working memory, with coefficient: 0.215 (CI: 0.001–0.429), $p = .049$.

Discussion: For the meta-analysis, the dispersion percentage reflected high levels of methodological or sample differences between studies, and the result was, therefore, inconclusive. The result from PATH, for the *anxiolytics* stratification, was examined for the meaning of the direction of change, and for effect size among other criteria, and was found to be of marginal credibility. Analytical methods adopted in past research and in the operationalisation of anxiety, were likely to have contributed to the inconclusive nature of these results. Recommended future developments of methods are discussed to resolve these limitations. Additionally, all previous studies, including PATH, were observational. To establish causation, randomised control studies would be necessary, using treatment interventions, to determine if reversal of the risk factor is protective.

Conclusions: A predictive association between anxiety and cognitive ageing has not been established. A strategic approach is recommended for future research which should include: (A) development of a more valid operationalisation of anxiety; (B) Statistical analysis methods which account for long term effects of anxiety; (C) Further investigation of the biological mechanisms and the possibility of neurological feedback loops; and, (D) placebo controlled, randomised anxiety treatment intervention trials, establishing whether there is a causal link between anxiety and cognitive ageing.

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Acronyms

Acronym	Represents
ALSA	Australian Longitudinal Study of Ageing
ANSMHW	Australian National Survey of Mental Health and Well-being
ANU	Australian National University
APOE	Apolipoprotein
AUC	Area Under Curve
AVLT	Auditory Verbal Learning Test
BIS	Inhibition component of Behavioural Inhibition and Behavioural Activation Scales
BISBAS	Behavioural Inhibition and Behavioural Activation Scales
BPHQ	Brief Patient Health Questionnaire
CES-D	Centre for Epidemiological Studies Depression Scale
CI	Confidence Interval
COMT	Catechol-O-Methyltransferase
CV	Covariate
DHEAS	Dehydroepiandrosterone or Dehydroepiandrosterone Sulphate
DR	Delayed Recall
DSB	Digit Span Backwards
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DV	Dependent Variable
EPQ	Eysenck Personality Questionnaire
GAS	Goldberg Anxiety Scale
GDS	Goldberg Depression Scale
GEE	Generalized Estimating Equations
HPA	Hypothalamic Pituitary Adrenal
HR	Hazard Ratio
HREC	Human Research Ethics Committee
IR	Immediate Recall
IV	Independent Variable
K10	Kessler Psychological Distress Scale
KMO	Kaiser–Meyer–Olkin
LMM	Linear Mixed Models
MCI	Mild Cognitive Impairment
MET	Methionine
MGLS	Maximum Guttman's Lambda statistic
MMSE	Mini Mental State Examination
NCD; major-NCD; mild-NCD	Neurocognitive Disorder; major and mild Neurocognitive Disorder, respectively

Acronym	Represents
OR	Odds Ratio
PAS	Positive Affect, or Positive Affect Schedule
PATH	Personality and Total Health Through Life study
PFC	Prefrontal Cortex
PPd, PPn, PPb	Purdue Pegboard: for dominant, non-dominant, and both hands respectively.
PsD, PsDA, PsDM	Psychological Distress, A: by addition, B: by multiplication
RCTs	Randomised Control Trials
RCPM	Raven's Coloured Progressive Matrices
ROC	Receiver Operating Characteristics
RR	Relative Risk Ratio
SDMT	Symbol Digit Modalities Test
SEM	Structural Equation Modelling
StW	Spot the Word
VAL	Valine

CHAPTER ONE:

Concepts, Constructs, and Theory

Abstract

As foundation for the investigations to follow, this opening chapter provides an overview of: the motivation and theory for the present research; the constructs available for the principal predictor, anxiety; and, the possible neuropsychological mechanisms linking anxiety to cognitive change. Also developed here are the primary research questions:

1. Is anxiety a risk factor for the rate of age-associated, cognitive decline?
2. Is anxiety a risk factor for age-associated, incident, cognitive impairment?

These concepts guide the research to follow, and they provide important insights for the final chapter in which theory, limitations, and statistical findings are combined to shape a strategic approach to future research.

1.1 Introduction

1.1.1 Background

Although the evidence is not yet conclusive, anxiety has been posited as a risk factor for age-associated cognitive decline, mild cognitive impairment (MCI), and dementia (Gulpers et al., 2016). "Cognitive decline" refers here to the pre-impairment stages of age-associated decline in cognitive performance. "Cognitive impairment" is specifically MCI or dementia. These two stages, cognitive decline and cognitive impairment, are referred to collectively, as "cognitive ageing" which includes both normal and accelerated cognitive changes in older individuals.

The research interest has been motivated by the modifiability of anxiety (a variety of treatments are available) together with the pervasive and devastating nature of dementia. Without intervention, worldwide dementia is expected to increase by 60% from 46.8 million cases in 2015 to 74.7 million in 2030, and by 281% between 2015 and 2050 to 131.5 million cases (Prince, 2015). The estimated global cost of dementia in 2015, was US$817.9 billion and was projected to rise to US$2 trillion by 2030 (Wimo et al., 2017). Because these numbers are large, even a small change in percentage terms could make an important difference financially and in the lives of many people. Additionally, even small postponements in onset of dementia could make substantial differences in overall disease burden. For example, delaying onset of Alzheimer's disease by just 0.4 years could reduce its prevalence by 5% (Access Economics, 2004). The impact of pre-dementia cognitive decline has not been well defined or globally costed but would be additional to these statistics.

Whether anxiety is a risk factor for cognitive ageing has emerged in the research literature as a complex question. This is so, both in terms of the neuropsychological mechanisms, and in the challenges in designing and interpreting the research into statistical associations. To begin with a less encumbered observation, there was an established

elementary association between anxiety and MCI. Anxiety was approximately three times more prevalent among individuals with MCI than among similarly aged people without MCI (Forsell, Palmer, & Fratiglioni, 2003; Geda et al., 2008). However, such correlations were based on cross-sectional studies, which cannot demonstrate an association over time and, therefore, can say nothing about whether one variable predicts, or can be a risk factor for, another. It is as valid to speculate that mild cognitive decline would trigger anxiety, as it is that anxiety may bring about cognitive changes. Singer and Willett (2003) explained also that, "cross-sectional studies confound age and cohort effects . . . and are prone to selection bias". By contrast with such cross-sectional studies, evidence that anxiety predicted cognitive ageing was provided by a recent review and meta-analysis of longitudinal studies. With a census date of January 2015, Gulpers et al. (2016) found anxiety predicted progression from cognitively healthy to MCI, and from cognitively healthy to dementia. However, the study was unable to pool results for cognitive decline. And, for progression from cognitively healthy to cognitive impairment, the analysis was limited by the small number of accepted studies, just four for progression to MCI, and six for progression from cognitively healthy to dementia. Further, when adjustment for depression (an important confounder discussed below) was taken fully into account (by rejecting studies that had not controlled for this variable), the refined MCI result was based on only two studies, and the other association was attenuated. Thus, the research so far has been inconclusive.

1.1.2 Key Research Principles

The complexity of causal relationships mentioned above, and the influence of confounding variables such as depression, are just two of the many issues influencing research design which, if not well considered, can render research results of reduced validity or, at least, of less usefulness. Clarity is necessary. In the published literature, the need for brevity has typically obviated more than a minimal discussion of such strategies underlying

the description of methods. However, with the space and opportunity to discuss the research design in this dissertation, this opening chapter provides an outline of the more important principles.

1.1.2.1 Normality of cognitive ageing.

Associations between anxiety and subsequent cognitive ageing, need firstly to be distinguished from questions of normality. If anxiety does indeed increase the risk of cognitive ageing, then a logical expectation might be that anxiety would cause accelerated cognitive ageing. However, accelerated or abnormal cognitive decline is not clearly distinguished from normal rates of age-associated cognitive change (Fjell, McEvoy, Holland, Dale, & Walhovd, 2014). Additionally, abnormal decline does not necessarily lead to MCI or dementia; nor does normal decline necessarily exclude such impairment (Fjell et al., 2014). If anxiety can be demonstrated to add risk over time to the probability of cognitive ageing, then this is sufficient (and parsimonious) without factoring in characteristics of normality. The research literature appears not to have discussed this point. Articles have addressed questions of normality, only to establish a "normal" baseline. However, apparently, all past research has adopted this perspective.

1.1.2.2 Causal relationships.

1.1.2.2.1 Temporal Associations.

If anxiety is found to be a *risk* for cognitive ageing, then it must at least *predict* cognitive ageing. This temporal question can be difficult especially when dealing with Alzheimer's disease (which is the dominant disease within the cluster of dementia types) with a prodromal period of 17 years or more, and a specific memory impairment phase of 2.5 to 4.5 years before onset of Alzheimer's disease (Villemagne et al., 2013). So, for quite long periods, the incipient impairment could be a source of worry and anxiety. In such circumstances, the prodromal cognitive impairment would be a risk factor for anxiety rather than the other way

around. With or without impairment, cognitive ageing has a complex temporal relationship with anxiety. Such questions have not always been well considered or included in study design strategies. In others, the temporal issues have been carefully evaluated, most notably by Petkus, Reynolds, Wetherell, Kremen, and Gatz (2017) who investigated the "Temporal dynamics of cognitive performance and anxiety across older adulthood", and found a bidirectional association between anxiety and both cognitive decline and cognitive impairment.

1.1.2.2.2 Randomised Control Trials.

A related complication is that all studies so far have been observational. Such studies cannot determine cause. Randomised control trials (RCTs) to test direct associations between anxiety and cognitive decline or cognitive impairment would not be possible, simply because potentially harmful anxiety could not be ethically assigned. Additionally, assignment of long-term anxiety conditions would be impractical. However, ascertaining causality may be possible using RCTs for intervention of anxiety treatment (S. Mulhall, personal communication, 2017), while measuring the efficacy of treatment as well as any influence on subsequent cognitive decline and cognitive impairment. Although the design of such RCTs might be straightforward, apparently none has been undertaken (no such RCT was reported by the recent intervention reviews on cognitive ageing: Kane et al., 2017; Leshner, Landis, Stroud, & Downey, 2017; Livingston et al., 2017).

1.1.2.2.3 Confounds.

Without an RCT, there may remain an unresolved cluster of potential effects possibly confounding the influence of anxiety on cognitive ageing and the interpretation of findings. These confusions could mask alternative possible causes, which are principally: (1) Confounding variables (rather than, or as well as, anxiety) directly causing cognitive ageing. For example, depression is highly comorbid with anxiety (Burton, Campbell, Jordan, Strauss,

& Mallen, 2013) and predicts cognitive ageing (Diniz, Butters, Albert, Dew, & Reynolds, 2013), so may be a confounding variable; (2) Cognitive decline (such as memory loss) may cause increased anxiety (the *reverse effect*); and (3) Anxiety may also be present either as a symptom or marker of prodromal dementia. As presented below, the research literature has sometimes either overlooked, or chosen to avoid, some of the critical issues of confounding variables.

1.1.2.2.4 Theory Suggesting Causality.

Despite the clear need for causal investigation, an RCT will not be attempted here. On the other hand, theory suggesting anxiety is a direct cause of cognitive ageing will be considered in this chapter as part of a wider overview of the relevant neuropsychological mechanisms. If a case can be made for the theory that anxiety causes cognitive ageing then evidence for anxiety as a *predictor* can be interpreted to infer anxiety is potentially, also a *risk factor*. Without direct evidence for causality, the theory, therefore, occupies an important place in this investigation.

1.1.3 Research Questions

The primary research questions can now be identified but further consideration will be required to qualify how they might be operationalised and interpreted. As part of this further development of the primary research questions, additional, subordinate questions will be added (Chapter Three). The two primary, research questions are:

(1) Is anxiety a risk factor for the rate of age-associated, cognitive decline?

(2) Is anxiety a risk factor for age-associated, incident, cognitive impairment?

The primary research questions nominate cognitive decline and cognitive impairment as the prognostic outcomes, but these are broad-level terms. They need to be delineated into categories. For example, cognitive decline can be categorised by cognitive domain, and for

cognitive impairment there are types of MCI and dementia. For each category, there may be different associations with anxiety. This issue will be examined further, below.

1.1.4 Sequence of the Balance of this Chapter

I will next examine the meaning of *anxiety* and related constructs such as stress. A brief description will follow, of the relevant categories of cognitive decline and cognitive impairment. These understandings will then support an exploration of the neurological and psychological mechanisms linking anxiety to cognitive ageing, in which causality will be examined. Conclusions from these considerations will inform a strategy adopted in following chapters for the investigations of evidence presented by the literature, and new data available to this PhD study.

1.2 Anxiety

1.2.1 The Nature of Anxiety

Anxiety is worry, apprehension, fear of the future or some perceived threat, and is associated with uncertainty, indecision, inability to concentrate, vigilance, avoidant behaviour, and autonomic arousal such as muscle tension, rapid heartbeat, trembling, and sweating (American Psychiatric Association, 2013; Gross & Hen, 2004; Grupe & Nitschke, 2013; Mah, Szabuniewicz, & Fiocco, 2016; VandenBos, 2006). In its milder forms, transient anxiety is adaptive (Endler & Kocovski, 2001; Spielberger, 2010), allowing the individual to be more observant about prospective threats and to be physically ready to respond. Intense, chronic anxiety (long term, clinical levels) or even low-level but enduring anxiety, without a corresponding likelihood of real risk, is not adaptive and can harm the individual psychologically and physiologically, and can interfere with relationships and daily activities (American Psychiatric Association, 2013; Mah et al., 2016; Rosen & Schulkin, 1998). In the absence of real threat, the inability to relax can be a debilitating condition.

Anxiety can be experienced as clinical disorders or in milder forms. Four anxiety disorders have been described by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; American Psychiatric Association, 2013). They are, *Generalised Anxiety Disorder*, *Panic Disorders*, *Social Phobia*, and *Specific Phobias*. Of these, Generalised Anxiety Disorder (GAD) is most commonly referred to in the research on associations with cognitive ageing. GAD is described by the *DSM-5* as "Excessive anxiety and worry … occurring more days than not for at least 6 months"; Worry is distressing, excessive, hard to control, and is typically about everyday life circumstances; symptoms cause clinically significant impairment in important aspects of life such as psychosocial functioning. "The intensity, duration, or frequency of the anxiety and worry is out of proportion to the actual likelihood or impact of the anticipated event". Three or more of six symptoms are required to be present for at least six months, with at least some present on more days than not. The symptoms are:

1. "Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance".

Diagnosis of GAD according to the *DSM-5*, requires also that "The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning" (Criterion D; American Psychiatric Association, 2013).

Researchers interested in identifying anxiety can use either formal diagnosis or self-report or informant-report questionnaires. For illustration, three commonly used, self-report, anxiety questionnaires are:

- Spielberger state-trait anxiety inventory (STAI; Spielberger & Gorsuch, 1983): Two questionnaires representing state and trait anxiety. Each provides 20 questions on a Likert scale: 1 – Almost Never; 2 – Sometimes; 3 – Often; 4 – Almost Always. Examples of the "State" questions are: I feel calm; I feel secure: I am tense; I feel Strained". Examples of the "Trait" questions are: I feel pleasant; I feel nervous and restless; I feel satisfied with myself; I feel like a failure".
- Hospital anxiety and depression scale (HADS; Zigmond & Snaith, 1983): The anxiety component of the HADS consist of seven questions, each of which is scored from zero to three. Thus, the maximum score is 21. Examples of these questions are: 1 – I feel tense or wound up; 2 – I get a sort of frightened feeling as if something bad is about to happen; 3 – Worrying thoughts go through my mind; 4 – I feel restless and have to be on the move.
- Goldberg Anxiety and Depression scales (GAS and GDS; Goldberg, Bridges, Duncan-Jones, & Grayson, 1988): Nine anxiety questions are offered with yes/no answers, referring to the participant's experiences within the last four weeks. Administration of the questionnaire, according to its originators, was to ask the first four questions initially, and then if there are "Yes" responses to two or more of these four, then the remaining five questions are administered. The scale was based on GAD diagnosis criteria. Individuals returning anxiety scores of five have a 50% chance of having a clinically important disturbance. Examples of the first four questions are: 1 – Have you felt keyed up, on edge? 2 – Have you been worrying a lot? Examples of the remaining

five questions are: 5 – Have you been sleeping poorly? 6 – Have you had headaches or neck aches?

The common attribute of all these scales is that they report levels of anxiety, not merely a binary indicator (as the result of diagnosis). Both GAS and HADS provide depression scales but these are separated from the anxiety scales. The only scale to estimate separately, state (incident or short term) and trait (long-term or lifetime) anxiety is the STAI. There are similarities and dissimilarities between the items in the various scales. Whether they measure the same construct is an open question. This is an important question because deployment of the various questionnaires in research operationally defines the construct of anxiety.

Even beyond the dissimilarities in measurement instruments, there is disagreement about the meaning of *anxiety*. These disagreements are mostly about ambiguities between the constructs of anxiety, fear, stress, and depression. Notably, Mah et al. (2016), in their review of brain damage caused by anxiety, argued anxiety is not distinct from fear or stress. They noted these conditions have overlapping neurocircuitry, and common arousal and neuroendocrine mechanisms. Mah et al. contended the terms *anxiety*, *fear*, and *stress* are often interchangeable, and distinguishable only by virtue of the nature of the circumstances. The considerable research literature available on the impact of stress on cognitive performance (e.g., Gianaros et al., 2007; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Sweis, Veverka, Dhillon, Urban, & Lucas, 2013) may, therefore, be just as relevant to anxiety. To comprehend the nature of anxiety and to evaluate mechanisms correctly that may explain links between anxiety and cognitive performance, it becomes necessary to consider in greater depth, the equivalences, and differences between the three constructs. I will also review the potential overlap with depression. This is because, again, there are ambiguities between the constructs, and because it emerges from the research that depression is an important confounding variable.

1.2.1.1 Anxiety versus Fear.

Fear is defined by the *DSM-5* as, "An emotional response to perceived imminent threat or danger associated with urges to flee or fight". The APA Dictionary of Psychology (VandenBos, 2006) is more descriptive, but essentially agrees. This latter definition includes a note on the distinction between fear and anxiety that, "fear has an object (e.g., a predator, financial ruin) and is a proportional response to the objective threat, whereas anxiety typically lacks an object or is a more intense response than is warranted by the perceived threat".

According to Grupe and Nitschke (2013), the key difference between fear and anxiety is the presence of uncertainty, greater uncertainty applying in the anxious condition. The American Psychiatric Association (2013) comprehended the difference differently, asserting persistent worry is a common feature of anxiety but not of fear.

There is neurological evidence for the differences between fear and anxiety. In both conditions, signals are sent to the brain stem and hypothalamus but the sources of those signals are different; signals originating from the amygdala result in fear, and from the stria terminalis result in anxiety (Davis, Walker, Miles, & Grillon, 2010). A further distinction is available from the fact that anxiolytics influence anxious behaviour but not fear responses (Graeff, 1994; Gray & McNaughton, 2003). Finally, Etkin and Wager (2007) identified (using functional magnetic resonance imaging [fMRI]) differences in active brain regions engaged in fear and two anxiety disorders: social anxiety, and specific phobia. See Figures 1.1 and 1.2. These images do not show comparisons with regions activated in GAD. But the point is made on this evidence there are substantial dissimilarities between fear and two of the potential four anxiety disorders. On the other hand, these figures also illustrate there are differences in hyperactivation between the two anxiety disorders, thus leaving as unexplained whether differences between fear and anxiety could be typified by such fMRI results unless all known forms of fear and anxiety were examined and compared.

Despite the identified distinctions between anxiety and fear, Perusini and Fanselow (2015) argued neither *fear* nor *anxiety* have consistent definitions, that the distinctions are subjective and that there is no agreed differences in terms of their causes or outcomes. Perusini and Fanselow described the neurocircuitry general to fear and anxiety, which they outlined in their figure reproduced here as Figure 1.3. In summary, they described fear and anxiety as executing similar connections between the hippocampus, prefrontal cortex, amygdala, dorsal raphe nucleus, stria terminalis, and periaqueductal gray.

Further complicating the questions of similarities and distinctions between fear and anxiety is that neurologically, there is a case to be made for more than one type of fear. Klumpers, Kroes, Baas, and Fernández (2017) found, under fMRI examination, that electric shock anticipation and shock confrontation were associated with predominant activity of the bed nucleus of the stria terminalis (BNST) and amygdala, respectively. They noted the BNST has been previously associated with responses to uncertain conditions and the amygdala to acute danger. However, the experimental procedure by Klumpers et al. did not introduce uncertainty, only a short time delay for the "anticipation" condition. Thus, the BNST may have been less reflective of uncertainty (and, therefore, anxiety) and more indicative of a sub-category of fear. These authors discussed the ambiguities, noting "little is known about potential differential contributions of the BNST and amygdala".

In sum, there is disagreement about whether fear and anxiety are clearly distinguished, and these constructs have yet to be fully defined neurologically.

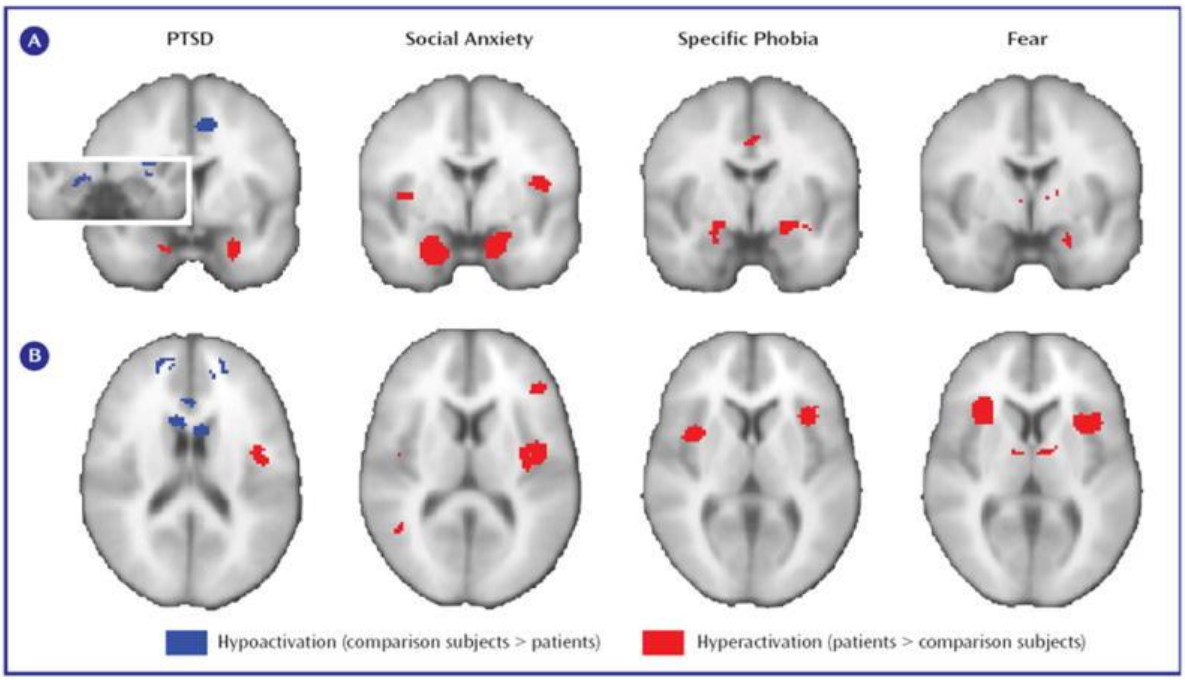


Figure 1.1. "Clusters in Which Significant Hyperactivation or Hypoactivation Were Found in Patients With PTSD, Social Anxiety Disorder, and Specific Phobia Relative to Comparison Subjects and in Healthy Subjects Undergoing Fear Conditioning[a]*."*

[a] Results are shown for the amygdala (A) and insular cortices (B). Note that within the left amygdala there were two distinct clusters for PTSD, a ventral anterior hyperactivation cluster and a dorsal posterior hypoactivation cluster. The right side of the image corresponds to the right side of the brain." Reproduced with permission from Etkin and Wager (2007).

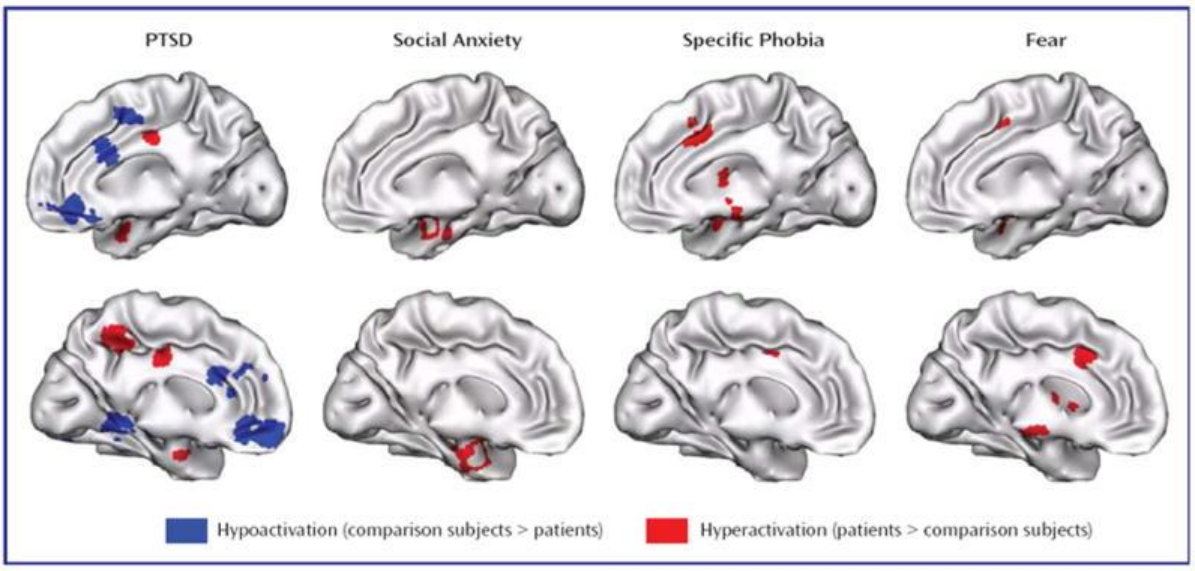


Figure 1.2. "Significant Clusters of Hyperactivation or Hypoactivation in Medial Prefrontal Regions for Patients with PTSD, Social Anxiety Disorder, and Specific Phobia, and in Healthy Subjects Undergoing Fear Conditioning."

Reproduced with permission from Etkin and Wager (2007):

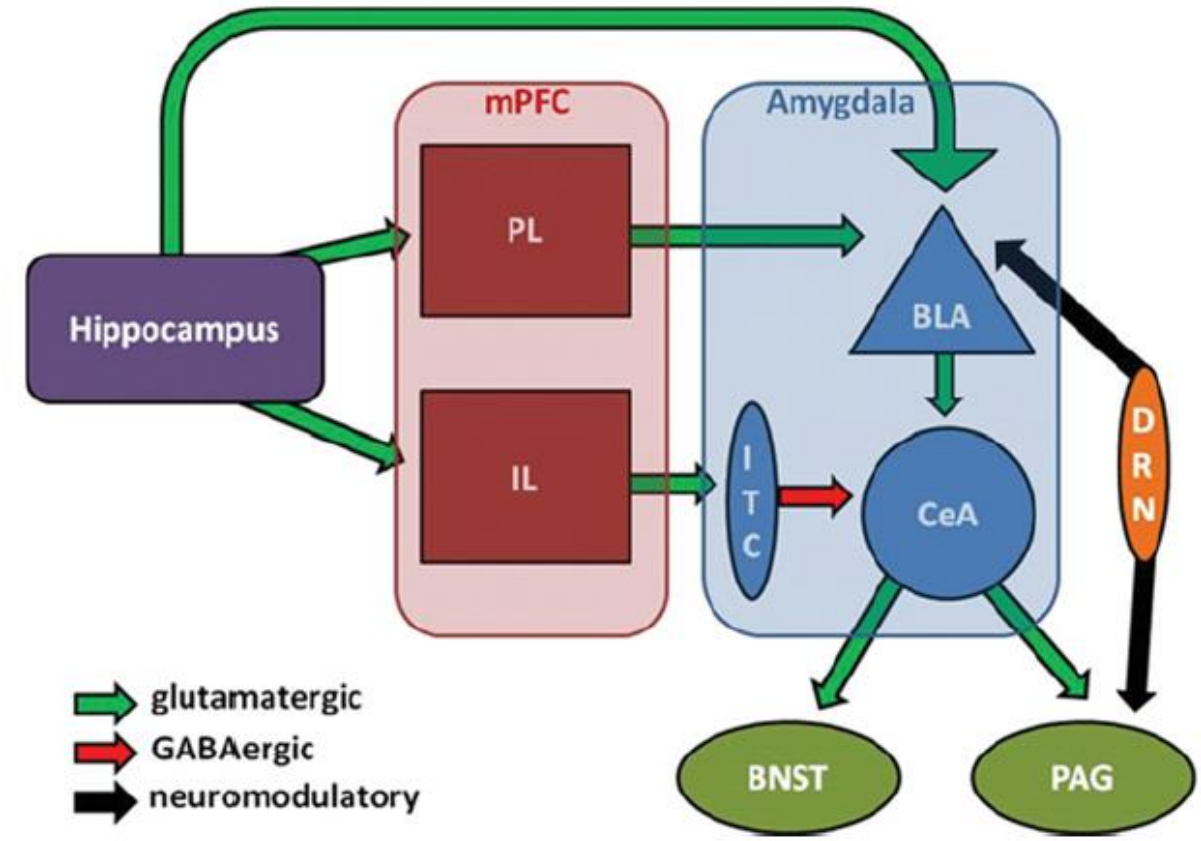


Figure 1.3. Circuit diagram depicting a general model of neural circuitry of fear and anxiety.

(Reproduced with permission from Perusini and Fanselow (2015) and Cold Spring Hector Laboratory Press.)

"Circuit diagram depicting a general model of neural circuitry of fear and anxiety. The basolateral amygdala (BLA) gathers sensory information from both thalamic and auditory cortical regions, both involved in relaying CS (e.g., tone) information, as well as from the hippocampus for contextual information. The BLA projects to the central nucleus (CeA) both directly and indirectly, via the GABAergic intercalated cell (ITC) masses that lie between these two regions. The CeA output to the periaqueductal gray (PAG) and bed nuclei of the stria terminalis (BNST) drive fear responding. Ascending projections from the brainstem and midbrain to the amygdala, such as from the dorsal raphe nucleus (DRN) projects to the dorsal PAG and to the amygdala in a manner that modulates defensive behaviors. Descending projections from the medial prefrontal cortex also differentially modulate the behavioral outputs of this circuit—the prelimbic (PL) cortex projects to the BLA possibly to enhance fear responding while the infralimbic cortex (IL) indirectly projects to the CeM via ITC to mediate extinction. Green arrows represent glutamatergic projections, red arrows represent GABAergic projections, and black arrows represent neuromodulatory projections (e.g., DRN to BLA is serotonergic)."

1.2.1.2 Anxiety versus Stress.

The *DSM-5* described *stress* as "the pattern of specific or nonspecific responses a person makes to stimulus events that disturb his or her equilibrium and tax or exceed his or her

ability to cope." A *stressor* is, "Any emotional, physical, social, economic, or other factor that disrupts the normal physiological, cognitive, emotional, or behavioural balance of the individual" (American Psychiatric Association, 2013). By the definitions so far, one distinction between anxiety and stress is that anxiety emphasises *anticipation* of stressors, but stress is a *response* to stressors.

Despite the conceptual differences, operationally there is not necessarily a clear distinction in measurement scales. For example, the Perceived *Stress* Questionnaire (Levenstein et al., 1993) asks how often the individual has the following experiences: (1) many worries (2) being irritable or grouchy (3) having trouble relaxing. Similarly, the Goldberg *Anxiety* Questionnaire (Goldberg et al., 1988) includes the questions: (1) Have you been worrying a lot? (2) Have you been irritable? (3) Have you felt keyed up or on edge? Thus, on these questions, there is clear overlap between these stress and anxiety scales. There is also no distinction (between these two measuring instruments) on the criteria mentioned above about *anticipation* or *response* to stressors. Some other questions also could be interpreted as referring to similar underlying constructs. For example, the stress questionnaire asks how often, "you are afraid for the future". Fear of the future is a symptom of anxiety. The stress questionnaire asks how often, "You feel tense". Tension is a symptom of anxiety. There appears to be no analysis available in the literature on the convergent and discriminant validity of these two questionnaires. There can be considerable ambiguity between constructs as applied by measuring instruments such as these scales.

The HADS questionnaire for anxiety (described above at Section 1.2.1) does question whether there was worry about the future (with item 2, "I get a sort of frightened feeling as if something bad is about to happen"), but some other instruments do not. Therefore, the choice of instruments appears to be an important element of study design on this point. However, the choice of instruments is unlikely to resolve a further ambiguity between anxiety and stress

questionnaires, which rests on the examination of whether the individual's response is disproportional to the threat. A disproportion in the response to threat is implied in most definitions or descriptions of anxiety. More specifically, most studies that specify a category of anxiety for their investigation, designate GAD, or they imply this by choice of self-report instrument such as GAS. Diagnosis of GAD requires "excessive . . . worry", or their estimate of the threat is "out of proportion to the actual likelihood or impact of the anticipated event". Without embarking upon an exhaustive examination, by this PhD study, of relevant self-report instruments, the questionnaires that have been examined here can be safely described as not attempting to make this distinction. Further, it would be difficult to conceive of a way to capture self-report data which, reliably and validly, acknowledges such disproportion, when the distortion is probably hidden from the individual who is required to declare it. Diagnosis appears to be the only reliable method for capturing this information.

Finally, both stress and anxiety are implicated in the production of cortisol (Boudarene, Legros, & Timsit-Berthier, 2002; Lenze et al., 2012; Mah et al., 2016; Mantella et al., 2008; Rosnick, Rawson, Butters, & Lenze, 2013; Thompson et al., 2007) and therefore also in long term hippocampal atrophy and consequent memory decline (Boudarene et al., 2002; Landgraf, Wigger, Holsboer, & Neumann, 1999; Lenze et al., 2012; Lupien et al., 2007; Mah et al., 2016; Mantella et al., 2008; McEwen, 1999). Mah et al. (2016) described the impact of chronic stress on fear neurocircuitry as augmenting amygdala flight/fight responses and (through the mentioned hippocampal atrophy) inhibiting hippocampal/prefrontal cortex (PFC) control over the stress response. Cortisol triggers a cascade of changes including the fight/flight response and inhibitory feedback from the hippocampus to the amygdala and hypothalamic-pituitary-adrenal (HPA) axis at various points. There is no definitive distinction between stress and anxiety in these cortisol-related mechanisms.

The observations and interpretations above support the proposition argued by Bystritsky and Kronemyer (2014) that stress and anxiety are complementary and overlapping constructs for which definitions are not categorically different.

1.2.1.3 Anxiety versus Depression.

Because of the high comorbidity of anxiety and depression (Burton et al., 2013), difficulties have arisen in differentiating between their respective associations with cognitive ageing (e.g., Gallacher et al., 2009). This comorbidity has been speculated to derive from GAD and depression sharing a genetic aetiology (Kendler, 1996; Mineka, Watson, & Clark, 1998; Zimmerman & Chelminski, 2003), suggesting a degree of overlap between the two conditions. Also, there is evidence linking anxiety and depression through inflammatory conditions as a possible predictor of both (Duivis, Vogelzangs, Kupper, de Jonge, & Penninx, 2013; Koyama et al., 2012). Grupe and Nitschke (2013), observed measurement of anxiety could be confusing the differentiation with depression because the originating (and still often used) state-trait anxiety inventory, developed by Spielberger and Gorsuch (1983) has been associated equally with anxiety and depression (Nitschke, Heller, Imig, McDonald, & Miller, 2001).

On the other hand, effective differentiation of measurement instruments for the two constructs (anxiety and depression) has been reported, demonstrating convergent and discriminant validity (Watson et al., 1995), and some studies have reported successful differentiation in the associations of each with cognitive ageing (Beaudreau & O'Hara, 2008). Progress has also been demonstrated in establishing their independent and interactive associations with cognitive ageing (Sinoff & Werner, 2003).

Considering the differences at a conceptual level, the constructs for anxiety and depression can be distinguished on their different perceptions of threat. For anxiety, future threat is uncertain; for depression, future threat is inevitable, and leads to hopelessness; and

finally, comorbid anxiety and depression, are characterised by perception of the threat as uncertain while experiencing helplessness about control over impending events (Abramson, Metalsky, & Alloy, 1989; Alloy, Kelly, Mineka, & Clements, 1990; Garber, Miller, & Abramson, 1980; Grupe & Nitschke, 2013; Watson et al., 1995). These distinctions warrant consideration in the design or redesign of the relevant measurement instruments. For example, The Goldberg anxiety and depression scale (Goldberg et al., 1988) is a frequently used scale which makes no such distinction; it focuses on past and current experiences. There is no reference to any future threat, except as implied by the question, "Have you been worrying a lot?", where "worrying" may be interpreted as worrying about some impending threat. Notwithstanding these interpretations of the items, confirmatory factor analysis on the Goldberg scale typically describes two oblique factors, one for anxiety and one for depression, and these factors conform with the delineation of the items for anxiety and depression (e.g., Christensen et al., 1999; Goldberg, Bridges, Duncan–Jones, & Grayson, 1987).

The overall status of the distinctions between anxiety and depression is clearer than for the other two sets of ambiguities (anxiety with fear, and with stress). Yet a degree of ambiguity remains with depression, at least regarding the application of the mentioned state-trait anxiety inventory.

In summary, the boundaries between anxiety and the three constructs of fear, stress, and depression, are ambiguous, to varying degrees. These ambiguities have mostly been ignored in studies of anxiety as a predictor of cognitive performance.

Next, a description of the prevalence of anxiety will provide dimension to its importance as a disorder.

1.2.2 Prevalence of Anxiety

Prevalence estimates have ranged widely for anxiety disorders, from 2.4% to 15% of the general population (Bryant, Jackson, & Ames, 2008). When sub-clinical anxiety was included, estimates were as high as 24% (Bryant et al., 2008). From the Australian national survey of mental health and wellbeing (NSMHWB), and using a modified version of the world mental health survey initiative version of the composite international diagnostic Interview (WMH-CIDI), McEvoy, Grove, and Slade (2011) reported the 12-month prevalence of any anxiety disorder was 11.8%. This included 1.9% for GAD. The any-anxiety-disorder (12-month) was greatest at 35 to 54 years of age (14.7%) reducing to 5.2% for 65 to 74-year-olds, and 2.3% for 75 to 85-year-olds. Women were more likely to exhibit anxiety than men. For example, at 65 to 74 years, 4.7% of men experienced any anxiety (over 12 months); while the female prevalence was 5.7%.

Estimates in epidemiological studies have been based variously on professional diagnoses, and a variety of symptom scales with cut-point scores to indicate a clinical level of the disorder (Murphy, 2002). Under these diverse arrangements, prevalence estimates have varied with methodological differences.

Additionally, the literature is inconsistent with respect to whether late-life anxiety differs from anxiety in younger people and, therefore, whether it should be measured differently (Bryant et al., 2008; Gould et al., 2014; Kogan, Edelstein, & McKee, 2000; Lenze & Butters, 2016; Osman et al., 2012; Pachana et al., 2007). Of these reports, particularly notable are Pachana et al. (2007) who developed the Geriatric Anxiety Inventory, and Miloyan and Pachana (2015) who advocated specialised measurement for aged individuals. Miloyan and Pachana demonstrated self-reported worry was of less utility than frequency of physical symptoms, for identifying GAD in later life. This contrasts with emphasis on worry by the *DSM-5*. Thus, the identification of anxiety symptoms that are more relevant to ageing

individuals may account for some of the inconsistencies in anxiety prevalence according to age.

Despite these questions about measurement, most estimates conclude anxiety is less common as age progresses after the forties. However, among older individuals experiencing MCI or early stages of dementia, the prevalence of anxiety is higher than in the general population of older adults (Beaudreau & O'Hara, 2008). For example, anxiety diagnosis was associated cross-sectionally with MCI with odds ratio (OR), 3.6 (95% CI 1.1–6.1) compared to those without MCI (Forsell et al., 2003). Similarly, anxiety (by informant questionnaire for neuropsychiatric inventory) was associated cross-sectionally with MCI with an OR 3.0 (95% CI 2.0–4.5) compared to those without MCI (Geda et al., 2008). More women than men experience anxiety into old age although, again, estimates vary widely (Bryant et al., 2008). Prevalence of anxiety symptoms in geriatric institutions is estimated to be as high as 44% and these organisations are often excluded from general population estimates (Bryant et al., 2008). However, it has also been observed within institutions, for residents with dementia, anxiety levels declined over time (Wetzels, Zuidema, Jansen, Verhey, & Koopmans, 2010). Although some of these reports do not provide prevalence estimates in percentage terms, they can be collectively interpreted as indicating that anxiety reduces in older age except for individuals experiencing MCI. Further, these same individuals experiencing increased anxiety while afflicted with MCI, subsequently experience a decline in anxiety as the impairment progresses to dementia.

Comorbidity with depression, adds another dimension of uncertainty to the prevalence statistics. Braam et al. (2014) found for community dwelling Europeans aged 65–104 years, that prevalence of three or more anxiety symptoms (regarded as a clinical level of anxiety) on the geriatric mental state examination scale, was 32% when there was no depression present, 67% when there was a sub-clinical level of depression, and 87% for those with a clinical level

of depressive symptoms. Depression has thus been recognised as an important confounding variable, pointing to the need to take careful account of comorbidity. These statistics have also indicated much higher prevalence of clinical levels of anxiety than found by other studies mentioned above (noteably, Bryant et al., 2008), underlining even further the wide range of prevalence estimates based on a diversity of measurement instruments.

Having described some of the ambiguities of the meaning of anxiety and then the uncertainties about its prevalence, the next step is to consider categories of anxiety. These categorisations will provide additional meaning to each of these terms and serve to introduce how the constructs are operationalised and how they relate within a causal model for cognitive decline.

1.2.3 Categories and Dimensions of Anxiety

Notwithstanding the ambiguities in the definition and uses of the term *anxiety*, the meaning has been developed and explored in another ways. Previously mentioned categories of anxiety were the disorders (listed at Section 1.2.1). But other opinions have been expressed about categories and dimensions of anxiety.

1.2.3.1 State and Trait Anxiety.

Spielberger (1972) introduced the categorical distinction between *state* and *trait* anxiety. State anxiety was defined as a transient emotional condition of apprehension and activation of the autonomic nervous system. Trait anxiety was regarded as a relatively stable condition, reflecting the individual's perception of a wide range of situations as unsafe (Spielberger, 1972), and has sometimes been referred to as a personality trait (e.g., Devier et al., 2009). Trait anxiety underlies state anxiety by providing the internal reference system by which incidental, external or internal stimuli are interpreted as threatening (Spielberger, 1972). A single measure of current or recent anxiety may reflect either a transient condition or an underlying condition. Without verification by follow-up observation (or retrospective report),

the applicable condition (state or trait) may remain unknown. There can be ambiguity. Therefore, it is worth noting that studies have demonstrated on average, state anxiety is not a stable condition and that trait anxiety is relatively stable (Hong, 1998; Usala & Hertzog, 1991). These results were not influenced by the age of the participants. Thus, these two forms of anxiety are sufficiently different not to accept one to stand for the other. Studies relying on state anxiety measures as an indication of long-term anxiety, may be in error.

The Spielberger state-trait anxiety inventory (Spielberger & Gorsuch, 1983) attempted to distinguish between the short-term and longer-term experiences of anxiety symptoms by providing symptom counts separately for state and trait conditions. Items exploring *state* anxiety addressed current feeling states with statements (to rate on a Likert scale) such as, "I am worried". Items exploring *trait* anxiety address feelings experienced day-to-day, with statements such as, "I worry too much over something that really doesn't matter". These distinctions between current and ongoing experiences are useful. However, as described above (Section 1.2.1.3), the Spielberger scale introduced ambiguities between anxiety and depression. There may be a more effective way to describe the types, levels, and duration of anxiety.

1.2.3.2 Clinical Staging: Duration, Frequency, and Intensity of Anxiety.

The terminology of state and trait anxiety provides only a preliminary attempt to distinguish between the experiences of short- and long-term symptoms. Anxiety can vary also in frequency of episodes, intensity, and persistence over a lifetime (Endler & Kocovski, 2001). For example, GAD is both intense and of moderate to long duration. There can also be periods of greater or lesser intensity. Panic episodes are perhaps more intense but of short duration; a pattern of episodes may continue indefinitely; and they can be more or less frequent. Variations in duration, frequency, intensity, and persistence occur also in sub-clinical anxiety. Such observations suggest anxiety should be regarded as a dimensional

construct rather than a categorical disorder, so that sub-clinical conditions or sub-clinical periods of anxiety are not overlooked (Miloyan, Byrne, & Pachana, 2014). To address some of the omissions in methodologies for reporting anxiety symptoms, a *clinical staging model* of anxiety disorders in the elderly was proposed and discussed by Oude Voshaar, Beekman, and Pachana (2015). This diagnostic model was comprised of four stages of intensity, frequency, and duration of anxiety. Stage 1 represented sub-clinical symptoms; stage 2, first episode of a clinical level syndrome; stage 3, ongoing impairment with chronic symptoms and frequent relapses; and stage 4, represented constant, severe disorder. The reasoning of Oude Voshaar et al. (2015) was based in part on earlier work by McGorry et al. (2014). The staging model would be similar to existing models for some non-mental-health conditions such as Parkinson's disease. This model, or a similar approach to distinguishing stages of anxiety, may be more useful than the simple labels of *state* and *trait*, particularly when attempting to identify long-term associations such as with cognitive performance. This observation will contribute to strategic planning for future research but also serve to underline how little is known about anxiety conditions in epidemiological studies, which use coarser instruments of measurement and evaluation.

Having considered categories of anxiety, this will be a convenient point to consider also the categories of cognitive change. These combined understandings will underpin the subsequent development of a theoretical model for possible causal connections between anxiety and cognitive change.

1.3 Categories of Cognitive Decline and Cognitive Impairment

Cognitive Decline is reducing cognitive ability, over time. It includes both normal, age-associated decline, and accelerated decline due to additional influences of physical or mental health and environmental stressors. Instruments, which test cognitive abilities, do so either at a global level such as Intelligence Quotient, or within cognitive domains such as memory,

attention, and processing speed. Examples of instruments designed to measure cognitive abilities within specific domains, are set out in Table 1.1. These variables will be used in the empirical parts of this thesis.

Table 1.1
Examples of Instruments for Testing Cognitive Ability within Specified Domains

Cognitive Domain	Test
Cognitive Processing Speed	Symbol Digit Modalities Test. Participant has 90 seconds to pair specific numbers with given geometric figures; (Smith, 1982).
Immediate & Delayed Recall	Californian Verbal Learning Test. Immediate & delayed recall 16 words to recall, same words provided in immediate & delayed recall test). Measures episodic memory; (Delis, Kramer, Kaplan, & Ober, 1987).
Verbal Intelligence	Spot the Word. 60 items, pairs of words with one real and one made up. The task is to select the real word (Baddeley, Emslie, & Nimmo-Smith, 1993)
Working Memory	Wechsler Memory Scale. Five items, each with two questions, repeating backwards a string of digits, ranging from 3 to 7 digits. Scores range from 0 to 10. (Wechsler, 1945).
Executive Function	Trail Making Test B. Speed and accuracy test for tracing a path through numbers or letters on a page. (Strauss, Sherman, & Spreen, 2006)

As mentioned, *cognitive impairment* refers either to MCI or to dementia. MCI is an early level of impairment experienced during prodromal dementia but the impairment is not sufficiently significant to interfere with daily activities (Langa & Levine, 2014). MCI can be either amnestic (usually associated with prodromal Alzheimer's disease), or non-amnestic. The non-amnestic type is more typically associated with the prodrome of dementias other than Alzheimer's disease and is diagnosed on the basis of cognitive measures in multiple domains. Of the dementia types, Alzheimer's disease is the most common, with a prevalence of about 70–75%, relative to all dementias (Ebly, Parhad, Hogan, & Fung, 1994; Ott et al., 1995). Other dementia types include: vascular dementia; dementia with Lewy bodies; and, Frontotemporal dementia.

1.4 Genetics and Neuropsychological Mechanisms

Having outlined the categories of both anxiety and cognitive decline & cognitive impairment, the next consideration is the set of neuropsychological mechanisms which provide a theory for associations between them; that is, between predictor (anxiety) and prognostic outcome (cognitive ageing). To begin, I will examine the aetiology of anxiety then link this to the neuropsychological mechanisms of association with decline in cognitive performance.

To serve an earlier context, some information on the neuropsychological mechanisms underlying anxiety, appear above at Sections 1.2.1.1 and 1.2.1.2.

1.4.1 Aetiology of Anxiety

A natural question to ask of anxiety is why some people have greater or lesser experiences of anxiety. In describing the aetiology for anxiety, Gross and Hen (2004) referred to an established diathesis model, meaning anxiety is the product of both genotype and environmental stressors. They noted estimates for the proportional effects were 30–40% of the variance between individuals due to genetic differences and 5% environmental, with the balance most likely due to interaction between the two. Prior to this large interaction, genetics appear to be the dominant influence.

A variant of the 5-HTT gene (serotonin transporter protein) influences anxiety by modulating fear circuits (Gross & Hen, 2004). Another gene identified as influencing anxiety is the catechol-o-methyltransferase (COMT) gene, otherwise known as the *warrior-worrier gene* (Montag et al., 2008; Stein, Newman, Savitz, & Ramesar, 2006). At codon 158 of the COMT gene, variants are valine (VAL) and methionine (MET) alleles. Under conditions of stress, individuals with VAL alleles exhibit warrior performance. MET alleles are related to worrier strategies, inefficient neurotransmission, and poorer performance generally except for better memory and attention (Stein et al., 2006). For further information, possible

mechanisms to explain the differences in performance between individuals with these two polymorphisms are discussed by Stein et al. (2006) and Montag et al. (2008).

1.4.2 Mechanisms Relating Anxiety to Cognitive Performance

1.4.2.1 Earlier theories.

To begin with the earlier concepts, I describe Eysenck's attentional control theory (Darvishzadeh, Aguilar-Vafaie, & Moradi, 2012; M. W. Eysenck, Derakshan, Santos, & Calvo, 2007), which is a development of the processing efficiency theory (M. W. Eysenck & Calvo, 1992). This theory was built in part upon the tripartite working-memory model of Baddeley (1986). Eysenck proposed that anxiety compromises goal-directed attentional mechanisms of the central executive by impairing the inhibition function, and thus allowing diversion of cognitive resources to distracting threats.

Similar to the attentional control theory, is the hypothesis that poor working memory might be revealed directly by the additional cognitive load represented by anxious experience. Owens, Stevenson, Hadwin, and Norgate (2014) found, in adolescents, an interaction between trait anxiety and low working memory. High anxiety was negatively associated with cognitive performance in those with low working memory.

A different example of the effects of anxiety is from Bierman, Comijs, Rijmen, Jonker, and Beekman (2008) who concluded anxiety predicts a short term improvement in cognition. They reported an inverse, U-shaped curve, describing the relationship between state anxiety and cognitive performance. In this relationship, cognitive performance was highest when a *moderate* level of state or incident anxiety existed and lowest when anxiety symptoms were either at low or high levels. This inverse, U-shaped-curve finding corroborated a previous and similar theory by Yerkes and Dodson (1908), which demonstrated an inverted U-shaped relationship between stress and performance. As noted above at Section 1.2.1, such

conclusions in the considerable literature on stress and performance, might in fact, have been based on measures of anxiety.

These observations might appear to explain mechanisms for the influence of anxiety on cognitive performance. However, neither the diversion of attention, nor anxiety overloading low cognitive resources, nor improved cognition as a short-term effect of moderate levels of anxiety, reveal anything about the prospect that anxiety could act as an agent over time (months, years, or decades) to contribute to the age related causes of ongoing decline in cognitive skill. Immediate and long-term effects are conceivably different. Thus, longer-term impact of anxiety opens the prospect for categorically different cognitive responses.

1.4.2.2 Alternative, contemporary approaches.

The central body of theory on mechanisms relating anxiety to cognitive ageing is outlined in the next Section (1.4.2.3) but others have been hypothesised. These alternative theories are: (1) Anxiety associated inflammatory responses, through increased cytokine levels, and subsequent memory decline and Alzheimer's disease (Duivis et al., 2013; Furtado & Katzman, 2015; Koyama et al., 2012; Reichenberg et al., 2001); (2) Anxiety related somatic responses such as blood pressure and heart rate, may lead to cardiovascular disease and vascular dementia (Tully, Cosh, & Baune, 2013); and, (3) Anxiety may be a symptom or marker of prodromal dementia, rather than a causal factor (Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, & Cauley, 2017).

These alternative hypotheses may emerge as providing stronger arguments and evidence at some point, or they may be identified as additional mechanisms.

1.4.2.3 The central, neuropsychological theory.

This central theory for how anxiety influences cognitive ageing, embraces a collection of mechanisms. These mechanisms are principally: allostatic load; glucocorticoid regulation;

neuroendocrine breakdown; atrophy of the HPA axis, hippocampus, and PFC; and feedback loops.

In their literature review, Mah et al. (2016) brought together the neurological explanations for mechanisms linking anxiety directly with progressive decline in cognition, and neurological mechanisms explaining anxiety itself, particularly how it arises and declines. The latter were necessary in explaining the former. These authors described firstly, how anxiety is regulated in tandem by top-down and bottom-up, neurological processes, or more formally the *dorsal and ventral neural systems*. Balance of the two processes is called *allostasis*, which represents stable emotional regulation. Imbalance is called *allostatic load*. Figure 1.4 illustrates these relationships. Figure 1.4 is an original illustration for this thesis, drawing mostly on the theory as presented by Mah et al. (2016). The dorsal neural systems (blue and green segments of Figure 1.4) are initiated by cognitive (voluntary) appraisal by the PFC for prospective or salient threat. This top-down threat appraisal is followed by inhibition by the PFC (when required) of the autonomic system. The autonomic system is linked to the amygdala and HPA which comprises part of the limbic, sub-cortical regions. The ventral neural system (involuntary) processing of threat arousal is shown in the yellow and green segments at Figure 1.4. The green segment is the amygdala, which is central to the entire process, and is integral to both the expression of fear and to the learning of cues that predict threat. Conscious and voluntary distraction or suppression of emotion, and threat re-appraisal are supported by the dorsal systems. Automatic, unconscious, involuntary responses and autonomic reactions are mediated mostly by interactions between the amygdala and PFC.

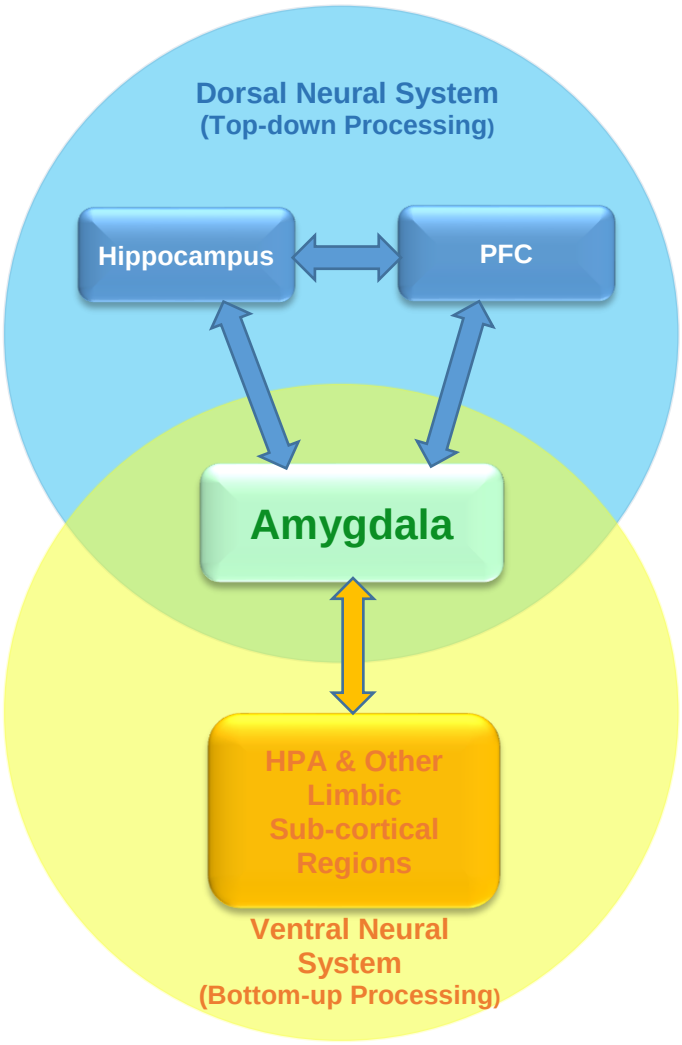


Figure 1.4. Dorsal/Ventral neural model of anxiety

PFC = Prefrontal cortex;
Other limbic sub-cortical regions are: hypothalamus, pituitary & adrenal glands (HPA); periadequeductal grey; insula; and ventral regions of: striatum, and the anterior cingulate cortex.

Anxiety disorders are characterised by an impaired ability to achieve allostasis and by amplified sensitivity to threat (Mah et al., 2016). Allostatic load has been demonstrated to result from a hyperactive response by the amygdala (bottom-up) and a hypoactive response by the prefrontal cortex and hippocampus (top-down; Mah et al., 2016). The allostatic load has also been identified with the physiological breakdown of the neuroendocrine systems, which, in turn, have been implicated in cognitive ageing (Mah et al., 2016; Seeman, McEwen, Rowe, & Singer, 2001).

The hyperactive amygdala function is enhanced by chronic stress, which also impairs neurogenesis of the hippocampus and causes structural deterioration of the prefrontal cortex (Mah et al., 2016). The consequences of this structural breakdown include emotional deregulation and generalisation of fear across stimuli. This impaired discrimination has been associated also with hippocampal atrophy (Mah et al., 2016). Memory functions of the hippocampus also regulate emotion by contextual extinction during fear conditioning while the amygdala responds more directly to threat. Without extinction of fear conditioning, the bottom-up process prevails to habituate the threat response. This reduced extinction control by the compromised hippocampus leads to reinstatement of previously conditioned fear, and is likely to be an element within the mechanism for the development of anxiety disorders (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Kim et al., 2013; Liston, McEwen, & Casey, 2009; Mah et al., 2016).

Acute stress increases cortisol levels (influenced by the HPA), leading to autonomic reactions which, among other things, focus attention on the perceived threat. Effects of cortisol can be counterbalanced by dehydroepiandrosterone and dehydroepiandrosterone sulphate (collectively referred to here as DHEAS; Boudarene et al., 2002; Hartaigh et al., 2012; Kamin & Kertes, 2017; van Niekerk, Huppert, & Herbert, 2001). These same studies together describe the complimentary roles of cortisol and DHEAS. Cortisol and DHEAS are both adrenal steroids, which have been implicated as antagonistic products of the HPA during responses of anxious individuals to stressful circumstances. DHEAS were shown to provide a calming effect offsetting the impact of cortisol. Individuals with higher anxiety scores, when placed in the same stressful circumstances as those with lower scores, demonstrated higher plasma cortisol levels. Individuals with lower trait anxiety scores exhibited higher DHEAS blood content. When cortisol levels are not balanced by DHEAS, chronic HPA activation predicts hippocampal atrophy, decreased brain derived neurotropic factor (BDNF), and

decreased hippocampal neurogenesis (referred to as the "neurotoxicity hypothesis" and formerly termed the "glucocorticoid cascade hypothesis"; Lupien, McEwen, Gunnar, & Heim, 2009). These deficits have been associated with anxiety disorders (Mah et al., 2016; Mantella et al., 2008).

1.4.3 Diathesis-Anxiety Heuristic of Cognitive Ageing

The Diathesis-Anxiety Heuristic of Cognitive Ageing (Figure 1.5) is an original model and illustration for this thesis. It represents an overview of mechanisms (from within the central neuropsychological theory) explaining predictive associations between anxiety and cognitive ageing. The model provides an overview of endogenous effects and natural environmental stressors. In this heuristic, vulnerability to anxiety is predicated upon both genetics and environmental stressors (Gross & Hen, 2004). Mechanisms linking anxiety to cognitive ageing, include: (1) Allostatic load (imbalance of dorsal and ventral neural mechanisms [details at Figure 1.4]); (2) Imbalance of cortisol and DHEAS; atrophy of the prefrontal cortex (PFC), hypothalamus, pituitary & adrenal glands (HPA) axis, and hippocampus (plus decreased BDNF, and decreased hippocampal neurogenesis); and, (3) Physiological breakdown of the neuroendocrine systems (Mah et al., 2016; van Niekerk et al., 2001). Collectively, these are the theoretical, intermediate mechanisms describing a causal flow from anxiety to cognitive ageing, and are linked by the blue arrows in Figure 1.5. There are also links back the other way, the amber arrows, representing a hypothetical causal flow in the direction from cognitive ageing to anxiety, and including some of the intermediate mechanisms.

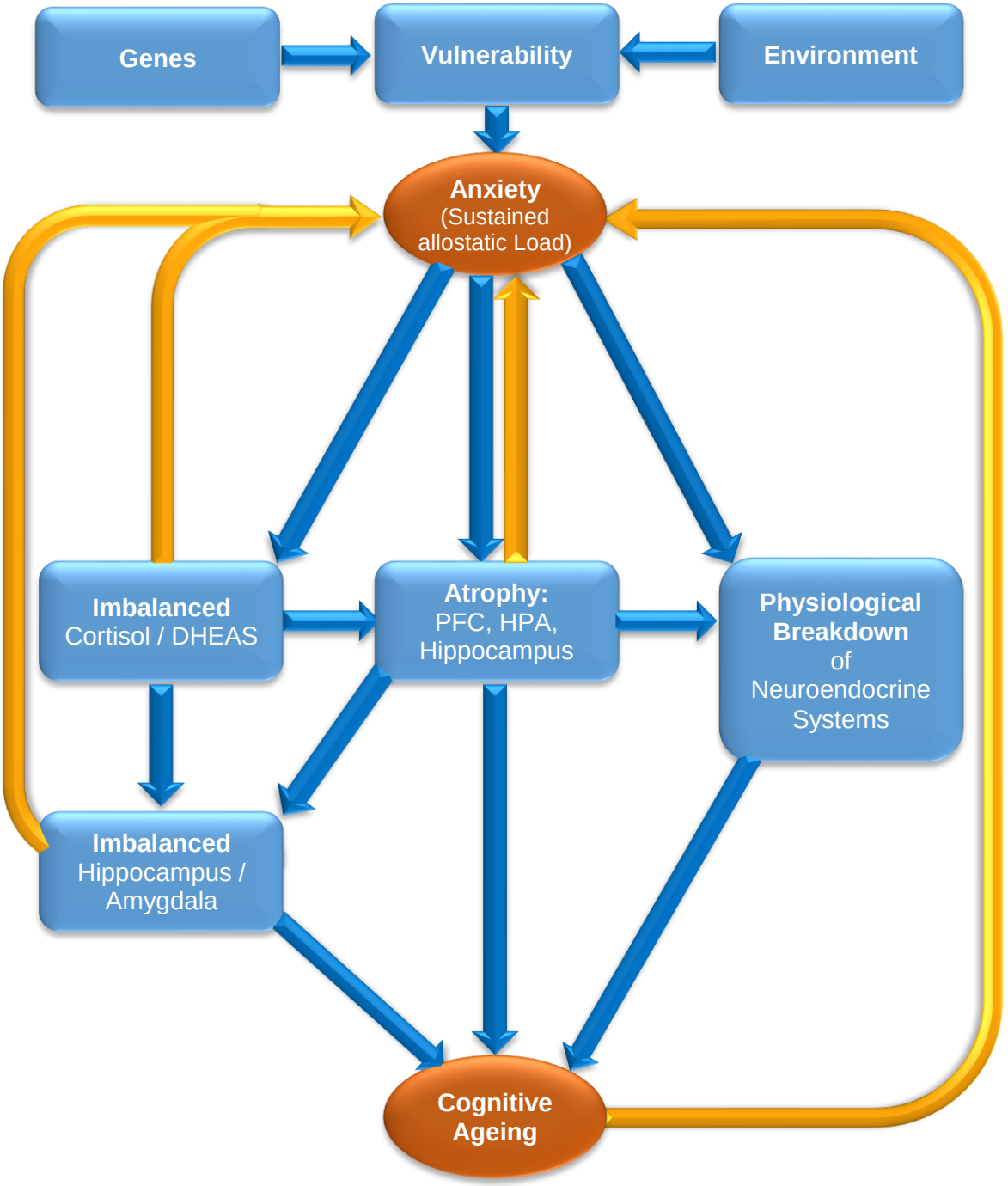


Figure 1.5. Diathesis-Anxiety Heuristic of Cognitive Ageing.

Blue arrows represent implicated causal links between anxiety and cognitive ageing via neurobiological mechanisms. **Amber** arrows represent reciprocal links back to anxiety; Allostatic load = imbalance between top-down and bottom-up processing of anxiety, as overviewed in Figure 1.4; DHEAS = dehydroepiandrosterone sulphate; PFC = prefrontal cortex; HPA = Hypothalamus, pituitary & adrenal glands; cognitive ageing = Cognitive decline plus cognitive impairment; Functions represented by the box headed, "Atrophy", include also, decreased brain-derived neurotropic factor, and decreased hippocampal neurogenesis.

The specific, reciprocal effect that cognitive ageing predicts anxiety (outer amber arrow on the right hand side of Figure 1.5), was one of the main findings of Petkus et al. (2017), in their study of "Temporal dynamics of cognitive performance and anxiety across older adulthood". This reciprocal effect may not be the result of neurological functions but simply a conscious fear arising from the recognition of failing, cognitive ability. And, there may then be consequential behavioural responses not presented within the heuristic. For example, self-medication to modify anxiety could take the form of excessive alcohol consumption, or reliance on other drugs to alter affect. Responses could also take the forms of denial, or avoidance of anxiety inducing experiences such as challenging social situations. Such cognitive-behavioural implications of the reciprocal effect represented by the right-most upward arrow of Figure 1.5 are many and potentially complex and their delineation is, therefore, not attempted within the heuristic. On the other hand, these same implications do need to be carefully considered when designing the statistical research into associations between predictors and outcomes, as they are in later chapters of this thesis.

The excess of cortisol over DHEAs (Figure 1.5, box labelled "Imbalanced cortisol/DHEAS") was associated not only with atrophy and decreased neurogenesis of the hippocampus, plus imbalance of the hippocampus/amygdala connection, but also increasing anxiety (Mah et al., 2016). The dominance of the amygdala in its partnership with the hippocampus was associated with increased anxiety (Mah et al., 2016; Phelps & LeDoux, 2005). Finally, atrophy of the PFC, HPA, and hippocampus, were implicated as influencing anxiety (Mah, Binns, & Steffens, 2015; Mah et al., 2016).

Researchers have generally not interpreted these bidirectional arrangements (blue and amber arrows combined) as *feedback loops*, using this term. Just two "feedback loops" have been mentioned in the literature in context of the psychology or neurology of anxiety. Firstly,

anxiety causes increased threat attention leading to increased perception of threat (termed, *interpretation bias*) which in turn increases the symptoms of anxiety (Grupe & Nitschke, 2013). This loop can escalate (an outcome of *positive feedback*) to catastrophic interpretations (M. W. Eysenck, 1997). Secondly, (as described at Section 1.2.1.2), Mah et al. (2016) noted the HPA axis and cortisol regulation provide *negative feedback* mechanism to inhibit the stress response. The first feedback loop illustrates growth in anxiety by interpretation bias but not through neurological mechanisms and does not form a part of Figure 1.5. The second feedback loop is neurological, resulting in inhibition of stress and, therefore, possibly reduction of anxiety. Such a mechanism would fit into the link from "Imbalanced Cortisol/DHEAS" to Anxiety (in Figure 1.5), and would provide a negative feedback component, helping to bring anxiety to rest. Beyond this second neurological feedback loop, the term appears not to have been used in a systematic way to characterise the return links between anxiety and cognitive ageing.

The term, *feedback loop*, has an important meaning. Engineered systems use feedback loops extensively, in the control of complex systems (Zeigler & Praehofer, 2000), and controlled feedback loops are common in biology (to achieve homeostasis*).* A positive feedback loop refers to a mechanism, which increases the intensity of the process. A negative feedback loop decreases the intensity (Zeigler & Praehofer, 2000). And in biology, a homeostatic feedback mechanism maintains an appropriate balance, such as for constant temperature of the body. The Dorsal/Ventral neural system for anxiety regulation may be such an example of a controlled feedback loop that maintains balance when in a normal or healthy state. By this logic, enduring anxiety might be described as a consequence of a sustained positive feedback loop.

The possibility has not been suggested in the literature that any of the feedback loops in Figure 1.5 might be responsible for stabilising or destabilising the overall effect on anxiety or

cognitive ageing. Further research is required to establish whether unstable feedback loops, as potential secondary effects of allostatic load, amplify the decline in cognitive function, and, if so, by what neuropsychological mechanisms. If clinical anxiety is the product of dysfunctional feedback control, then such biological mechanisms may be revealed in due course.

There is a further limitation of the heuristic in Figure 1.5. It is important to underline this is a hypothetical model. It suggests causal links based on theory which itself is drawn from a combination of human, observational, and some neurological studies, as well as animal studies.

1.4.4 Influence of Anxiolytics

Having deliberated upon the heuristic at Figure 1.5, anxiolytics are relevant to consider now as a potentially confounding influence on the associations between anxiety and cognitive ageing. Three main classes of anxiolytics are: benzodiazepines for rapid therapy, selective serotonin reuptake inhibitors (SSRI) for slow therapy involving plastic changes in the brain; and two specific serotonin–norepinephrine reuptake inhibitors (SNRI), venlafaxine, and buspirone (Gross & Hen, 2004). Benzodiazepines have been associated longitudinally with dementia, and the association is stronger with greater exposure to these drugs (Billioti de Gage et al., 2012; Billioti de Gage et al., 2014). However, because benzodiazepines are prescribed for both depression and anxiety (each associated with cognitive ageing), the independent causal effects of benzodiazepines remain speculative (Billioti de Gage et al., 2014). The SSRI appear not to present such risk. SNRI may also be relatively risk free but cognitive effects are not well reported (Rosenblat, Kakar, & McIntyre, 2016). Consumption of benzodiazepines, whether prescribed for depression or anxiety, threatens to confound apparent associations between anxiety and cognitive ageing. Therefore, where possible,

statistical analyses for predictors of cognitive ageing should be adjusted for benzodiazepine consumption.

1.5 Summary

The main conclusions above have been:

A. The constructs for *anxiety, fear, stress,* and *depression,* are not well defined and there are overlapping definitions between anxiety and each of the other three constructs.

B. Categories and dimensions, identified for the construct of anxiety, appear to be inadequate for contemporary research into the associations and mechanisms relating anxiety to cognitive performance.

C. The prevalence of anxiety has not been well measured. This may be a result of the diversity of measurement and diagnostic methodologies, and construct definitions for anxiety.

D. Neurologically, anxiety can be understood as a short- or long-term imbalance (allostatic load) of top-down (dorsal) and bottom-up (ventral) neural systems. See Figure 1.4. Anxiety disorders are characterised by an impaired ability to achieve balance between top-down and bottom-up systems (allostasis) and by amplified sensitivity to threat (Mah et al., 2016).

E. The *Diathesis-Anxiety Heuristic of Cognitive Ageing* at Figure 1.5 is based on genetic and environmental conditions as well as neuropsychological mechanisms for anxiety and its influence on cognitive performance. The heuristic represents a hypothetical causal model that includes feedback loops.

Additional to these observations, it was also noted investigation of longitudinal associations between anxiety and cognitive ageing, would need to:

a) Be confined, parsimoniously, to the direct association without reference to constructs or calculations of normal rates of cognitive decline, or normal incidence of cognitive impairment.

b) Observe the possibility of temporal confounding by prodromal cognitive impairment preceding chronic, clinical anxiety.

c) Control for other confounding variables, notably sex, age, education, depression, and consumption of benzodiazepines.

The primary research questions derived above were:

(1) Is anxiety a risk factor for the rate of age-associated, cognitive decline?

(2) Is anxiety a risk factor for age-associated, incident, cognitive impairment?

To be specific about the possible associations, these prognostic outcomes, cognitive decline and cognitive impairment, should be categorised respectively, into cognitive domains and impairment types.

1.6 Conclusion

Associations between anxiety and cognitive decline are problematic to investigate for a variety of reasons explored above, but notably: ambiguities in the construct and operationalisation of anxiety and anxiety measurement; and complex temporal relationships between anxiety and cognitive ageing. These observations, and others about neuropsychological mechanisms, will shape interpretation and evaluation of the literature (Chapter Two) and provide foundation for forming a methods strategy (Chapter Three) for statistical analysis of new data available for this PhD study.

CHAPTER TWO:

Systematic Review and Meta-Analysis

Abstract

Background: The research concepts and theoretical basis for this dissertation were discussed in Chapter One. The present Chapter evaluates the published evidence regarding associations between anxiety and cognitive ageing.

Methods: Thirty-seven articles, published between January 2002 and July 2017, were accepted into a systematic review. Of the 37 articles, seven, providing ten relevant studies, were suitable for meta-analysis of associations between anxiety and cognitive impairment. These studies comprised five for association between anxiety and progression from cognitively healthy to MCI, and five for association between anxiety and progression from cognitively healthy to dementia. Studies examining association of anxiety with rates of cognitive decline, were not suitable for meta-analysis because of excessive heterogeneity of methodologies and results. Results from this meta-analysis were compared with results from the most recent, published meta-analysis (with census date of January 2015), relating to similar associations.

Results: From the selected studies for an updated meta-analysis, the adjusted association between anxiety and progression from cognitively healthy to MCI, was relative risk (RR): 1.07 (95% confidence interval [CI]: 0.90–1.26), and for association with progression from cognitively healthy to dementia, was RR: 1.81 (95% CI: 1.22–2.70). These results were inconsistent with those of the most recently published meta-analysis, due to different methods and some differences in the studies examined.

Conclusions: The present meta-analysis results, adjusted for key confounds, were not significant for association of anxiety with incident MCI. Anxiety appears to add about 81% to the risk of progression from cognitively healthy to dementia, although this is open to interpretation about levels and duration of anxiety. The wider literature review, including analysis of the recently published meta-analysis, identified critical limitations of the research to date.

2.1 Introduction

The title of this dissertation nominates the research goal which is to discover whether anxiety is a risk factor for cognitive ageing. Chapter One expatiated upon implications of this goal, to derive two, primary, research questions (Section 1.1.3), which were:

(1) Is anxiety a risk factor for the rate of age-associated, cognitive decline?

(2) Is anxiety a risk factor for age-associated, incident, cognitive impairment?

In the literature review to follow, and meta-analysis, published evidence for these two research questions will be investigated and evaluated. In the process, conclusions will be formed about how well the literature supports examination of associations between anxiety and the important cognitive categories within cognitive decline and cognitive impairment, discussed in Chapter One (Section 1.3). In summary, the relevant categories for cognitive decline were cognitive domains such as memory and attention; and for cognitive impairment were amnestic and non-amnestic MCI, plus Alzheimer's disease, and other dementias.

The following structure is firstly to consider a general review of evidence provided by relevant articles published between 2002 and July 2017; and secondly to provide a meta-analysis of selected studies in this same time frame. This updated, meta-analysis will be compared with the most recent published meta-analysis (Gulpers et al., 2016) for which the census date was January 2015.

2.2 Methods

This Section is divided into two parts: methods for a general systematic review of the literature, and then methods for a meta-analysis of a subset of studies from the general review. This arrangement allows the general review to consider important studies even though they do not meet criteria for meta-analysis.

2.2.1 General Systematic Review

Longitudinal studies examining associations between anxiety and cognitive decline, MCI, or dementia, were identified through a search of PsycINFO and PubMed for peer-reviewed, human studies, English language articles, published between January 2002 and July 2017. Search terms were: anxiety AND (longitudinal OR predict OR prospective OR "risk factor") AND ("cognitive aging" OR "cognitive decline" OR "neurocognitive disorder" OR "cognitive impairment" OR dementia OR Alzheimer's). The results are summarised at Figure 2.1. Of 568 studies identified from this search, 37 were retained after excluding duplications, cross-sectional and animal studies, and investigations of carer and other irrelevant participant groups.

Data were extracted from these studies for: recruitment source; sample size; sample age-range, mean and standard deviation of ages; characteristics of specialised samples such as depressed participants; whether the measured anxiety was identified as state (or chronic) anxiety; whether anxiety was assessed by symptom count or diagnosis; baseline cognitive status; prognostic outcomes relevant to the present study (detailed below); whether association was confirmed or disconfirmed against each prognostic outcome; limitations against a key list (details below); and any unusual features of the study design.

The prognostic outcomes were: MCI (and whether amnestic or non-amnestic, or not specified), dementia (and whether Alzheimer's disease or other type, or not specified); and cognitive decline by domain. The specific cognitive domains measured, were extracted, and whether the results were significant.

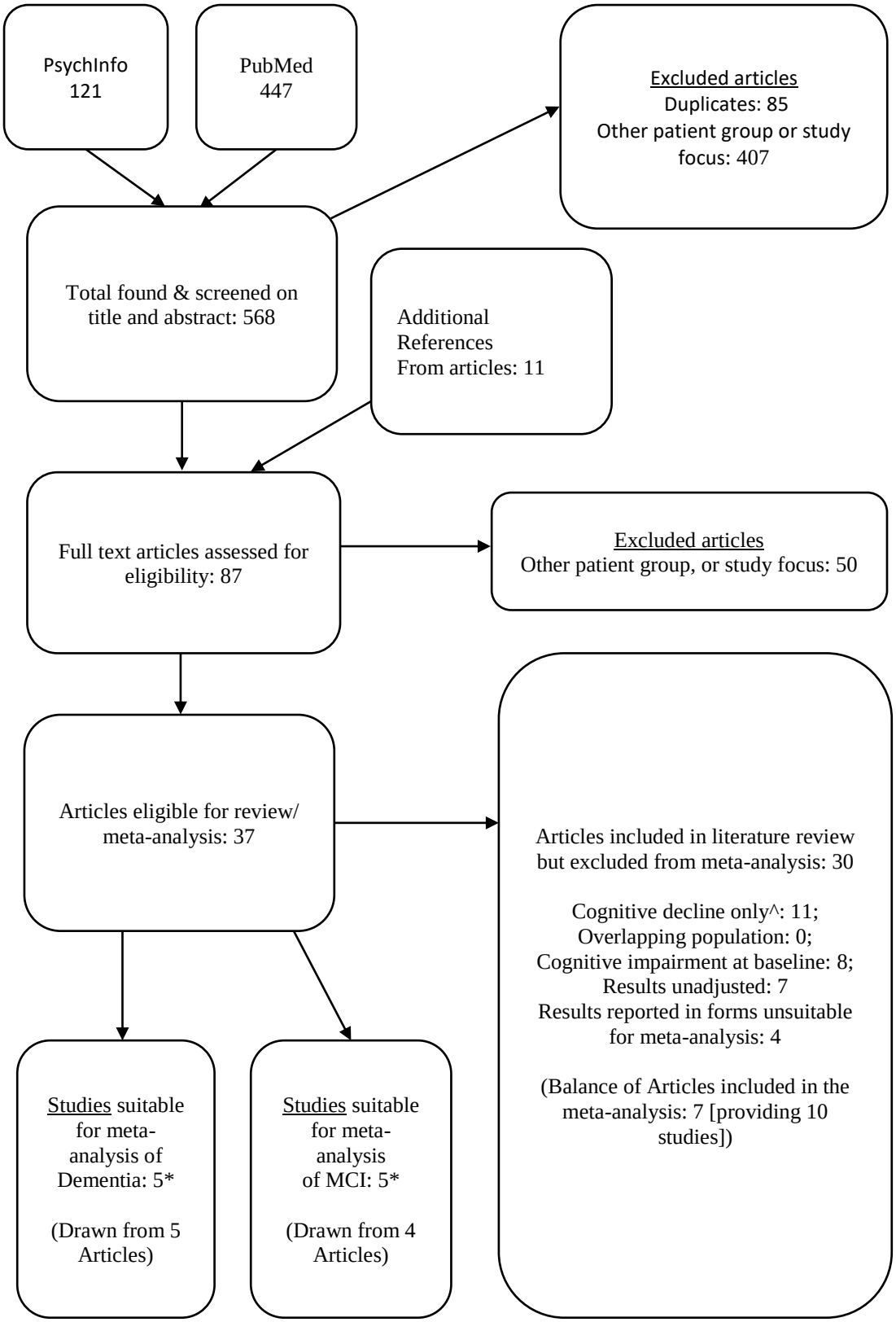


Figure 2.1 Study selection flow diagram.

*Note: Two articles each provided meta-analysis studies for both MCI and dementia. One other article for MCI (only) provided two (MCI) studies. In total, 7 articles provided 10 studies. This is better understood by inspecting Tables 2.5 and 2.6.

^Articles or studies based on cognitive decline were excluded because the heterogeneity of methods was not able to be accommodated in a meta-analysis.

The key limitations identified for each article, were:

A. Whether the statistical analysis was adjusted for at least the main confounds of sex, age, education, and depression;
B. Whether the sample was specialised (such as a clinical group of people all with apolipoprotein E [*APOE*] e4 genes) or clearly biased in any way such as including only one gender;
C. Whether only a proxy for anxiety was obtained (such as worry);
D. Whether associations were adjusted for consumption of benzodiazepines;
E. Whether or not the method for collecting data on anxiety either identified state anxiety directly or by inference from data collected over time; and
F. Whether there were temporal confounds such that the precedence of anxiety before cognitive ageing would be seriously compromised. An important example is that many studies investigated if anxiety was associated with progression from MCI to dementia. For individuals in such a sample, baseline memory difficulties (or challenges with activities of daily living) would have been likely to cause anxiety. Thus, anxiety could no longer be assumed to precede cognitive decline, and the temporal prerequisite for anxiety to predict cognitive performance, would be confounded.

2.2.2 Meta-Analysis

2.2.2.1 Background.

The only recent meta-analyses offering results applicable to the scope of the present study, was Gulpers et al. (2016). In the updated meta-analysis here, there will be points of

comparison with Gulpers et al. The first such comparison point is about methods. One of the analyses by Gulpers et al. considered anxiety as a predictor of progression from MCI to dementia. As noted in the previous paragraph at point F, progression studies with MCI at baseline, overlook critical, temporal, confounding effects. Therefore, such associations are of no greater value that cross-sectional correlations. So, this category of the meta-analyses will not be pursued, here. The principal remaining analyses by Gulpers et al. were for progressions from cognitively healthy to MCI and cognitively healthy to dementia. Each provided useful information for comparison the present review. The general systematic review described above (Section 2.2.1) considered categories of MCI and dementia as more specific prognostic outcome variables. However, the updated meta-analysis here, will consider only the broader outcome categories of MCI and dementia because the small number of studies accepted into the meta-analysis does not permit such categorisation into even smaller sub-analyses. Similarly, the small number of studies accepted by Gulpers et al. did not permit this further categorisation of meta-analysis.

Meta-analysis of association between anxiety and cognitive decline, for individual domains (such as attention or memory), were not possible for the data available. Gulpers et al. (2016) were unable to pool results within such categories of cognition, for any suitable combination of studies. For the updated meta-analyses reported below, the same conclusion applies. The heterogeneity of results and methods has not facilitated meta-analysis for cognitive decline.

Since the census date (January 2015) for the meta-analysis by Gulpers et al. (2016), relevant new studies have been published. These contribute to the meta-analyses to follow.

2.2.2.2 Study selection.

Of the 37 articles rated as suitable for the literature review, 30 were excluded from meta-analysis for one or more of the following reasons:

1) Results were only for cognitive decline (which has been excluded from this meta-analysis because the heterogeneity of methods was not able to be accommodated);
2) The baseline sample included participants with cognitive impairment;
3) The results were unadjusted for key confounds (particularly depression); or
4) Results were presented in the article in a form that was unsuitable for inclusion in the meta-analysis (e.g., important parameters were missing) and suitable information could not be obtained directly from the authors.

Among these exclusions were studies presenting results in the form of hazard ratios (HR) rather than odds ratios (OR) or relative risk (RR). Meta-analysis requires conversion of ratios to one type. Here, the type chosen was RR, while noting conversion from OR to RR is straight forward. However, conversion of HR to RR is not valid. Firstly, Stare and Maucort-Boulch (2016) explained many studies have used RR and HR interchangeably, but there appears to be no derivation to support this assumption of equivalence.

Explanation of differences between RR and HR are available from Kaewkungwal (2018) and Stare and Maucort-Boulch (2016). Put simply, RR is a function of the cumulative events over the observation period, while HR is a function of the rate of such events within the observation period. HR could be understood also as the slope of the survival curve. Stare and Maucort demonstrated approximate equivalence (between RR and HR) would apply only in the special, combined conditions of: identical time frames; small hazard ratios; and, small probabilities. Further, given that time is treated differently for each of RR and HR, inclusion of time-varying predictors and outcome variables in regression models, would seem, in my opinion, to add confusion to any proposition of equivalence.

If RR and HR are not equivalent, the next logical question is whether one can be transformed to the other. However, I searched the literature and found no published derivation of a transformation between RR and HR. The lead author of Stare and Maucort-Boulch

(2016), advised me that it was unlikely an equation would be available for conversion from HR to RR (Janez Stare, personal communication, May 29, 2019). The Australian National University Statistical Consulting Unit expressed the same view (Marijke Welvaert, personal communication, May 30, 2019).

Thus, there is no suitable transformation available, and I have chosen not to introduce an unknown degree of error by simply declaring equivalence, without theoretical foundation.

2.2.2.3 Data extraction.

In addition to data extracted for the wider literature review described above, data extracted for the meta-analysis was: The odds ratios, relative risks, *p* values, the covariates, baseline cognitive status, inclusion and exclusion criteria, impairment definition or cognitive scale, anxiety scale or diagnosis criteria, follow-up criteria and metrics, loss to follow-up description and analysis, and conclusion of the study.

2.2.2.4 Assessment of methodological quality.

The method for assessing quality of the studies was adapted from methods recommended by Altman (2001) and Hayden, Côté, and Bombardier (2006), and partially modelled on these methods as deployed by Gulpers et al. (2016). The resulting summary framework for quality assessment is described at Table 2.1. This framework included additional criteria for the key limitations identified above (Section 2.2.1). Each of the 25 items at Table 2.1 was rated between zero and one and aggregated for each study then converted to a mean with value lying between zero and one.

Table 2.1
Framework for Quality Assessment

Category	Item #	Item
Study sample	1	Selection explained
	2	Inclusion & exclusion criteria described
	3	Sample size

Category	Item #	Item
	4	Diagnostic criteria described
	5	Relevant characteristics described
	6	Representative of the general population
Length of study	7	Study length suitable, relative to temporal confounding from prodromal effects
Follow-up	8	Follow-up at regular intervals
	9	Number of follow-ups
	10	Follow-ups included re-measurement anxiety
	11	Reasons for loss to follow-up
	12	Analysis of loss to follow-up, examining differences in characteristics
Outcome	13	Defined
	14	Objective unbiased
	15	Measured for all participants, or a high proportion
Prognostic outcome	16	Defined
	17	Measured precisely
	18	Valid method
	19	Measured for all participants, or a high proportion
	20	All results described
Predictor variables	21	Defined
	22	Appropriate category for the study (e.g., “trait anxiety”)
Analysis	23	Appropriate analysis method
	24	Adjusted for key confounds
	25	Temporal issues explained and analysed appropriately

2.2.2.5 Statistical analysis.

The software for this meta-analysis was Stata, version 15.0 (StataCorp, College Station, Texas USA), using the metan command for meta-analysis with random effects (Borenstein, Hedges, & Rothstein, 2009; DerSimonian & Laird, 1986). This software was used to calculate pooled RR with 95% CI. Reported OR were converted to RR. Only fully adjusted results were included in the analysis, except where noted in the tables.

2.3 Results

2.3.1 General Systematic Review

Table 2.2 summarises the 37 studies in this review and reports key limitations which many of these studies had in common. Aggregates of the numbers of studies with limitations in each of the limitation categories (A to F; See Section 2.2.1), are indicated in the final row of Table 2.2. These aggregates of limitations ranged from 14% (of all 37studies), for Limitation C — "not anxiety" (meaning a proxy was measured in place of anxiety), to 86% for Limitation E — "not trait anxiety" (meaning *state* anxiety was measured, rather than *trait* anxiety, or more typically the category of anxiety was not specified or described). Sample sizes ranged from 44 to 16,351. The total sample size for the 37 studies was 56,098. This figure was corrected for duplicated recruitment sources among the studies. The total is a notional figure only, because of the methodological diversity of these studies, and is not relevant to meta-analysis. The duration of studies ranged from 1 to 28 years. The minimum ages of participants were typically at least 60 years but the study with the lowest minimum age included participants from 41 years. Results for these 37 studies are indicated in Tables 2.3 and 2.4, for cognitive decline and cognitive impairment, respectively. Of the 37 studies, 27 (73.0%) reported (at least one result) that anxiety predicted either cognitive decline or cognitive impairment.

2.3.1.1 Anxiety and cognitive decline.

Table 2.3 summarises 16 longitudinal studies which reported associations between anxiety (or a proxy such as worry) and cognitive decline. These are results within nominated cognitive domains. Study duration ranged from 1 to 28 years. Sample sizes ranged from 44 to 16,351 participants. The total sample for all studies was 26,349 (corrected for sample duplications). Of the 16 studies, seven measured anxiety by means of diagnosis and therefore accounted for anxiety as a binary variable. Thirteen measured anxiety by symptom count and included sub-clinical levels. Four studies used both methods. The table summarises results across cognitive domains, allowing studies to be compared vertically in the table. Fifteen studies examined association with memory and learning, with association found in eight. Similarly, nine studies examined association with attention. Of these, two found an association. Further such aggregated results are at the bottom of the table. The domain for which the greatest number of studies examined association with anxiety, was memory and learning. The domain for which the highest proportion of significant results were obtained, at 71%, was executive function, with five studies out of seven finding association. Most of the studies listed in Table 2.3 used a variety of analytical techniques. Among these, the common methods for testing longitudinal association were multilevel linear regression or logistic regression (e.g., S. J. Banks et al., 2014; Bierman et al., 2008; DeLuca et al., 2005; Petkus et al., 2016; Pietrzak et al., 2014; Pietrzak et al., 2012; Wilson, Begeny, Boyle, Schneider, & Bennett, 2011). Some studies (e.g., Bierman, Comijs, Jonker, Scheltens, & Beekman, 2009; de Bruijn et al., 2014; Sinoff & Werner, 2003) used linear regression where repeated measures of the outcome variable were not an issue (of independence of repeated measurements) by the simple expedient of using a single calculation of cognitive decline (between baseline and a single follow-up). Some used two or three groups or control group comparisons by defining groups with different levels of baseline anxiety (e.g., Brodaty et al.,

2012; Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, & Cauley, 2017; Pietrzak et al., 2015; Pietrzak et al., 2012; Sinoff & Werner, 2003).

Of the 16 studies, nine were notable because of their methods or findings. These were:

- Three studies, Sinoff and Werner (2003), Bunce, Batterham, Mackinnon, and Christensen (2012), and Petkus et al. (2017), all analysed the associations using structural equation modelling (SEM), among other methods. Sinoff and Werner found that anxiety predicted cognitive decline (as measured by MMSE), and was partially mediated by depression, with a resultant, standardised (beta) path coefficient of 0.203 ($p < .05$). Similarly, multiple linear regression demonstrated anxiety explained 20% of the variance in cognitive decline. The relative risk ratio for the presence of anxiety in relation to cognitive impairment was 3.96 (95% CI 1.69-9.08). Bunce et al. took SEM a step further to examine latent growth curves for effects of anxiety and depression, both over four time-points. No association was found for anxiety. Petkus et al. (2017) provided a comprehensive temporal analysis which is outlined at the last dot point below.
- Brodaty et al. (2012), grouped their sample into categories of baseline levels of anxiety. These authors measured anxiety as a component of a neuropsychiatric inventory (NPI) and categorised the results into presence or absence of a score. Cognitive, outcome variables were also dichotomised, for each cognitive domain, into impaired or not impaired, according to whether the level of decline exceeded 1.5 SD. The results for anxiety-associated-decline in executive function were: OR 3.04 (1.3–9.9). Results for decline in other cognitive domains were not significant. Results were adjusted for gender, age, and education but not for depression. The regressions for anxiety and depression as predictors were run in separate models.

- Pietrzak et al. (2012) conducted mediation analysis on associations between worry (as proxy for anxiety) and cognitive decline by domain. They found working memory fully mediated the association between worry symptom levels and visual learning, and memory performance. They also found worry symptoms remained stable over the two years of the study and that worry was independently associated with reduced processing speed. The authors speculated worry symptoms might be more accurately related to cognitive decline, than would be the broader measures of anxiety.
- Pietrzak et al. (2014) and Pietrzak et al. (2015), both used data from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study, finding higher anxiety levels moderated the predictive association of beta-amyloid status with rates of decline in cognitive performance. The earlier study (2014) found moderation effects for episodic and verbal memory but executive function was associated with anxiety independently of beta-amyloid. In the second study (2015), the moderation effect was found for global cognition, verbal memory, language, and executive function.
- Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, and Cauley (2017) categorised levels of baseline, state anxiety symptoms into three levels: none; mild; and moderate to severe. The sample was men only. Executive function was tested, using Trails B, at baseline and at a three-year follow-up. By comparison to the no-anxiety group, the odds of the mild anxiety group ending in the worst decile of change, were: OR 1.41 (CI 1.03–1.93). Comparing the moderate to severe anxiety group with the no-anxiety group, the odds of ending in the worst decile of change were: OR 1.35 (0.81–2.27). The categories of anxiety level used by Kassem et al. were determined according to symptom levels measured by the Goldberg Anxiety Scale (GAS) which is a nine-item questionnaire, reporting symptoms within the preceding four weeks. The anxiety categories deployed on this scale were: none = 0 symptoms; mild = 1 to 4 symptoms;

and moderate/severe = 5 to 9 symptoms. Goldberg et al. (1988) designed the scale so that a score of 5 represented a 50% probability of a clinical level of GAD. The important point to note from this analysis by Kassem et al. is that there was a stronger association with cognitive decline by individuals with mild anxiety (sub-clinical) than with stronger levels of anxiety. Various interpretations are available. The authors noted these findings violate dose-response expectations, suggesting anxiety was not a cause of cognitive decline and may be only a symptom or marker of prodromal dementia. The findings were declared independent of psychotropic medication but other anxiety treatments were not mentioned.

- Petkus et al. (2017) analysed their data using bivariate dual-change score models. This method provided structural equation modelling of the bidirectional influence of two variables (anxiety and cognitive performance) on each other as they each varied over time. Anxiety and cognitive performance of participants were measured up to eight times in the 26-year period of the study. The models were adjusted for gender, baseline depression, and baseline physical health. Results demonstrated anxiety predicted greater decline in cognitive processing speed and attention, and that decline in non-verbal memory, working memory, processing speed, attention, and visuospatial ability, each predicted an increase in anxiety during the following three years. These results served to provide a temporal analysis confirming a bidirectional, predictive association between anxiety and cognitive decline.

2.3.1.2 Anxiety and cognitive impairment.

Table 2.4 summarises 24 studies examining association between anxiety and progression to MCI or dementia. These studies included progression from cognitively healthy at baseline to MCI or dementia, and progression from MCI to dementia. Study duration ranged from 1 to 28 years, and sample size ranged from 132 to 13,568. Of the 24 studies, eight measured

anxiety by diagnosis, and 20 by symptom count; four used both methods. Eight studies examined MCI as the prognostic outcome. MCI results were broken down into results for amnestic MCI, non-amnestic MCI, and unspecified type of MCI. The unspecified category had the most results, six reporting an association and two indicating no association with prior anxiety. Twenty studies examined dementia as the prognostic outcome. For table 2.4, these 20 dementia studies were broken down into Alzheimer's disease, other than Alzheimer's disease, and all dementia types (or unspecified). Of these 20, 14 (70%) found an association in at least one dementia type. Eight of the 20 studies considered progression from MCI to dementia rather than from cognitively normal. Seven (50%) of the dementia studies examining Alzheimer's disease, found an association. One of two studies (50%) considering non-Alzheimer's disease dementia, found an association. Nine (82%) of studies looking at unspecified, or all dementia types, found an association.

Despite a variety of methods, many studies shared common approaches. Thirteen studies (of the 24) used Cox Proportional Hazards regressions to calculate the risk of cognitive impairment based on earlier anxiety (e.g., de Bruijn et al., 2014; Geda et al., 2014; Mah et al., 2015). The alternative, common method, deployed by 11 studies, was logistic regression based on MCI or dementia as a binary outcomes (e.g., Chan et al., 2011; Jessen et al., 2010; Ramakers et al., 2010). Control groups were used by two studies (Devier et al., 2009; Petkus et al., 2016), and case control was used by two (Burton et al., 2013; Zilkens, Bruce, Duke, Spilsbury, & Semmens, 2014).

Table 2.2.
Summary of 37 Studies Accepted for Review.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A Unadjusted	B Specialised sample	C Not Anxiety	D Benzodia-zepines	E Not Trait Anxiety	F Temporal Issues	
Wetherell, 2002	Swedish Adoption Twin Study of Aging.	9	704	(63.7, 8.6)	Cognitive performance by domain.	X		X	X			Results not adjusted for depression or benzodiazepines. Neuroticism used as proxy for *trait* anxiety.
Sinoff, 2003	HaGefen community-based geriatric assessment unit. Israel.	3.1	100	≥60 (75.9, 5.02)	Cognitive performance by MMSE.		X		X	X		Baseline sample excluded depression. Anxiety measured by researcher's own scale, no confirmation of trait anxiety Vs state. Anxiety measured at baseline only.
DeLuca, 2005	Depressed patients recruited from the Mental Health Intervention Research Center for the Study of Late-Life Mood Disorders. USA.	4	79	≥60	Cognitive performance by domain.	X	X					Clinical sample, all with major depressive disorder and some with cognitive impairment at baseline. Therefore, adjustment for depression was not possible. Mixed linear effects model and comparison of two groups with and without anxiety (by diagnosis). Effect of benzodiazepines was not significant.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A	B	C	D	E	F	
						Unadjusted	Specialised sample	Not Anxiety	Benzodia-zepines	Not Trait Anxiety	Temporal Issues	
Palmer, 2007	Kungsholmen Project. Sweden.	3.4	185	75–95 (84.0, 5.1)	Dementia				X	X	X	**Progression study**, MCI to dementia. Cases with and with MCI at baseline. Controls without. Anxiety + MCI doubled 3-year risk of Alzheimer's disease with each anxiety symptom. No association unless MCI present. This was partly a study on progression from MCI to dementia. These results (for progression) were excluded from the meta-analysis. Results for non-MCI participants were used for meta-analysis.
Teng, 2007	UCLA Memory Disorders Clinic. USA.	2	51	≥50	Dementia		X		X	X	X	Progression from MCI to dementia. Excluded from Meta-analysis.
Bierman, 2008	Longitudinal Aging Study Amsterdam.	9	2,351	≥62 (69.5, 8.6)	Cognitive performance by domain.					X		Only association found was for immediate effects. But, this was equivalent to a multi-level model without using lagged predictors. Anxiety measure was the Hospital Anxiety and Depression Scale. Does not identify trait/state anxiety.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A Unadjusted	B Specialised sample	C Not Anxiety	D Benzodia-zepines	E Not Trait Anxiety	F Temporal Issues	
Bierman, 2009	Patients with early stage Alzheimer's disease, recruited from several general hospitals and mental health care institutes. Netherlands.	1	44	(78.52, 6.1)	Cognitive performance by domain.		X			X	X	Small, clinical sample: **all with early Alzheimer's disease at baseline**. Changes in medication may have influenced results which showed a small improvement in memory associated with anxiety. Anxiety was measured during cognitive decline thus confounding temporal effects.
Cherbuin, 2009	PATH Through Life Study. Canberra, Australia.	4	2,082	60–64	MCI				X	X		MCI outcome: no association. Small cell size for conversion to MCI.
Devier, 2009	Memory Disorders Clinic, or the Center for Memory and Behavioral Disorders, Columbia University. USA.	1-9	148	41–85 (66.6, 9.7)	Alzheimer's disease		X		X		X	MCI patients. **Progression** to Alzheimer's disease. Cox survival analysis. No association for state anxiety but trait anxiety was protective for Alzheimer's disease. Unusual result.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A	B	C	D	E	F	
						Unadjusted	Specialised sample	Not Anxiety	Benzodia-zepines	Not Trait Anxiety	Temporal Issues	
Gallacher, 2009	Caerphilly Prospective Study. United Kingdom.	17	755	48–67	MCI and Dementia		X		X			Men only. Trait anxiety established. Baseline cognitive function was measured five years after baseline anxiety. Adjustment was for psychological distress (anxiety and depression) rather than for depression alone.
Jessen, 2010	German Study of Aging.	3	2,415	≥75	MCI and Dementia			X	X	X	X	Worry about subjective memory, as proxy for anxiety. Worry about memory at baseline suggests worry follows prodromal dementia. Thus, temporal issues, and exclusion from meta-analysis.
Ramakers, 2010	Maastricht Memory Clinic, Maastricht University hospital. Netherlands.	10	263	(66.9,)	MCI, Alzheimer's disease		X		X	X	X	**Progression** from MCI to dementia. Not adjusted for depression. Anxiety found to be protective against dementia. Trait anxiety not identified. Survival analysis–not strictly longitudinal.
Chan, 2011	Ethnic Chinese, randomly recruited. Hong Kong.	2	321	≥60	Alzheimer's disease, Cognitive performance by domain.		X		X	X	X	MCI at baseline. Measured **progression** to Alzheimer's disease. Anxiety identified as component of neuropsychiatric symptoms.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A	B	C	D	E	F	
						Unadjusted	Specialised sample	Not Anxiety	Benzodia-zepines	Not Trait Anxiety	Temporal Issues	
Gallagher, 2011	"Memory clinic". Location unstated, possibly in Ireland.	2.25	161	52–88 (73.7, 7.1)	Dementia	X	X		X		X	**Progression** from MCI to dementia. **Unadjusted for depression**, but result was non-significant so adjustment would not have been meaningful. Temporal issue with duration of study < period of memory decline before dementia.
Potvin, 2011	Study on Older Adults' Health. Canada.	1	1,942	65-96	MCI					X		Adjusted for psychotropic drug use.
Wilson, 2011	Memory and Aging Project, Rush University. USA.	3.4	785	(80.7, 7.4)	Alzheimer's disease, Cognitive performance by domain.	X			X	X	X	Not adjusted for depression. Anxiety identified as component of trait neuroticism scale. Cox proportional hazards for dementia outcomes and MLM for cognitive decline. Temporal issue with duration of study < period of memory decline before dementia. Recruited from retirement communities.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A Unadjusted	B Specialised sample	C Not Anxiety	D Benzodia-zepines	E Not Trait Anxiety	F Temporal Issues	
Brodaty, 2012	Sydney Memory and Ageing Study.	2	630	70–90	MCI, dementia, Cognitive performance by domain.	X			X	X	X	Progression: Cognitively healthy to MCI and dementia, plus MCI to dementia. Results for baseline anxiety predicting dementia were unavailable due to small cell size. Sample included participants with and without cognitive impairment at baseline. Temporal issue with duration of study < period of memory decline before dementia. Description a little unclear but implies models were not adjusted for depression.
Bunce, 2012	Canberra Longitudinal Study.	12	836	70–97 (76.55, 4.94)	Cognitive performance by domain.				X	X		
Pietrzak, 2012	Recruited from greater Melbourne.	2	263	50-86 (61.6, 7.0)	Cognitive performance by domain.	X	X	X	X	X		Unadjusted for education, gender, or anxiolytics. Mild worry as a proxy for anxiety.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A	B	C	D	E	F	
						Unadjusted	Specialised sample	Not Anxiety	Benzodia-zepines	Not Trait Anxiety	Temporal Issues	
Wadsworth, 2012	Alzheimer's disease Neuroimaging Initiative. USA.	2.7	229	(76.0,)	MCI, Alzheimer's disease.		X			X	X	**Progression** study to MCI and Alzheimer's disease. Anxiety as a single question from a neuropsychiatric brief inventory. Participants included normal controls plus MCI and mild Alzheimer's disease subjects.
Burton, 2013	Consultations in Primary Care Archive. United Kingdom.	2.7	400	≥65 (81.4, 6.6)	Dementia.				X	X	?	**Cognitively healthy** at baseline, progression to dementia. 400 cases; 1353 controls. Anxiety diagnosis reported in patients' records. Anxiety associated with dementia.
Okereke, 2013	Nurses' Health Study. USA	4.4	16,351	≥70 (74,)	Cognitive performance by domain.		X	X	X	X		Women only. Phobic anxiety assessed then 10 years later a 4.4 year longitudinal study of cognition comparing associations with high and low anxiety levels. No sig. result.
Rosenberg,2013	National Alzheimer's Coordinating Center database, USA	2.4	1,821	(75.3, 9.3)	Dementia	X	X		X	X	X	**Progression**: MCI to dementia. Adjustment excludes depression

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A	B	C	D	E	F	
						Unadjusted	Specialised sample	Not Anxiety	Benzodia-zepines	Not Trait Anxiety	Temporal Issues	
Somme, 2013	Recruited from the Memory Unit in Cruces Hospital. Spain.	M=3.5 ±2.9	132	(69.8, 8.7)	Dementia	X	X		X	X	X	Progression: MCI to dementia. Anxiety as subscale of neuropsychiatric symptoms.
Banks, 2014	Alzheimer's disease Cooperative Study Prevention Instrument Project. USA	4	417	75–93 (79.52, 3.62)	MCI, dementia, Cognitive performance by domain.			X	X	X	X	Progression to MCI or dementia. Cognitively healthy at baseline. Separate home and clinic groups. Anxiety estimated from four questions in a broader survey adapted from other scales. Results not provided in form suitable for meta-analysis. Temporal issue with duration of study < period of memory decline before dementia.
de Bruijn, 2014	Rotterdam Study. Netherlands	11.8	2,317	(68.6, 8.5)	MCI, dementia, Cognitive performance by domain.				X	X		Fully adjusted except for anxiolytics. Some specific results not published, e.g., cognitive decline for executive control. Adjusted for distress (including depression and anxiety). This is an additional confound.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A	B	C	D	E	F	
						Unadjusted	Specialised sample	Not Anxiety	Benzodia-zepines	Not Trait Anxiety	Temporal Issues	
Geda, 2014	Mayo Clinic Study of Aging. USA	5	1,587	79.3 (median)	MCI				X	X		NPI therefore not specifically trait anxiety. Adjusted for depression
Pietrzak, 2014	Australian Imaging, Biomarkers and Lifestyle. (AIBL)	3	178	(71.5, 7.4)	Cognitive performance by domain.		X		X	X	X	Baseline anxiety modified association of beta-amyloid with decline in verbal and episodic memory. Also anxiety linked to decline in exec function. Detailed results unpublished or unsuitable for meta-analysis.
Zilkins, 2014	Western Australian Data Linkage System, linked to state health-related data sets, and Hospital Morbidity Data Collection.	10, 20	13,568	65–85	Dementia.				X	X		Case control. Anxiety present at least 10 years before dementia diagnosis.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A	B	C	D	E	F	
						Unadjusted	Specialised sample	Not Anxiety	Benzodia-zepines	Not Trait Anxiety	Temporal Issues	
Mah, 2015	Alzheimer's disease Neuroimaging Initiative. USA	3	376	(75.0, 7.26)	Alzheimer's disease	X	X		X	X	X	**Progression** Study: MCI to Alzheimer's disease
Pankratz, 2015	Randomly selected, population-based sample of Olmsted County, MN. USA	4.8	1499	70–89	MCI				X	X		Fully adjusted except that medication were not specified.
Pietrzak, 2015	Australian Imaging, Biomarkers and Lifestyle. (AIBL)	4.5	333	60–89 (70.0, 6.8)	Cognitive performance by domain.		X		X	X	X	Pre-clinical Alzheimer's disease at baseline. Anxiety modified association of A β with cognitive decline.
Petkus, 2016	Swedish Adoption Twin Study of Aging.	28	1082	≥50 (67.61, 7.63)	Dementia, Cognitive performance by domain.					X	X	State-trait questionnaire, but state anxiety component chosen without explanation. Adjusted for benzodiazepine; these were not associated with dementia but this finding had serious limitations. Baseline status not necessarily cognitively healthy.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A	B	C	D	E	F	
						Unadjusted	Specialised sample	Not Anxiety	Benzodia-zepines	Not Trait Anxiety	Temporal Issues	
Kassem, 2017 A	Osteoporotic Fractures in Men Study. USA.	3.4	2380	≥65 (76.1, 5.3)	Cognitive performance by domain.		X			X		All men. Global cognition and executive function tested. Significant decline in executive function. Accounted for benzodiazepines.
Kassem, 2017 B	SOF data set. Community based listings. USA. Women	5	1425	>65 (82, 3.1)	MCI, dementia, Cognitive performance by domain.					X		All women. Anxiety predicted dementia but not MCI. Accounted for benzodiazepines.
Petkus, 2017	Swedish Adoption/Twin Study of Aging.	26	721	50–99	Cognitive performance by domain.				X	X		Bivariate, dual-change score (SEM) model for anxiety and cognitive performance. Comprehensive, temporal analysis.

Author, year (Chronological then alphabetical)	Recruitment source	Study dur-ation years	Sample Size	Partici-pant ages (Mean, SD)	Prognostic Outcomes	Summary of Key Limitations						Comments
						A Unadjusted	B Specialised sample	C Not Anxiety	D Benzodia-zepines	E Not Trait Anxiety	F Temporal Issues	
Pietrzak, 2017	Imaging, Biomarkers and Lifestyle. Australia (AIBL)	6	416	60-100	Cognitive performance by domain.		X		X	X	X	Testing cognitive decline in preclinical Alzheimer's disease. Association found between Aβ, cortisol and cognitive decline, were INDEPENDENT of anxiety. However, effects were also independent of *APOE*. It only means these biological links appear not to be involved with anxiety. [Or, perhaps that cortisol mediated effects of anxiety?]
TOTAL PARTICIPANTS	Duplications excluded from sample total		56,098			8	20	5	29	32	7	

Notes.

Key Limitations:
A = unadjusted for depression and possibly other important confounds
B = Specialised sample such as all one sex or all with MCI.
C = Not Anxiety but a proxy such as neuroticism or worry.
D = Benzodiazepines were not accounted for
E = Not Trait Anxiety. But either state anxiety or an unknown mixture of the two.
F = Temporal Issues: the temporal relationship between anxiety as predictor and cognitive ageing as outcome was distorted. For example, studies based on progression from MCI to dementia

introduced the prospect that baseline anxiety may have been
caused by cognitive decline such as memory loss

Disambiguation: Specific References for Tables 1.1 – 1.3
Kassem 2017 **A** = Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, and Cauley (2017) [all male sample]
Kassem 2017 **B** = Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, Ensrud, et al. (2017) [all female sample]

Table 2.3
Results for Cognitive Decline over 16 Studies

Author, Year (Chronological then alphabetical)	Anxiety determined by		Association Reported for Cognitive Decline, Summary of Cognitive Domains						Cognitive Domains Examined	Recruited from	Study Duration Years	N	Ages (M, SD)
	Diagnosis	Symptom Count	Memory, Learning	Attention	Processing Speed	Fluid Intelligence/ Global Cognition	Executive Function	Verbal , Visual, Spatial					
Wetherell, 2002		*	1	0	0	0	1	0	Visual memory, Working memory, Attention, Processing speed, Visual reasoning, Intelligence, Executive function, Visuospatial, Verbal reasoning.	Swedish Adoption/Twin Study of Aging.	9	704	(63.7, 8.6)
Sinoff, 2003	*					1			Global Cognition (MMSE).	HaGefen community based geriatric assessment unit. Israel	3.1	100	≥60 (75.9, 5.02)

Author, Year (Chronological then alphabetical)	Anxiety determined by		Association Reported for Cognitive Decline, Summary of Cognitive Domains						Cognitive Domains Examined	Recruited from	Study Duration Years	N	Ages (M, SD)
	Diagnosis	Symptom Count	Memory, Learning	Attention	Processing Speed	Fluid Intelligence/ Global Cognition	Executive Function	Verbal , Visual, Spatial					
DeLuca et al. (2005)	*		1	0		0			Memory, attention, Cognition (MMSE); Dementia rating scale on five scales: conceptualisation, construction, initiation/perseveration.	Depressed patients recruited from the Mental Health Intervention Research Center for the Study of Late-Life Mood Disorders. USA.	4	79	≥60
Bierman, 2008	*	*	0		0	1			Memory, Processing Speed, MMSE, Fluid Intelligence.	Longitudinal Aging Study Amsterdam.	9	2,351	≥62 (69.5, 8.6)

Author, Year (Chronological then alphabetical)	Anxiety de-termined by		Association Reported for Cognitive Decline, Summary of Cognitive Domains						Cognitive Domains Examined	Recruited from	Study Dur-ation Years	N	Ages (M, SD)
	Diagnosis	Symptom Count	Memory, Learning	Attention	Processing Speed	Fluid Intelligence/ Global Cognition	Executive Function	Verbal , Visual, Spatial					
Bierman, 2009	*	*	-1					0	Episodic memory as Verbal Learning & Recall, Cognition (MMSE),.	Patients with early stage Alzheimer's disease, from several general hospitals and mental health care institutes. Netherlands.	1	44	(78.52, 6.1)
Wilson, 2011		*	1		0	1		0	Working memory, Episodic memory, semantic memory, perceptual speed, visuospatial ability.	Rush Memory and Aging Project, Rush University. USA	3.4	785	(80.7, 7.4)

Author, Year (Chronological then alphabetical)	Anxiety de-termined by		Association Reported for Cognitive Decline, Summary of Cognitive Domains						Cognitive Domains Examined	Recruited from	Study Dur-ation Years	N	Ages (M, SD)
	Diagnosis	Symptom Count	Memory, Learning	Attention	Processing Speed	Fluid Intelligence/ Global Cognition	Executive Function	Verbal , Visual, Spatial					
Brodaty, 2012	*	*	0	0	0	0	1	0	Memory, Attention, Processing speed, Global intelligence, Language, Executive function, Visuospatial	Sydney Memory and Ageing Study.	2	630	70–90
Bunce, 2012		*	0			0		0	MMSE, memory, Processing speed, Executive function.	Canberra Longitudinal Study. Australia	12	836	70–97 (76.55, 4.94)
Pietrzak, 2012		*	0		1			0	Memory, Visual attention, Psychomotor speed.	Recruited from greater Melbourne. Australia	2	263	50–86 (61.6, 7.0)
Okereke, 2013	*		0	0		0	0	0	General cognition, Memory, Verbal fluency, language, Executive function, Attention.	Nurses' Health Study. USA	4.4	16,351	≥70 (74,)

Author, Year (Chronological then alphabetical)	Anxiety determined by		Association Reported for Cognitive Decline, Summary of Cognitive Domains						Cognitive Domains Examined	Recruited from	Study Duration Years	N	Ages (M, SD)
	Diagnosis	Symptom Count	Memory, Learning	Attention	Processing Speed	Fluid Intelligence/ Global Cognition	Executive Function	Verbal , Visual, Spatial					
De Bruijn, 2014	*	*	0	0	0		0	0	Memory, Working memory, Attention, processing speed, Executive function, Verbal fluency.	Rotterdam Study. Netherlands	5.8	1115	(75.5, 6.2)
Pietrzak, 2014		*	1	0			1		Memory, Attention, Language, Visuospatial, Executive function.	Australian Imaging, Biomarkers and Lifestyle. Australia (AIBL)	3	178	(71.5, 7.4)
Pietrzak, 2015		*	1	0		1	1	0	Verbal & Visual memory, Global cognition, Attention, Executive function, Language, Visuospatial ability.	Australian Imaging, Biomarkers and Lifestyle. Australia (AIBL)	4.5	333	60–89 (70.0, 6.8)

Author, Year (Chronological then alphabetical)	Anxiety determined by		Association Reported for Cognitive Decline, Summary of Cognitive Domains						Cognitive Domains Examined	Recruited from	Study Duration Years	N	Ages (M, SD)
	Diagnosis	Symptom Count	Memory, Learning	Attention	Processing Speed	Fluid Intelligence/ Global Cognition	Executive Function	Verbal , Visual, Spatial					
Petkus, 2016		*	1	1	1			1	Nonverbal memory processing and perceptual speed, working memory, attention, visuospatial abilities.	Swedish Adoption Twin Study of Aging.	28	1082	≥50 (67.61, 7.63)
Kassem 2017 A		*	0			0	1	0	Immediate and delayed memory, Global cognition with components for: orientation, concentration, language, praxis, &; Executive function.	Osteoporotic Fractures in Men Study, USA	3.4	2,380	≥65 (76.1, 5.3)
Petkus, 2017		*	0	1	1			0	Working memory, nonverbal memory, Processing speed, attention, visuospatial ability	Swedish Adoption/Twin Study of Aging.	26	721	50–99

Author, Year (Chronological then alphabetical)	Anxiety determined by		Association Reported for Cognitive Decline, Summary of Cognitive Domains						Cognitive Domains Examined	Recruited from	Study Duration Years	N	Ages (M, SD)
	Diagnosis	Symptom Count	Memory, Learning	Attention	Processing Speed	Fluid Intelligence/ Global Cognition	Executive Function	Verbal , Visual, Spatial					
TOTALS	7	13	7A 8NA	2A 7NA	3A 5NA	4A 6NA	5A 2NA	1A 11NA		Total sample size excludes duplications		26,349	

Notes.
Empty cell = association not reported.
0 = association examined but not found
1 = significant association found
-1 = evidence found for a reverse association;
anxiety at baseline was related to subsequently reduced frequency of MCI or dementia.
MCI = Mild Cognitive Impairment
M = Mean
SD = Standard Deviation
Under: "Anxiety determined by", an * indicates whether the method was diagnosis or symptom count by questionnaire.
Under: "Associations Found …", '0' indicates association was tested but not found significant; '1' indicates association with cognitive decline was significant; '-1' indicates a negative association (greater anxiety predicted less cognitive decline); a space indicates no association was tested.
Totals: These are counts, except for the total sample size which aggregates all unique samples sizes (duplicates are excluded).
Within the counts,
A = association found
NA = no association

Table 2.4
Results for 24 Studies Reporting Association between Anxiety and Cognitive Impairment

Author, year (Chronological then alphabetical)	Anxiety		Cognitive Impairment						Recruited from	Study duration years	Sample Size	Participant ages (M, SD)
			MCI			Dementia						
	Diagnosis	Symptom Count	Amnestic	Non-amnestic	All MCI, or Type not specified	Alzheimer's disease	Other Type	All types, or type not specified				
Palmer, 2007		*				0, 1^			Kungsholmen Project. Sweden	3.4	185	75-95 (84.0, 5.1)
Teng, 2007		*				0^			UCLA Memory Disorders Clinic. USA	2	51	≥50
Cherbuin, 2009		*			0				PATH Through Life Study. Australia	4	2,082	60-64
Devier, 2009		*				-1^			Memory Disorders Clinic, or the Center for Memory and Behavioral, Columbia University. USA	1-9	148	41-85 (66.6, 9.7)

Author, year (Chronological then alphabetical)	Anxiety		Cognitive Impairment						Recruited from	Study duration years	Sample Size	Participant ages (M, SD)
			MCI			Dementia						
	Diagnosis	Symptom Count	Amnestic	Non-amnestic	All MCI, or Type not specified	Alzheimer's disease	Other Type	All types, or type not specified				
Gallacher, 2009		*			1			1	Caerphilly Prospective Study. United Kingdom	17	755	48-67
Jessen, 2010		*				1	1	1	German Study of Aging. Germany	3	2,415	≥75
Ramakers, 2010		*				-1^, 0^ for 5 & 10 year follow-ups			Maastricht Memory Clinic, Maastricht University hospital. Netherlands	10	263	(66.9,)
Chan, 2011		*						0^	Ethnic Chinese, randomly recruited. Hong Kong	2	321	≥60

Author, year (Chronological then alphabetical)	Anxiety		Cognitive Impairment						Recruited from	Study duration years	Sample Size	Participant ages (M, SD)
			MCI			Dementia						
	Diagnosis	Symptom Count	Amnestic	Non-amnestic	All MCI, or Type not specified	Alzheimer's disease	Other Type	All types, or type not specified				
Gallagher, 2011		*				0^			Recruited from "a memory clinic". Location unstated, possibly in Ireland.	2.25	161	52-88 (73.7, 7.1)
Potvin, 2011	*	*	0, 0 Wo-men, Men	0, 1 Wo-men, Men	0, 1 Wo-men, Men				Study on Older Adults' Health. Canada	1	1,942	65-96
Wilson, 2011		*				1			Rush Memory and Aging Project, Rush University. USA	3.4	785	(80.7, 7.4)
Brodaty, 2012	*	*	1[#]	0				0	Sydney Memory and Ageing Study.	2	630	70-90
Wadsworth, 2012		*				0			Alzheimer's disease Neuroimaging Initiative. USA	2.7	229	(76.0,)

Author, year (Chronological then alphabetical)	Anxiety		Cognitive Impairment						Recruited from	Study duration years	Sample Size	Participant ages (M, SD)
			MCI			Dementia						
	Diagnosis	Symptom Count	Amnestic	Non-amnestic	All MCI, or Type not specified	Alzheimer's disease	Other Type	All types, or type not specified				
Burton, 2013	*							1	Consultations in Primary Care Archive. United Kingdom	3	400	≥65 (81.4, 6.6)
Rosenberg, 2013		*				1^		1^	National Alzheimer's Coordinating Center database. USA	2.4	1,821	(75.3, 9.3)
Somme, 2013		*						1	Memory Unit in Cruces Hospital. Spain	≤10	132	(69.8, 8.7)
Banks, 2014		*			1			1	Alzheimer's disease Cooperative Study Prevention Instrument Project. USA	4	644	75-93 (79.52, 3.62)

Author, year (Chronological then alphabetical)	Anxiety		Cognitive Impairment						Recruited from	Study duration years	Sample Size	Participant ages (M, SD)
			MCI			Dementia						
	Diagnosis	Symptom Count	Amnestic	Non-amnestic	All MCI, or Type not specified	Alzheimer's disease	Other Type	All types, or type not specified				
De Bruijn, 2014	*	*				0			Rotterdam Study. Netherlands	11.8	2,708	(68.6,)
Geda, 2014	*				1				Mayo Clinic Study of Aging. USA	5 (median)	1,587	79.3 (median)
Mah, 2015		*				1^			Alzheimer's disease Neuroimaging Initiative. USA	3	376	(75.0, 7.26)
Zilkens, 2014	*					0	0	1	Western Australian Data Linkage System, linked to state health-related data sets, and Hospital Morbidity Data Collection. Australia	10, 20	13,568	65-84

Author, year (Chronological then alphabetical)	Anxiety		Cognitive Impairment						Recruited from	Study duration years	Sample Size	Participant ages (M, SD)
			MCI			Dementia						
	Diagnosis	Symptom Count	Amnestic	Non-amnestic	All MCI, or Type not specified	Alzheimer's disease	Other Type	All types, or type not specified				
Pankratz, 2015		*			1				Randomly selected, population-based sample of Olmsted County, MN. USA	4.8	1,499	70-89
Petkus, 2016	*							1	Swedish Adoption Twin Study of Aging.	28	1,082	≥50 (67.61, 7.63)
Kassem, 2017 B	*	*			1			1	Recruited from community-based listings in USA.	5	1,425	>65 (82, 3.1)
TOTALS	8	20	1A 2NA	1A 2NA	6A 2NA	7A 7NA	1A 1NA	9A 2NA			34,980	

Notes.
Empty cell = association not reported.
0 = association examined but not found
1 = significant association found

-1 = evidence found for a reverse association;
anxiety at baseline was related to subsequently reduced frequency of MCI or dementia.
^ = progression from MCI to dementia
# = amnestic multi-domain MCI
MCI = Mild Cognitive Impairment
M = Mean
SD = Standard Deviation
Under: "Anxiety determined by", an * indicates whether the method was diagnosis or symptom count by questionnaire.

Under: "Associations Found …", '0' indicates association was tested but not found significant; '1' indicates association with cognitive decline was significant; '-1' indicates a negative association (greater anxiety predicted less cognitive decline); a space indicates no association was tested.
Totals: These are counts, except for the total sample size which aggregates all unique samples sizes (duplicates are excluded).
Within the counts,
A = association found
NA = no association

Four studies offered specific insights meriting further description:

- Gallacher et al. (2009) identified trait anxiety and tested whether baseline symptom levels predicted MCI or dementia, 17 years later. They used a piecewise linear logistic regression, testing the association between anxiety score and cognitive impairment. The knot point was at the 30th centile of anxiety level, representing the point at which risk of conversion to either MCI or dementia began, and continued in roughly a linearly increasing size of effect. Thus there was implied a non-effect for low levels of trait anxiety and a dose-response relationship above the knot point. Among the limitations were that the models were not adjusted for depression and the authors considered the study under-powered.
- Another study of interest is Potvin, Forget, Grenier, Préville, and Hudon (2011) which investigated gender differences, whether anxiety symptoms or disorders were associated differently, and whether there were different associations for amnestic and non-amnestic MCI. "Anxiety symptoms" included sub-clinical levels. They found significant anxiety *disorders* in men and anxiety *symptoms* for women were associated with MCI. They found also that the associations were stronger for men when linked to non-amnestic MCI, and stronger for women when linked amnestic MCI.
- Burton et al. (2013) found anxiety was independently more strongly predictive of dementia than depression and that comorbid anxiety and depression was not more strongly predictive of dementia than anxiety alone.
- Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, Ensrud, et al. (2017) found, in a sample of women only, that mild anxiety was predictive of dementia but for moderate to strong levels of anxiety the association was attenuated. This is similar to the findings of Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, and Cauley (2017)

as described above, that for men, the association of mild levels of anxiety with cognitive decline, were stronger than for moderate to severe anxiety.

Although these illustrations of results offer useful information, the overall literature, as summarised in Tables 2.2 to 2.4, suggest the results for longitudinal associations of anxiety with cognitive ageing are diverse and conflicting.

2.3.2 Meta-Analysis

Meta-analysis now needs to be explored, to draw on all suitable data including those delivering non-significant results, and thus to investigate the prospect of some coherence between studies. Studies included in this meta-analysis were divided into two categories according to their prognostic outcomes, either MCI or dementia. As noted previously, meta-analysis is not possible for the studies of association between anxiety and cognitive decline, because of the heterogeneity of methods and results.

Five studies accepted into the meta-analysis for MCI as outcome, are listed at Table 2.5 and five studies for dementia, at Table 2.6. Two articles (Gallacher et al., 2009; Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, Ensrud, et al., 2017) are represented in both tables because they contributed to both the MCI and dementia analyses. At Table 2.5, one article (Potvin et al., 2011) provided two studies, dividing the total sample into male and female. Overall, there was a total of seven articles for 10 meta-analysis studies.

2.3.2.1 Anxiety and Mild Cognitive Impairment.

Four papers provided five sets of results (Table 2.5) for pooled association between anxiety and MCI. Meta-analysis results were:

RR = 1.07 (95% CI: 0.90–1.26), z = 0.77, $p = 0.440$, $I^2 = 70.8\%$, where I^2 is a descriptive statistic, indicating the dispersion was due to real rather than spurious differences between studies (Borenstein et al., 2009). However, for association between anxiety and progression

from cognitively healthy to MCI, these pooled results were non-significant. The forest plot is displayed in Figure 2.2.

2.3.2.2 Anxiety and Dementia.

Five studies provided results (Table 2.6) for pooled association between anxiety and progression from cognitively healthy to dementia. Results were: RR = 1.81 (95% CI: 1.22–2.70), z = 2.94, $p = 0.003$, $I^2 = 78.6\%$. Thus, for association between anxiety and progression from cognitively healthy to dementia, the pooled results indicate approximately an 81% increase in risk of progression, for individuals with anxiety compared to those who do not have anxiety. This result was significant. The forest plot for these dementia studies is at Figure 2.3. The 78.6% dispersion is due to real differences between studies, such as age differences in the samples or methodological differences in the measurement of anxiety or cognitive performance (Borenstein et al., 2009). These differences are demonstrated at Table 2.7, by a diversity of sample and methods characteristics. Meta-regression was unavailable (for such a small sample of studies) to verify effects of important variables such as *sex*, *age*, *education*, *depression*, and major differences in methodology such as length of study.

Table 2.5

Results for Adjusted Association between Anxiety and Progression from Cognitively Healthy to Mild Cognitive Impairment

Author, Year	Setting	Recruited From	Sample Size	Participant ages (M, SD)	Anxiety Scale or Diagnosis	MCI Cognitive Scale or Diagnosis	Results for Adjusted Associations (95% CI)	Method-ological Quality	Meta-analysis weight %
Cherbuin, 2009	Community	PATH Through Life Study. Australia	2,082	60–64	Goldberg	Diagnosis	OR 0.98 (0.79–1.21) , p = 0.8	0.80	50.46
Gallacher, 2009	Community	Caerphilly Prospective Study. UK	755	48-67	STAI (trait)	Cambridge Cognitive Examination of the Elderly	OR 2.98 (1.20–7.38, p = 0.019	0.80	3.56
Potvin, 2011	Community	Study on Older Adults' Health. Canada	1,942	65-96	Diagnosis	MMSE<15 percentile	Female OR 0.42 (0.06–3.18), p=0.40; Male OR 6.27 (1.39–28.29), p = 0.02.	0.74	1.32 1.61
Kassem (B), 2017	Community	Community based listings in USA	1,425	>65 (82, 3.1)	Goldberg	Diagnosis	OR 1.07 (0.78–1.47) , p = 0.663	0.92	43.05

Table 2.6

Results for Adjusted Association between Anxiety and Progression from Cognitively Healthy to Dementia

Author, Year	Setting	Recruited From	Sample Size	Participant ages (M, SD)	Anxiety Scale or Diagnosis	Dementia: Cognitive Scale or Diagnosis	Results for Adjusted Associations (95% CI)	Methodological Quality	Meta-analysis weight %
Gallacher, 2009	Community	Caerphilly Prospective Study. UK	755	48-67	STAI (trait)	Diagnosis	OR 5.04 (1.24–20.45), $p = 0.024$	0.80	8.02
Burton, 2013	Community	Consultations in Primary Care Archive. UK	400	≥65 (81.4, 6.6)	Diagnosis	Diagnosis	OR 2.67 (2.01–3.54), $p = 0.001$	0.52	27.54
de Bruijn, 2014	Community	Rotterdam Study. Netherlands	2,708	(68.6,)	HADS	MMSE; Informant interview; plus neuropsychological testing.	RR 0.99 (0.33–2.97)	0.75	9.26
Zilkins, 2014	Community	Western Australian Data Linkage System, linked to state health-related data sets, and Hospital Morbidity Data Collection. Australia	13,568	65-84	Diagnosis	Diagnosis	OR 1.37 (1.14–1.65), $p = 0.001$	0.76	29.92
Kassem (B), 2017	Community	Recruited from community-based listings in USA.	1,425	>65 (82, 3.1)	Goldberg	Diagnosis	OR 1.56 (1.07–2.26), $p = 0.02$	0.92	25.26

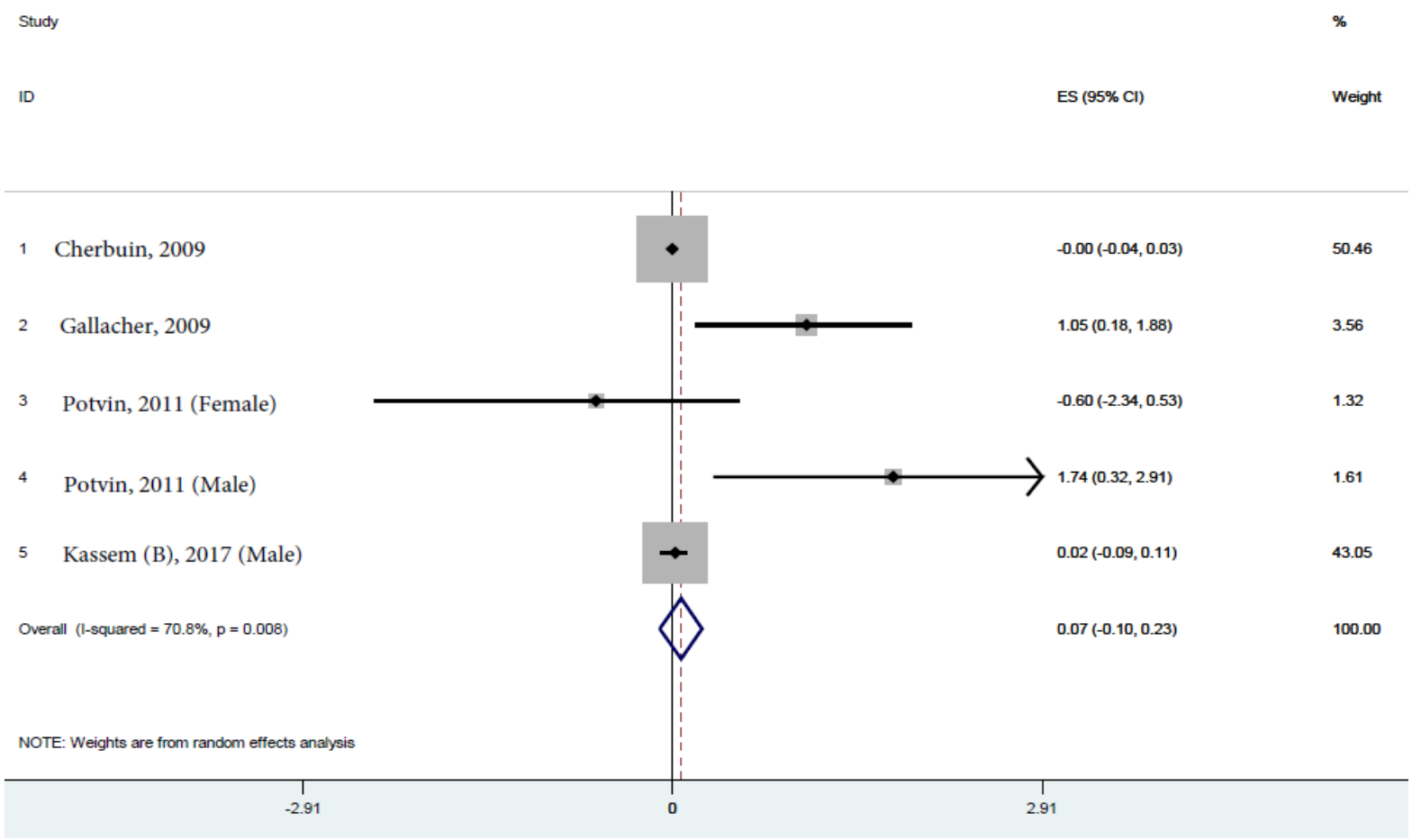


Figure 2.2. Forest plot for MCI studies at Table 2.5

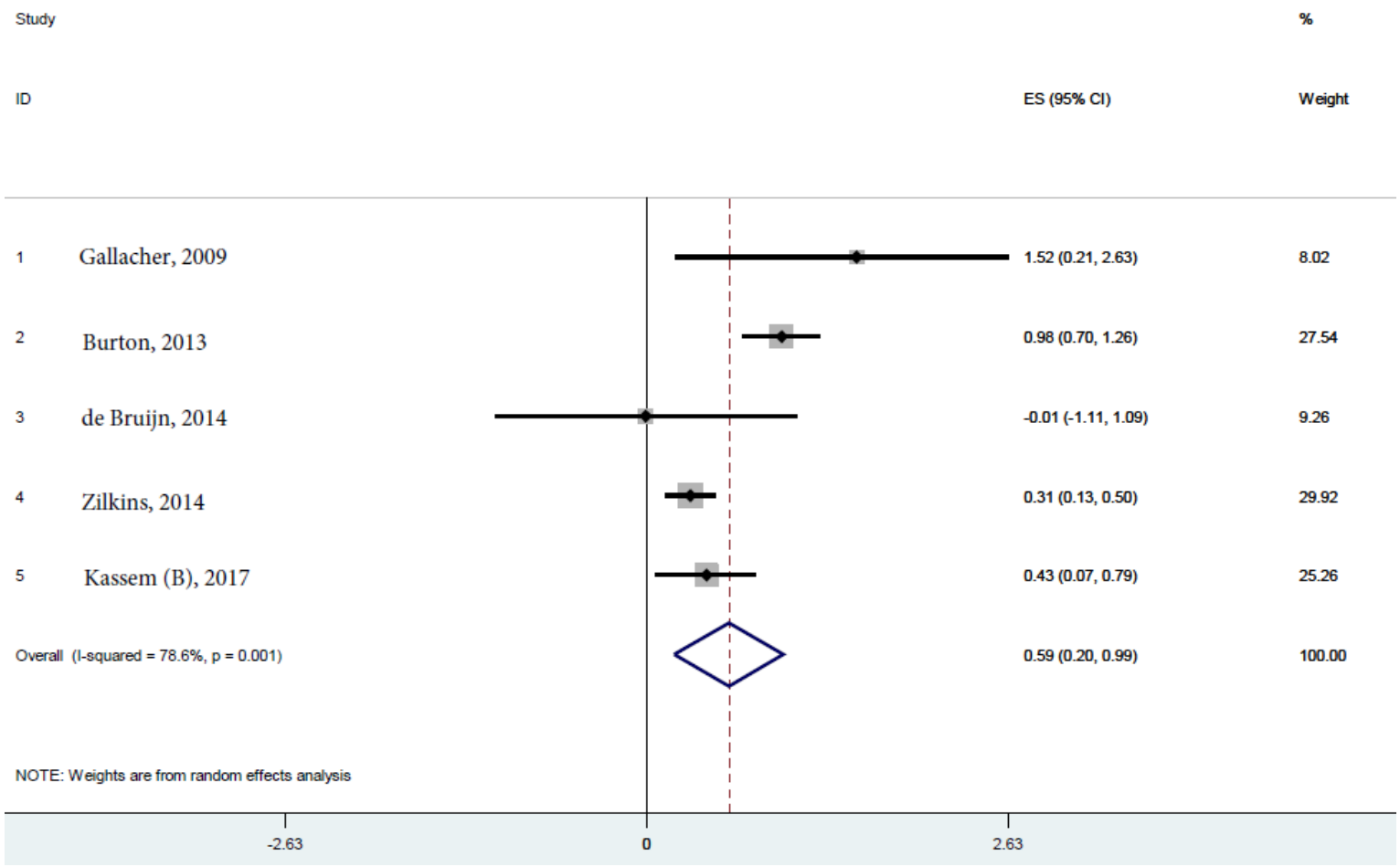


Figure 2.3. Forest Plot for Dementia Studies at Table 2.6

Table 2.7
Results for Adjusted Association between Anxiety and Progression from Cognitively Healthy to Dementia

Author, Year	Recruited From	Study duration Years	Sample Size	Participant ages (M, SD)	Anxiety Scale or Diagnosis	Results RR
Gallacher, 2009	Caerphilly Prospective Study. UK	17	755	**48-67**	**STAI (trait)**	4.50 (1.23–13.94)
Burton, 2013	Consultations in Primary Care Archive. UK	**2.7**	**400** (**men only**)	≥65 (81.4, 6.6)	Diagnosis	2.67 (2.01–3.53)
de Bruijn, 2014	Rotterdam Study. Netherlands (**Alzheimer's disease only**)	11.8	2,708	(68.6,)	**HADS**	**0.99 (0.33–2.97)**
Zilkins, 2014	Western Australian Data Linkage System, linked to state health-related data sets, and Hospital Morbidity Data Collection. Australia	20s	13,568	65-84	Diagnosis	1.37 (1.14–1.65)
Kassem (B), 2017	Recruited from community-based listings in USA.	5	1,425 (**women only**)	>65 (82, 3.1)	**Goldberg**	1.54 (1.07–2.20)

Notes: Bold items are distinctively different, compared to other studies in this table; "RR" is relative risk ratio; "STAI (trait)" is the trait scale of the Spielberger State-Trait Anxiety Inventory (Spielberger & Gorsuch, 1983); "HADS" refers to the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983).

2.3.3 Summary of Results

From the general systematic literature review:

i. A summary of studies accepted into the systematic review is provided at Table 1.1, with 37 articles, and an aggregate sample size of 56,098. Frequent limitations included: insufficient adjustment for confounding variables, and infrequent recognition of the importance of trait or chronic anxiety for determining associations with cognitive ageing.

ii. Key results from individual articles, were:

a) Working memory mediated the relationship between worry (as proxy for anxiety) and cognitive decline (Pietrzak et al., 2015);
b) Anxiety moderated the association between beta-amyloid status and cognitive decline (Pietrzak et al., 2014; Pietrzak et al., 2015);
c) Lower levels of anxiety symptoms were found to have a stronger relationship with cognitive ageing than higher levels, in: Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, and Cauley (2017); and, Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, Ensrud, et al. (2017).
d) Different associations between anxiety and MCI were found for various permutations of: anxious symptoms and anxiety disorders men and women, and amnestic and non-amnestic MCI (Potvin et al., 2011).

Meta-analysis results were obtained from five studies for longitudinal association between anxiety and progression from cognitively healthy to MCI, and five studies of progression from cognitively healthy to dementia. Results, were:

- For the association between anxiety and MCI, results were not significant at: RR = 1.07 (95% CI: 0.90–1.26), z = 0.77, $p = 0.440$, $I^2 = 70.8\%$;
- For association between anxiety and dementia, results were significant at: RR = 1.81 (95% CI: 1.22–2.70), z = 2.94, $p = 0.003$, $I^2 = 78.6\%$.

2.4 Discussion

From the general systematic literature review, the 37 articles accepted and summarised in Table 2.2, suggested an opportunity for a strong review of the evidence. However, the table also highlighted frequent, key limitations in these studies. This, and other extracted information, demonstrated a strong heterogeneity of methods and outcomes which collectively prevented any conclusion about whether anxiety predicts cognitive decline. The review by Gulpers et al. (2016) came to a similar conclusion.

Some of the individual results extracted for the general literature review remain of interest and signal possible analytical approaches in later chapters of this thesis. For example, Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, and Cauley (2017) and, Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, Ensrud, et al. (2017) reported their results may reflect that anxiety is not causal of cognitive ageing but only a marker or symptom of prodromal dementia. This was because the results indicated stronger effects size for lower levels of anxiety in association with cognitive decline and cognitive impairment. As noted previously, these results contradict dose-response expectations for a causal relationship. An alternative interpretation (to a non-causal hypothesis) is the prospect that higher levels of anxiety may have been more likely to receive treatment or might otherwise have been of shorter duration. The study did not measure anxiety levels at follow-up. For the analyses by this PhD study, these possibilities can be more fully examined.

Some of the other studies from the review, that will also inform the analyses, found: the association between beta-amyloid status and cognitive decline was moderated by anxiety; and different levels of association were found when anxiety was measured by diagnosis or by symptom count (Pietrzak et al., 2014; Pietrzak et al., 2015; Potvin et al., 2011).

The meta-analyses were limited by the number of suitable studies available. Had there been a greater number of studies, meta-regression may have been possible with adjustments for variables based on: diagnosis versus symptom count for anxiety; mean and standard deviation of the age the sample; education levels; gender; benzodiazepine consumption (where provided); sample size, and length of study. However, for successful meta-regression, Borenstein et al. (2009) recommended a ratio of 10 or more studies for each covariate. Thus, a useful meta-regression to determine the influence of these alternative methods, is unlikely to emerge in the near future.

The need for a greater number of suitable studies for meta-analysis is also reflected in the high dispersion score (I^2 = 78.6% for the dementia results), indicating there were substantive differences between the studies rather than just variation due to error (Borenstein et al., 2009). If these differences could be identified through meta-regression of a larger sample of studies, there may be highly useful information to be obtained about the nature of associations between anxiety and cognitive ageing. However, within the small sample, the high dispersion accompanied by the important differences between studies featured at Table 2.7, demonstrate this result may not be reliable.

Comparing the results for the present meta-analysis with those of Gulpers et al. (2016), provides further indication of variability between studies. Gulpers et al. found anxiety was associated with MCI (RR = 1.77 [1.38-2.26], p <0.001, with zero dispersion) and with dementia (RR = 1.57 [1.02–2.47], p = 0.040, with I^2 = 74.5% dispersion). After excluding studies without adjustment for depression, these results from Gulpers et al. changed, respectively, to RR = 1.92 (1.41–2.63), p =0.001, with zero dispersion, and RR = 1.68 (0.94–3.02), p = 0.081 with high dispersion (over just three studies) at I^2 = 87.5%. Therefore, when adjusted for depression, the association found by Gulpers et al. was stronger for MCI (but over just two studies) and attenuated for dementia. However, the updated meta-analysis (in this chapter) found the opposite i.e. significance for dementia but not MCI. Further, the dispersion was high in all results except for MCI from Gulpers et al., where it was zero (over two studies).

Part of the explanation for this contrast in results is that each meta-analysis was based on a partially different sample of studies. Differences were: (1) additional studies included here that were published since the census date (January, 2015) of Gulpers et al. (2016); (2) earlier studies, excluded from the current analysis because of non-adjustment for depression; (3) exclusion from the present analysis of studies reporting results in the form of HR (as invalid

for meta-analysis), but inclusion of such (HR) studies in the Gulper meta-analysis; and (4) inclusion in the current meta-analysis, of papers (published before the census date of Gulpers et al.) that were apparently not considered, or were excluded, by Gulpers et al.. These additional papers (in category 4) were: Cherbuin et al. (2009) and Gallacher et al. (2009) included in the present meta-analysis for associations with MCI, and Gallacher et al. (2009) included in the present meta-analysis for associations with dementia.

These results and qualifiers collectively place a degree of doubt on all of the meta-analyses presented here. With such contrasting results, it appears there is not a sufficiently consistent or reliable result upon which conclusions can be drawn with confidence, about the associations between anxiety and cognitive ageing.

Beyond the limitations specific to the meta-analyses, there have been generalised, systematic limitations observed throughout this review. These are most notably, that:

- as mentioned, anxiety is loosely defined;
- operationalisation of the measurement of anxiety has embraced widely contrasting methods including the fact that some studies (using self-report instruments) collected sub-clinical data while others (using diagnosis) did not;
- anxiety was rarely measured throughout the study period (rather than as a baseline observation only); and
- in 32 of 37 studies, there was no attempt to identify *trait* anxiety, or deploy alternative methods to establish that anxiety may have been chronic.

One further limitation in the literature is the common practice of observing cognitive change over just two observations. I have not featured this, for example in Table 2.2 (along with other limitations), because this limitation is of lesser consequence than others mentioned, and this two-measurement method applies to the majority of studies. The two-measurement method was criticised by Singer and Willett (2003), as confounding “true

change with measurement error". Temporal trends in data are not well identified with just two measurements.

Certain strengths of the present review are also evident. Chapter One presented a comprehensive overview of the relevant theory, especially regarding the neuropsychological mechanisms for anxiety and those linking anxiety to cognitive ageing. The review of the literature on evidence for the various associations also was comprehensive and provided an important update on the status of the research. Although the meta-analysis results are in doubt, this uncertainty justifies a new examination of methods and a fresh motivation for replication studies to provide sufficient data for more complete meta-analyses. Finally, having identified many of the weaknesses, redesign and future research can both be better informed by the oversights and limitations from the past.

For the balance of this dissertation, some of the observations above will inform methods for analysis of data. The data (described at Chapter Four) is secondary, and therefore predetermined. Consequently, alternative measurement methods for anxiety, and alternative construct definitions, and different measures of cognition, are limited or unavailable. Notwithstanding the limitations of secondary data, the next chapter will outline a strategy for analysis. Beyond this, future research in this field is recommended to consider the following:

1. Introduce randomised control trial (RCT), intervention studies to test effects of anxiety by treating the anxiety and observing consequential effects of the treatment upon both anxiety levels and cognitive change. Such trials will be described in the final chapter.
2. For both observational and RCT studies:
    a. Measure anxiety not just at baseline, but throughout the study, so that the effects of anxiety over time can be examined for effect on cognitive performance; and

b. Measure anxiety by a variety of methods for each individual in the sample, so that associations can be compared, between measurement methods. These methods need to include diagnosis, and symptom count for sub-clinical levels of anxiety. Ideally, one method should be the *Clinical Staging Model* of anxiety disorders in the elderly, proposed by Oude Voshaar et al. (2015). Another method should be the *Geriatric Anxiety Inventory*, developed by Pachana et al. (2007). These two methods would bring anxiety measurement method up-to-date with instruments which reflect the latest understandings of the nature of anxiety, and of old age experience of anxiety.

3. Ensure the study includes a comprehensive list of potentially confounding variables.
4. Ensure that the study length exceeds the time-frame of the prodromal effects that are likely to confound the associations being tested.
5. Research neuropsychological feedback mechanisms described at Figure 1.5, to determine their influence on the levels of anxiety and cognitive ageing.
6. Using fMRI or equivalent technology, investigate the neuropsychological differences between categories and levels of anxiety, stress, fear, and depression.

2.5 Conclusions

This systematic review and meta-analysis have critically evaluated the literature and analysed conflicting evidence on anxiety as a risk factor for cognitive ageing. Thirty-seven studies were identified which analysed associations between anxiety and cognitive data over time, and collectively drew on an aggregate sample of 56,098 individuals.

Associations between anxiety and cognitive decline are problematic to investigate for a variety of reasons explored above, but notably: ambiguities in the construct and operationalisation of anxiety and anxiety measurement; and, limited design of many studies regarding the temporal confounds deriving from the prodromal effects of dementia.

Notwithstanding the intrinsic challenges, study limitations, methodological differences, and differences in findings, tentative results have been found from an updated meta-analysis. Results for progression to MCI were not significant. However, from the updated meta-analysis, anxiety predicted progression from cognitively healthy status to dementia with approximately an 81% increased risk, compared to individuals without anxiety. There was theory (Chapter One) to suggest a plausible case that anxiety is a contributory cause of cognitive ageing. This *causal* hypothesis, together with the meta-analysis result for *prediction*, allow the tentative conclusion that anxiety is a *risk factor* for dementia.

These results include a wide variability of individual studies which has two implications. Firstly, there is likely to be an array of conditions (such as age profile within the sample, type of anxiety measurement, sub-categories of prognostic outcomes, and length of study), for which a meta-regression may yield important information about the conditional influences of anxiety on cognitive ageing. Secondly, to obtain a reliable and informative result from meta-analysis and meta-regression, the number of accepted studies will need to be larger, and methods more aligned.

CHAPTER THREE:

Methods: Strategic Overview

Abstract

To identify a strategic approach to methods for the present study, this chapter builds on the principles and theory presented in Chapter One, and published evidence for the relevant associations, described in Chapter Two. The present chapter structures the research, by: (1) Describing scope; (2) Extending the previous description of research questions; (3) Outlining analysis steps; and (4) Mapping the above into the thesis structure. These methods will be applied to new data to be introduced in Chapter Four.

3.1 Introduction

The primary research questions were described in Chapter One and were qualified by delineating cognitive decline and cognitive impairment into relevant categories. These are specified again below and then extended to describe specific investigations. There were also four major outcomes from Chapters One and Two, relevant to the present chapter. These were: (I) Description of the neuropsychological mechanisms posited to link anxiety and cognitive ageing; (II) Observation of a variety of analytical methods described in the literature; (III) Limitations of the research to date; and, (IV) Results of meta-analysis which updated the most recent published review.

The next step, following this chapter on methods, is to examine new data. The aim is to extend the investigation by analyses which are informed both by the theory described in Chapter One, and the limitations and findings of the previous research, described in Chapter Two. This current chapter maps how these later investigations will be organised.

3.2 Methods

3.2.1 Scope

The following observations from Chapters One and Two are foundational to scoping this investigation:

a) Parsimony:

   If anxiety can be demonstrated to predict change in the risk (over time) of cognitive ageing, then this is sufficient evidence of effect, without factoring in characteristics of the normality or abnormality of rates or incidence of cognitive decline or cognitive impairment (Section 1.1.2.1).

b) Temporal precedence of anxiety:

   If research is not to be confounded by the possibility of substantive memory

decline or other cognitive changes causing anxiety (the reverse effect discussed in Section 1.1.2.2) then baseline anxiety measurement must occur before cognitive impairment.

c) Chronic or persistent anxiety is expected to be more relevant than state or incident anxiety:

Anxiety can have positive or negative effects on cognitive performance and for different neuropsychological reasons. For example, incident or short term anxiety, has been associated with temporarily improved cognitive performance (Bierman et al., 2008). The Diathesis-Anxiety Heuristic of Cognitive Ageing (Figure 1.5) is instructive. From Figure 1.5, it is clear that the intermediate stages, in the effects of anxiety on cognitive ageing, include atrophy of the hippocampus (affecting memory) and other brain segments. The atrophy is progressive, and takes effect over years (Wang et al., 2003). If atrophy is partly a product of anxiety then incident anxiety is unlikely to contribute to such atrophy unless the incident anxiety is a symptom of chronic anxiety. Either way, it is the chronic anxiety which is, apparently, central to the mechanisms leading to cognitive ageing. Therefore, chronic anxiety must be identified. Notwithstanding the importance of recognizing the presence of long-term or chronic anxiety, most previous research has not done so. Even where the Spielberger State-Trait Anxiety Inventory (Spielberger, 2010) was used to measure anxiety, more often it was the state anxiety results used for analysis rather than the trait anxiety results (e.g., Petkus et al., 2016). Additionally, most analytic methods in past research, were geared only to baseline measurement of anxiety, placing further doubt on the valid identification of chronic anxiety. Ideally, therefore, the present study would examine data for chronic anxiety to determine if there is a result which supports the

theory. Examining also associations formed with incident anxiety would then be instructive as a direct comparison with the associations formed with chronic anxiety. The data available to this study (Chapter Four) are only measures of incident anxiety (symptoms during a four-week period), but measurements are available over four waves at four-yearly intervals. These can be used to form an estimate of the chronicity of the anxiety for each individual. Calculating both forms of association will also facilitate comparisons with the previous research.

d) Adjust models for confounding variables:

   i. Of the many potentially confounding variables, sex, age, education, and depression have most often been the central covariates for which adjustment has been made in the literature. Adjustment for depression may be problematic. Anxiety and depression are comorbid and often, highly correlated. Multicollinearity is not a problem in multiple regression analysis when the objective is prediction of the response variable (Williams, Grajales, & Kurkiewicz, 2013). However, for cross-level interactions formed in multi-level models, the correlation can lead to type two error, or false finding of non-significance for the main effects (Tabachnick & Fidell, 2007). Interestingly, of the 37 studies identified for the systematic review in Chapter One, precisely one article (Zilkens et al., 2014) mentioned a test for multicollinearity. Some studies chose not to adjust for depression (e.g., Brodaty et al., 2012), and others could not extract a meaningful adjustment (e.g., Beaudreau & O'Hara, 2008). For the analyses here, multicollinearity (among other assumptions) will be tested and evaluated. (Such tests will be reported only where assumptions are found to be violated.)

ii. Benzodiazepine consumption is an important additional confound for which adjustment should be made:

Benzodiazepines were discussed in Chapter One as associated with cognitive decline and cognitive impairment, and some prior studies have controlled their models for this class of anxiolytics. Similar adjustment in the present study will permit comparisons between models and with the previous study results.

iii. There are additional variables worth investigating for potential confounding effects by virtue of their possible influence on cognitive ageing, and their:

a) similarity or overlap in meaning with anxiety (e.g., stress); or

b) likely influence on anxiety levels (e.g. resilience).

In addition to *sex*, *age*, *education*, GDS (depression), and *benzodiazepines*, candidate variables meeting these criteria, and which are available for analysis in this present study (Chapter Four), are: *alcohol consumption*, *physical health status*, *behavioural inhibition*, *body mass index* (BMI), *neuroticism*, *life events* (as a measure of stressful environment), *mastery*, *positive & negative affect*, *physical activity*, *resilience*, *smoking*, *social support*, and *sleep problems*. Analysis of the data will be necessary to determine which of these variables are potentially confounding, by examining their associations with anxiety, and cognitive decline & cognitive impairment.

e) Alternative anxiety measures or proxies should be compared:

i. Anxiety is not well defined. Therefore, it would be useful to consider any available alternative measures for anxiety or proxies (e.g., neuroticism), in order to compare with the main measure of anxiety, for association effects,

and also to compare with results from studies using similar proxies. Some variables, such as neuroticism, might be considered as both proxies and confounds and will, therefore, need to be analysed for effect each way.

ii. Individual symptoms of anxiety, or symptom clusters, for worry and physical responses, should be tested separately as additional proxies for anxiety: Some studies have placed most emphasis on worry which is also an important symptom of GAD. On the other hand, aged anxiety may be more about the physical symptoms (Miloyan & Pachana, 2015). Therefore, isolating such items from the primary anxiety scale, and comparing their associations with those of the full measure of anxiety, may provide different and relevant results. For both worry and physical symptoms, the following chapter offers an exploratory factor analysis identifying relevant latent factors derived from the Goldberg Anxiety Scale (GAS), and representing worry and physical symptoms of anxiety. These latent factors will be examined for association and compared with simple items or item clusters.

f) Association models should be tested with both symptom counts for anxiety, and anxiety diagnosis:

Some studies in the systematic review used anxiety scales, including sub-clinical symptom counts (Table 2.3). Other studies used binary diagnosis of anxiety, which excludes sub-clinical information. A small number of studies used both methods (e.g., Bierman et al., 2008; de Bruijn et al., 2014). Some studies used a scale but then converted the symptom counts to the dichotomised equivalent of diagnoses (e.g., Brodaty et al., 2012). There are advantages and disadvantages of each method. For example, diagnosis may be more accurate than a self-report symptom count, but it excludes information, not only about subclinical levels of anxiety but

also about the clinical levels (symptom counts above the "clinical" threshold). As noted in the next chapter, the PATH data available to this PhD study do not include diagnosis of anxiety. However, to the extent available within the data, each optional measure of anxiety should be tested for association with cognitive decline and cognitive impairment.

g) Association models should be tested using anxiety symptom counts, trichotomised as: none, mild, and moderate to severe:

Contrary to expectations from dose-response precedent, Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, Ensrud, et al. (2017) found low level anxiety had a stronger association with subsequent cognitive decline and cognitive impairment than either no anxiety or moderate to higher levels of anxiety. There are possible explanations for this outcome that do not rely on abandoning the hypothesis that anxiety is a risk factor for cognitive ageing (Section 2.3.4.ii.c). This same categorisation of anxiety scores should be tested on the new data, for comparison with Kassem et al.

h) Psychological distress also needs to be identified for comparison purposes:

Psychological distress has been variously interpreted (e.g., Andrews & Slade, 2001; Australian Bureau of Statistics, 2008; M. H. Banks, 1983; Gallacher et al., 2009). *Psychological Distress* will be calculated here by two alternative methods, as either the multiplication or addition of the two Goldberg scales, anxiety and depression. These are two forms of interaction of the component variables. These methods will be discussed in the next chapter (Four) and compared with strategies in the literature. Distress may have more influence (on cognitive decline and cognitive impairment) than anxiety or depression considered separately. There has been some research on these effects (e.g., Gallacher et al., 2009; Simard, Hudon, &

van Reekum, 2009). Testing this interaction may, again, add perspective to the results for anxiety and depression alone.

For the purpose of scoping, the items above provide both limitations and additional lines of inquiry. The more detailed delineation of research questions to follow, will be understood as referring to the scope described above.

3.2.2 Research Questions

3.2.2.1 Primary, research questions.

The two, primary research questions described in Chapter One, were:

(3) Is anxiety a risk factor for the rate of age-associated, cognitive decline?

(4) Is anxiety a risk factor for age-associated, incident, cognitive impairment?

Chapter One further described cognitive decline (Section 1.3) as referring to decline in cognitive performance within cognitive domains such as memory, attention, and cognitive processing speed. Similarly, Chapter One categorised cognitive impairment as comprising MCI and dementia, where MCI was further categorised as amnestic and non-amnestic, and where dementia was further categorised as Alzheimer's disease (AD), and all other dementias. References below to the primary research questions will be intended to infer also permutations with appropriate categories of these prognostic outcomes, but limited by the availability of data.

3.2.2.2 Secondary, research questions.

Subordinate to the primary, research questions above, the following, secondary, research questions will be investigated in later chapters and will address the scoping points above (Section 3.2.1).

A. *Is anxiety a baseline predictor of cognitive ageing?*

Firstly, and more fundamentally, is baseline anxiety *correlated* with subsequent cognitive decline or cognitive impairment? If there is correlation between baseline

anxiety and follow-up cognitive data, then various regression models (linear and logistic regression, and multilevel modelling) would be tested to ascertain if the association is sustained or attenuated when adjusted for key confounders such as depression. If such associations are demonstrated, then mediation analysis would be justified to determine effects of the principal confounding variables. Additionally, moderation by such confounding covariates can be investigated to determine if interactions have greater effect size than their component variables. These questions will be applied broadly, where appropriate, to the various measures available for anxiety, and proxies, and for derivatives of the GAS scale. Such analyses will not be considered for models that do not demonstrate significant associations.

B. *As a time-varying variable, does GAS, predict cognitive ageing?*

This simultaneously restricts the scope of question A to the single anxiety measure, GAS, and extends the analysis to include repeated measures. As will be demonstrated in Chapters Four and Five, there is no alternative measure for anxiety, available within the PATH data, likely to be more effective than GAS to identify associations with cognitive ageing. The numerous analyses possible require limitation of the permutations stemming from the many alternative measures for anxiety. Nonetheless, for the GAS predictor, where analyses of repeated measures justify further investigation, analyses of mediation and moderation will be considered, as suggested by question A above.

C. *Are there subsets of participants for whom associations are different?*

Comparisons will be performed between groups with and without persistently high or chronic anxiety, defined by persistence of anxiety at two symptom levels, for two or more waves of data. (Symptom levels for *persistently high* and *chronic*

anxiety will be defined, on the GAS scale, as five and seven symptoms respectively.) Secondly, subsets will be identified by confounding variables (Section 3.2.1.d.iii).

3.2.3 Mapping the Above into the Thesis Structure

Table 3.1 summarises the chapter structure of the remainder of this thesis and delineates how the research questions and methods will be incorporated into that structure.

Table 3.1.
Structure of Remaining Chapters and Summary of Planned Analyses

Chapter	Chapter Title / Research Question	Description
Four	Description of the data	Description of the PATH dataset and its derivation; demographic characteristics of the sample; distributions of key variables; variation of key variables over time; cross-sectional correlations; and analysis of missingness; and, correlations between baseline anxiety and subsequent cognitive decline & cognitive impairment. Possible confounding variables will be investigated by examination of correlations [Section 3.2.1.d.iii].
Five	Is Anxiety a baseline predictor of cognitive ageing? / Secondary Research Question A	Multivariate, linear, and logistic regression for cognitive decline and cognitive impairment categories, applied to *baseline* predictors (GAS, items, derivatives, and proxies), and generalized estimating equations applied to further test any associations found from the baseline modelling, by examining the effects of repeated measures for the relevant anxiety variables, but not repeated measures for the outcome variables.
Six	As a time-varying variable, does GAS predict cognitive ageing? / Secondary Research Question B	Extending the analysis of Chapter Five by applying repeated measures for both anxiety and outcome variables, but scoping this to the single anxiety variable, GAS. This will include *time-lagged*, *cognitive change*, and *autoregressive* models.
Seven	Stratifications of multilevel models / Secondary Research Question C	Subsets of participants will be analysed and compared, to identify any differences in association between GAS and cognitive change. Subsets will include cases with and without chronic anxiety, persistently high anxiety, and categories defined by covariates previously identified as confounding variables.
Eight	Overview of Statistical analyses, and revised meta-analysis results	Summary and interpretation of statistical results from Chapters Four to Seven, plus revision of the meta-analysis from Chapter Two with results from the PATH analyses.
Nine	Conclusions, Implications, and Recommendations	Conclusions, strengths & limitations, implications, future research, and recommendations.

3.3 Conclusion

There is no known, previous research which comprehensively applies all of these planned, analytical methods, to the one dataset. Results and interpretations from this present study should, therefore, be of value not only in comprehending associations within the PATH data, in this dissertation, but also in developing methods for future research.

CHAPTER FOUR:

The Data

Abstract

Background: Previous studies, drawing on a diversity of data sources, have produced conflicting results about associations between anxiety and cognitive ageing.

Methods: New data for this PhD research are drawn from the Personality and Total Health Through Life (PATH) study which is hosted by the Australian National University (ANU). Ethics for the present study were provided by the ethics approval for PATH. The data are described here, and basic analyses are reported, mostly based on correlations and distributions. Proxies for anxiety, and derivatives of the Goldberg Anxiety Scale (GAS) were examined as alternative measures for the full GAS scale. Baseline values for these variables were examined for correlation with cognitive change. Also considered were potential confounders, moderators, or mediators of the association between anxiety and cognitive change. Participants unavailable for follow-up were also evaluated for any distortion in the key associations.

Results: The main findings were: (1) Anxiety and some of the measures of cognitive ability were weakly correlated cross-sectionally (wave by wave); (2) With few exceptions, neither the main measure of anxiety (GAS) nor proxies for anxiety, were correlated with changes in measures of cognitive ability; (3) Some of the derivatives and items of GAS were weakly correlated with a small proportion of the measures of cognitive decline, and cognitive impairment; and, (4) Participants who became unavailable for follow-up had higher anxiety and depression levels at baseline, and lower cognitive skills, than those who remained for the full four waves (12 years).

Conclusion: Anxiety as measured by GAS was unrelated to cognitive change. Correlations between some proxies, derivatives, and items of GAS and cognitive change were small,

suggesting these variables may not be demonstrated to be predictors of cognitive ageing, after full adjustment.

4.1 Introduction

Previous investigation of longitudinal associations between anxiety and cognitive ageing has drawn upon a diversity of data. Examples of data sources were, Longitudinal Aging Study, Amsterdam (Bierman et al., 2008), Sydney Memory and Ageing Study (Brodaty et al., 2012), and Australian Imaging, Biomarkers, and Lifestyle (Pietrzak et al., 2015). Findings from such datasets have conflicted (Chapter Two). The present chapter describes new data available for this doctoral thesis. It also provides a preliminary analysis with the aim of identifying prima facia evidence for longitudinal associations between anxiety and cognitive change.

The data and key measures are described, including: demographic, genetic, and psychological characteristics; distributions; trends over time; prevalence; and unavailability for follow-up. Also provided is a preliminary examination of unadjusted associations between cognitive change over four waves, and baseline GAS (and its items, its derivatives such as latent factors, and anxiety proxies such as *neuroticism*). Potentially confounding variables are examined for correlation with anxiety, cognitive decline, and cognitive impairment. And finally, additional variables are identified which may act as mediators or moderators, potentially influencing any associations between anxiety and cognitive change.

4.2 Methods

4.2.1 Data Source & Ethics Approval

Data for this study were drawn from the Personality And Total Health Through Life (PATH) study, established in 1999 to collect information on depression, anxiety, cognitive ability, substance use, and genetic and environmental risk factors and moderators. PATH is a prospective, cohort study. Data collection is planned to extend over 20 years at four-yearly intervals (Anstey et al., 2012) and has, so far, been obtained for four waves over 12 years. The data collected are specified, and related publications are indexed, at:

http://crahw.anu.edu.au/research/projects/personality-total-health-path-through-life. The dataset and collection are managed by the Centre for Research in Ageing, Health and Wellbeing at the ANU. The original ethics approval for the PATH project was obtained from ANU Human Research Ethics Committee (HREC) in 1998 with protocol M9801. This original approval was followed by a long sequence of approvals referring to individual waves of data and specific, additional data collections, and continuing until approval for HREC 2010/542 (PATH main study for 20s, 40s and 60s Wave 4 and 60s wave 5). This sequence of HREC approvals for PATH all serve to provide ethics approval for this PhD research.

4.2.2 Participants

Participants were randomly recruited from the electoral roles for the Australian Capital Territory and the adjoining town of Queanbeyan, New South Wales (Anstey et al., 2012). Voting in Australia is compulsory, so electoral roles represent close to 100% of the targeted age demographic. There are three age cohorts. At baseline, participants were aged 20-24, 40-44, and 60-64. This thesis focuses on the oldest cohort (60+) which has an overall age range, for the four waves, from 60 to 76 years. PATH participants in the 60+ cohort numbered 2,551 at baseline, representing about 53% of individuals approached for participation.

Cognitively impaired participants at baseline were removed from the dataset (for use in this thesis) to ensure the initial starting sample was free from clinical and pre-clinical cognitive impairment. Cognitively healthy participants at baseline were identified as those with Mini Mental State Examination (MMSE) scores > 26 and as not classified as likely to be diagnosable with mild cognitive impairment (MCI) or dementia (by virtue of clinical assessment). This MMSE cut-point was more conservative than the more typical cutpoint of MMSE scores >24 (for example, Anderson, Sachdev, Brodaty, Trollor, & Andrews, 2007). The higher cutpoint reflects the purpose here of identifying cognitively non-impaired individuals in this relatively young cohort. The lower cutpoint is typically chosen to identify

cognitively impaired individuals conservatively, who might be diagnosable with MCI or dementia. The cut-point score >26, accords with suggestions of Anstey et al. (2008) in their examination of the PATH data, which reported mean MMSE for participants with cognitive impairment at a little over the MMSE score of 26. By these criteria, 161 participants were excluded from Wave 1 data, leaving a residual of 2,390 cognitively healthy participants. These exclusions, based on MMSE scores, included 36 participants identified at Wave 1 with dementia or MCI.

4.2.3 Measures

The primary research questions (Chapter Three) collectively query whether anxiety predicts cognitive ageing in cognitively non-impaired, older adults. Key variables are, therefore, repeated measures of anxiety (and derivatives and proxies for anxiety), cognitive performance, possible moderators (interacting with predictor variables), mediators (intervening between predictor and outcome variables), and confounds (influencing both predictor and outcome variables). Some variables conceivably fit more than one of these descriptions. These key variables can also be classified in the following categories: demographic, genetic, personality, physical health, mental health (including anxiety), cognitive measures, medications, and lifestyle measures. Relevant variables in each of these categories are described at Table 4.1.

Because of the large number of variable names introduced in this chapter, I have italicised PATH variable names (in the text but not in tables) to distinguish them from other uses of the same words. For example, “neuroticism” might be referred to both as a condition (not italicised) and as a PATH variable name (italicised). Additionally, acronyms are described at Table 0.1, p., xvi.

Table 4.1
Main Measures

Category	Name of Test or Scale	Variable Name	(Abbreviation); Description; (Source of Scale)
Anxiolytics		Any medication for anxiety	All current prescription medications identified by participant as for the purpose of treating anxiety.
Benzodiazepines		Benzodiazepines taken for any reason	Valium, Xanax, Mogadon, whether for anxiety, depression, or insomnia.
Cognition	California Verbal Learning Test Trial 1	Immediate Recall	(IR) 16 words to recall, same words provided in immediate & delayed recall test; Californian Verbal Learning Test (CVLT; immediate & delayed recall). Measures episodic memory; (Delis et al., 1987).
Cognition	California Verbal Learning Test Trial 2	Delayed Recall	(DR); Sixteen words to recall, same words provided in immediate & delayed recall test. Measures episodic memory; (Delis et al., 1987). Measurement method in Wave 4 was not equivalent to that of other waves. Consequently Wave 4 data for DR have not been used.
Cognition	Purdue Pegboard	Purdue Pegboard	(PPd), (PPn), (PPb): Purdue Pegboard test of dominant hand, non-dominant hand, and both hands together; using left, right, or both hands, respectively. Participant places as many pegs as possible in holes in left or right columns. Score for each of the three tests is the number of pegs placed in 30 seconds. This is a cognitive motor task, measuring psychomotor speed; (Tiffin, 1968).
Cognition	Spot-the-Word Test – Version A	Spot the Word	(StW) 60 items, pairs of words with one real and one made up. The task is to select the real word. Estimates premorbid, verbal intelligence; (Baddeley et al., 1993).
Cognition	Standardised Mini Mental State Examination	Mini Mental State Examination	(MMSE) 23 items with a maximum score of 30. Typically a screen for dementia; deployed in PATH as a measure of global cognitive impairment; (Molloy, Alemayehu, & Roberts, 1991).
Cognition	Symbol Digit Modalities Test	Symbol Digit Modalities Test	(SDMT) Participant has 90 seconds to pair specific numbers with given geometric figures; measures processing speed and cognitive dysfunction; (Smith, 1982). Normative data are available at Kiely, Butterworth, Watson, and Wooden (2014).
Cognition	Wechsler Memory Scale	Digit Span Backwards	(DSB) Five items, each with two questions; repeating backwards a string of digits, ranging from 3 to 7 digits. Scores range from 0 to 10. Measures working memory; (Wechsler, 1945).
Cognition	Multiple Tests plus Clinical Assessment	Dementia	Details of tests and assessments are at Section 4.2.3.1. Dementia was described by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 1994) as a "Syndrome that may be caused or characterised by

Category	Name of Test or Scale	Variable Name	(Abbreviation); Description; (Source of Scale)
			multiple cognitive deficits, which include memory impairment and at least one of the following: aphasia, agnosia or disturbance in executive functioning. Social or occupational function is also impaired." See also Section 1.3 for an overview of dementia and MCI – their relationship and their respective sub-categories.
Cognition	Multiple Tests plus Clinical Assessment	Mild Cognitive Impairment	(MCI) Details of tests and assessments are at Section 4.2.3.1. MCI is briefly described as a prodrome of dementia. MCI is the pre-dementia stage of cognitive impairment. See Petersen et al. (2001) for a description. It may include memory loss (amnestic MCI) or not (non-amnestic MCI). See also Section 1.3 for an overview of dementia and MCI – their relationship and their respective sub-categories.
Demographic		Age	Age of participant in years, at Wave 1.
Demographic		Education	Years of education at Wave 1.
Demographic		Racial Group	Caucasian, Aboriginal, Asian, Other.
Demographic		Sex	Sex (male or female).
General Health	PATH Medications questionnaire	Sleep Medications	PATH questionnaire on medications: Yes/no response to whether taken medications for sleep within the last month.
Genetic	Buccal Swabs	APOE e4 carrier status	(*APOE* e4); Apolipoprotein E, assessed by Buccal swabs; (Cherbuin et al., 2008).
Lifestyle Factors		Tobacco Use	Smoker: never, past, current; (Jorm et al., 1999).
Lifestyle Factors	Alcohol Use Disorders Identification Test (AUDIT)	Alcohol Consumption	Alcohol frequency — number of drinks per day; (Saunders, Aasland, Babor, De la Fuente, & Grant, 1993).
Lifestyle Factors	Brief life events questionnaire	Life Events	16 Life events (in past 6 months) – yes/no questions: The List of Threatening Experiences; (Brugha & Cragg, 1990).
Lifestyle Factors	Supportive Interactions	Social Support	Social support 20 questions: 10 general and 10 regarding partner relationship. Of the 10 general, 4 are positive, 6 are negative. Of the partner questions, 5 are positive and 5 are negative. Each score on Likert scale, reversed for analysis, to: 0=never; 1=rarely; 2=sometimes; 3=often. (Schuster, Kessler, & Aseltine, 1990).
Mental Health	Brief Patient Health Questionnaire	Trouble Sleeping	Primary care evaluation of mental disorders. One item referring to previous two weeks, asking, "Trouble falling or staying asleep, or sleeping too much?", with answers:

Category	Name of Test or Scale	Variable Name	(Abbreviation); Description; (Source of Scale)
			1. Not at all; 2. Several days; 3. More than half the days; 4. Nearly every day. (Spitzer, Kroenke, Williams, & Group, 1999)
Mental Health	Goldberg Depression and Anxiety Inventory	Goldberg Anxiety Scale	(GAS) Self-report; nine yes/no items; describe symptoms of anxiety during the preceding fortnight; (Goldberg et al., 1988).
Mental Health	Goldberg Depression and Anxiety Inventory	Goldberg Depression Scale	(GDS) Self-report; nine yes/no items; describe symptoms of depression during the preceding fortnight; (Goldberg et al., 1988).
Mental Health	Goldberg Depression and Anxiety Inventory	Psychological Distress	(PsD) Derived alternatively as the multiplication (PsDM) or the addition (PsDA) of the two Goldberg sub-scales: anxiety and depression.
Personality	Connor-Davidson Resilience Scale	Resilience	Resilience; (Connor & Davidson, 2003). Not available in W1 or W2.
Personality	PANAS	Positive Affect	(PAS); Positive and Negative Affect Schedule (PANAS) 10 questions; (Watson & Clark, 1994)
Personality	Pearlin's Mastery Scale	Mastery	Mastery — 7 individual questions with 4 options: 1-Strongly agree; 2- Agree, 3-Disagree, 4-strongly disagree; (Pearlin, Menaghan, Lieberman, & Mullan, 1981).
Physical Health		Body Mass Index	(BMI); Ratio of weight to height-squared.
Physical Health	Short Form Health Survey	Physical Health	General health: Item 1 of 12 item survey; (Ware Jr, Kosinski, & Keller, 1996).
Physical Health	Stress and Health Study. Health survey questionnaire	Physical activity	Physical activity-frequency & times — maximum scores for mild=90, moderate=50, vigorous=30; (Marmot et al., 1991).

4.2.3.1 MCI and dementia.

Most of the variables mentioned in Table 4.1 are measured by a single test or scale. Two important variables, indicating degrees of cognitive impairment, are based on multiple tests or scales, plus clinical assessment. These two variables are MCI and *dementia*. Screening (by

cognitive testing) and clinical assessment for MCI and *dementia* in PATH, were described by Anstey et al. (2008) and Anstey et al. (2013) for Waves 1 to 3. Wave 4 was similarly conducted except that there were two levels of screening instead of one, before the final clinical assessment which, in Wave 4, included a clinical interview. The results of screening and clinical assessment, across all waves, was that participants were either diagnosed with MCI or dementia or were recorded as free of both conditions. Data collected for Wave 4 included assessments by the criteria of both Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 1994) and *DSM-5*. For example, the equivalent of "dementia" by *DSM-IV* criteria, was the *DSM-5* disorder, Major Neurocognitive Disorder (major-NCD). MCI is close in definition to Mild Neurocognitive Disorder (mild-NCD). However, these disorders defined by *DSM-5* are not strictly equivalent to the disorders of MCI and dementia. Because major- and mild-NCD were not recorded for Waves 1 to 3, only the data for *DSM-IV* disorders of dementia and MCI are used here across all waves for longitudinal analysis.

4.2.3.2 Proxies for anxiety.

Table 2.2 listed five of the 37 accepted studies in the literature review, as analysing proxies for general anxiety, rather than a direct measure. Proxies mentioned at Table 2.2 were: neuroticism; worry about subjective memory; mild worry; phobic anxiety; and anxiety inferred from items in other scales. From PATH data, available proxies for anxiety, as suggested by those previously adopted, are listed at Table 4.2. Each prospective proxy is tested in this chapter for cross-sectional correlation with GAS. Table 4.2 describes also variables that are derived from GAS items, such as a latent factor representing somatic aspects of anxiety. The nature of, and arguments for using these derivatives of GAS, are delineated at Section 4.2.4.9.

Table 4.2
Description of PATH Variables Available as Derivatives[#] of, or Proxies for, GAS.

Name of Test or Scale (Abbreviation)	Variable Name	Description; (Source of Scale)
Behavioural Inhibition and Behavioural Activation Scales (BISBAS), Inhibition component (BIS)	Behavioural Inhibition (Abbreviation)	Seven BIS questions, on behavioural inhibition, from the BISBAS of 24 questions. "Indicate how much you agree or disagree with each statement": examples: "I feel pretty worried or upset when I think or know somebody is angry at me"; "Criticism or scolding hurts me quite a bit"; "I worry about making mistakes". Likert scale responses from: 1=Very false for me to 4=Very true for me. There are three items that are reverse scored before aggregating the total score; e.g., "I have very few fears compared to my friends"; (Carver & White, 1994)
BPHQ Anxiety component, Wave 2^	BPHQ-anxiety-W2	Questions 12, & 12a to12f of the Brief Patient Health Questionnaire (BPHQ), refer to Generalised Anxiety Disorder. These refer to the last four weeks with responses on a three point Likert scale: 1. Not at all; 2 Several days; 3. More than half the days. (Spitzer et al., 1999).
Eysenck Personality Questionnaire (EPQ)	Neuroticism	Neuroticism scale within EPQ is also referred to as the "introversion" scale. Twelve, yes/no questions, such as: "Are you often troubled by feelings of guilt?"; and "Would you call yourself tense or 'highly-strung'?" EPQ is available for Waves 1 & 2 only. (S. B. Eysenck, Eysenck, & Barrett, 1985)
Cortisol	Cortisol	Serum cortisol from blood sample
Goldberg Anxiety Scale (GAS)	Chronic GAS[#]	Individuals are identified as having a chronic GAS score, if their score ≥ 7, for either two or more, or three or more, of the available four waves. Chronic, by this definition, is the equivalent of persistently clinical GAS.
Goldberg Anxiety Scale (GAS)	Clinical GAS[#]	A binary indicator, derived from the GAS scale; defined by the cutpoint: score ≥ 7.
Goldberg Anxiety Scale (GAS)	GAS-Sleep[#]	By exploratory factor analysis (Appendix 4.A), this represents items 5 (sleeping poorly), and 9 (difficulty falling asleep) of the GAS scale, weighted at: .764, and .745, respectively (Goldberg et al., 1988).
Goldberg Anxiety Scale (GAS)	GAS-Somatic[#]	By exploratory factor analysis (Appendix 4.A), this represents items: 6 (head & neck aches), 7 (trembling, tingling, dizzy spells, sweating, diarrhoea, frequent urination), and 8 (worried about health) of the GAS scale, weighted at: .312, .671, & .421, respectively. (Goldberg et al., 1988).
Goldberg Anxiety Scale (GAS)	GAS-Worry[#]	By exploratory factor analysis (Appendix 4.A), this represents items: 1 (Keyed up), 2 (Worrying a lot), 3 (Irritable), and 4 (Difficulty relaxing), of the GAS scale with weightings: .774, .695, .568, and .483 respectively. (Goldberg et al., 1988).
Goldberg Anxiety Scale (GAS)	Persistently-high-GAS[#]	Individuals are identified as having a persistently-high-GAS score, if their score ≥ 5, for either two or more, or three or more, of the available four waves.

Name of Test or Scale (Abbreviation)	Variable Name	Description; (Source of Scale)
Goldberg Anxiety Scale (GAS)	Trichotomised GAS[#]	Separating GAS scores into three categories: zero, 1 — 4 (mild), and 5 — 9 (moderate to severe). This follows the method of (Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, & Cauley, 2017), who found strongest, predictive associations for low range GAS scores.
Positive and Negative Affect Schedule (PANAS)	Negative Affect	Ten questions from the PANAS scale of 24 questions. "Indicate to what extent you have been feeling this way the last 4 weeks. Likert scale from1=very slightly or not at all; to 5=extremely. Examples are: Irritable, afraid, upset, guilty. These data are available for Waves 1 to 3 only; (Kercher, 1992).
Ruminative Style	Rumination	Negative ruminative style. "How often do you? . . .: Ten questions with Likert scale responses 1 (never) to 4 (always): e.g., ""I think about how alone I feel" These data are available for Waves 1 to 3 only; (Nolen-Hoeksema & Morrow, 1991)

Notes. ^BPHQ, anxiety component is available only from Wave 2. BPHQ = Brief Patient Health Questionnaire. # Derivatives of GAS are further described and commented upon at Section 4.2.4.9.

4.2.4 Statistical Analysis

4.2.4.1 General analytical methods.

Tables and graphs were produced to demonstrate distributions, correlations, and trends across the four waves of data. The alpha level was entered as $p = .05$ for all tests of significance. Analyses were performed using IBM SPSS statistics package, version 25 (IBM Corp., Released 2017), unless otherwise specified below.

4.2.4.2 Key variables by wave.

To demonstrate trends across time of key variables, graphs are presented as boxplots for non-Gaussian data and error-bars for Gaussian data. Boxplots demonstrate the median, interquartile range, minimum & maximum values excluding outliers, plus the outliers. Error-bars demonstrate means and standard deviation at each wave, and, therefore, represent the 95% confidence intervals for the means.

4.2.4.3 Participants unavailable for follow-up.

Group comparisons were produced to demonstrate differences in key variables for participants who became unavailable for follow-up, compared to those who remained available. Group differences were assessed, using T-tests for continuous, parametric variables. For GAS and the Goldberg Depression Scale (GDS) which have non-normal distributions (illustrated below), nonparametric analyses were deployed, and compared with parametric calculations, to assist in the interpretation of results. The Mann-Whitney U-test was used for the nonparametric variables. However, the Mann-Whitney U-test does not report the direction or size of the difference between groups, or the confidence intervals. These tests of limited usefulness were not required for comparing results for most cognitive variables (parametric variables).

4.2.4.4 Prevalence.

Prevalence of clinical anxiety and clinical depression were calculated using cutpoints of scores ≥7 for GAS and scores ≥5 for GDS (Kiely & Butterworth, 2015). Psychological Distress (PsD) is defined here as the interaction of anxiety and depression either by multiplication of the GAS and GDS scores, or by their addition. Consequently, notional, "clinical" cutpoints for psychological distress were formulated by two methods: (1) multiplication, equivalent to the product of the clinical cutpoints for each of GAS and GDS (5 x 7=35); and, (2) Additive, as the sum of the individual cutpoints (5+7=12). Either method attributes a "clinical" status to PsD even if GAS or GDS is scored individually at a lower than clinical provided the other component is scored sufficiently highly to compensate and to still achieve the required minimum cutpoint. These are only notionally at "clinical levels" because there is no formally defined clinical level of psychological distress.

For each variable, the prevalence of clinical levels was calculated as a percentage of clinical cases from total sample tested. Confidence intervals (95%) for the percentage prevalence, were also derived.

4.2.4.5 Scales.

The GAS and GDS scales were examined for internal consistency (more typically referred to in the literature as reliability), at Wave 1. The Maximum Guttman's Lambda statistic (MGLS) was used in place of the more traditional Cronbach's alpha. MGLS is a more accurate reflection of internal consistency (Callender & Osburn, 1979). MGLS provided six calculations of internal consistency, λ_1 to λ_6. The maximum of these six calculations is regarded as the best option for calibrating internal consistency (Callender & Osburn, 1979). Of these, λ_3 is equivalent to Cronbach's alpha.

Factor analysis, particularly of the GAS scale, is relevant to the prospect that proxies for GAS and their associations with cognitive ageing, may reveal new information about how and whether anxiety predicts cognitive decline or cognitive impairment. Exploratory factor analysis using Mplus (Version 7.4; R. Burns, personal communication, 2015) options for binary data (at Wave 1) were used to ascertain whether there were latent factors underlying the scale. A principal axis factor analysis was applied with oblique rotation (direct oblimin). Oblique rotation was chosen because any latent factors were not expected to be independent within this well-defined, single construct. The Kaiser–Meyer–Olkin (KMO) measure was used as an indicator of sampling adequacy. Further details are at the Appendices 4.A & 4.B.

Scales other than GAS and GDS were not examined for internal consistency; nor were they factor-analysed. There was no use for such information for the proxies and confounders, etc. And, the cognitive scales were not designed or constructed in a way conducive to such analyses. For example, the SDMT score is achieved by completing as many (similar) items as

possible within a time limit, and, therefore, these questions are not individual items for this purpose.

4.2.4.6 Cross-Sectional correlations with GAS.

Correlations tested were in two categories: firstly, cross-sectional relationships, by wave, between GAS, and the main demographics; and secondly, cross-sectional relationships, by wave, between GAS, and GDS and the cognitive measures.

4.2.4.7 Cognitive change.

Change in cognitive performance is presented in several different forms. Firstly, graphical representation of performance at each wave (Section 4.3.3), demonstrates change in average scores, over time, for each cognitive measure. Secondly, (at Section 4.3.8) graphical representations are provided for the Wave 4 distributions of cognitive *change* (baseline to Wave 4 differential). Finally, graphical representation of incident MCI and dementia, by wave, demonstrate the trend in conversion to these impairments.

4.2.4.8 Confounding variables.

With regard to potential influence on associations between anxiety and cognitive change, potentially confounding variables considered were: *anxiolytics*; *education*; *sex*; *general health*; *physical health*; *mastery*; *physical activity*; *positive affect*; *life events* (stressors), *smoker status*; *sleeping problems*; and *resilience*. This list was derived by observation of the covariates considered in the literature, for adjustment of models, then matching such variables to the available variables in the PATH data.

4.2.4.9 Derivatives of GAS.

Table 4.2 (above), describes seven variables identified as derivatives of GAS and indicated with a hash mark (#). These constructed variables are derivatives by virtue of having been calculated from some or all of the nine items of the GAS scale. These derivatives

are presented as possible proxies for GAS, subject to verification of suitable correlations. They are:

1. GAS-Somatic [derived by exploratory factor analysis at chapter Appendix 4.A, Sections 1.2.2, 3.2.1.g, and 4.3.5.2.1; Miloyan and Pachana (2015)].
2. GAS-Worry [derived by exploratory factor analysis at chapter Appendix 4.A; Sections 1.2.1, 3.2.1.e., and 4.3.5.2.1; Pachana et al. (2007)].
3. GAS-Sleep [derived by exploratory factor analysis at chapter Appendix 4.A, Sections 3.2.1.d.iii, and 4.3.5.2.1]
4. Clinical GAS [Binary transformation: GAS scores ≥ 7 (Kiely & Butterworth, 2015).
5. Chronic GAS (equivalent to persistently clinical GAS [see 7. Below] — which is clinical GAS derived by two methods: either ≥ 2, or ≥ 3 waves of the available 4 waves).
6. Trichotomised GAS [Categorical transformation: zero, low (GAS score = 1 to 4), moderate to high (GAS≥5); Section 3.2.1.h; (Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, & Cauley, 2017)].
7. Persistently-high-GAS [Binary transformation: *High* if score ≥ 5, applied alternatively for ≥ 2 or ≥ 3 of the available 4 waves].

Each of these derivatives offers an alternative prospect for identifying useful associations between anxiety and cognitive change and is justified either by precedent from the literature or by the exploratory factor analysis (Sections 4.2.4.4, 4.3.5.2, and Appendix 4.A). Or, in the case of the fifth and seventh derivatives above, *chronic GAS* and *persistently-high-GAS*, the arguments and justification are summarised at Section 3.2.1.c which refers to Figure 1.5.

4.2.4.11 Associations with cognitive change, for GAS, GAS items, derivatives, and proxies.

Baseline GAS proxies were examined for correlation with each other and the main GAS scale. Baseline values of GAS, its items, derivatives, and proxies, were each tested for unadjusted association with cognitive change between baseline and Wave 4, as well as association with Wave 4 incident MCI and dementia.

4.2.4.12 Additional variables as potential moderators or mediators

a. In addition to the variables introduced above, there are potentially important moderators or mediators of associations between anxiety and cognitive decline or cognitive impairment. These additional variables are APOE carrier status, and BMI. For example: Pankratz et al. (2015) found the addition of APOE e4 carrier status improved their regression models for longitudinal association between anxiety and cognitive change, and Cherbuin et al. (2009) found (using PATH data) BMI was among the related predictors of conversion to mild cognitive disorders. APOE is divided into single and double e4 carrier status (heterozygous and homozygous). The potential of these variables to influence longitudinal associations between anxiety and cognitive change will be examined in later chapters. Here, they are examined for direct correlation with anxiety, anxiety proxies, and cognitive change.

4.3 Results

4.3.1 The Sample

Table 4.3 describes the PATH, 60+ cohort, sample sizes and participation rate, by wave. Table 4.4 provides frequencies by wave, of individuals classified as cognitively healthy

(MMSE > 26) at baseline. Table 4.5 provides Wave 1 data on demographics, cognitive ability, and mental health, for accepted cases.

Table 4.3.
PATH Sample Size and Participation Rate by Wave: 60+ cohort

	Wave 1 N (%)	**Wave 2 N (% of wave 1 interviewed)**	**Wave 3 N (% of wave 1 interviewed)**	**Wave 4 N (% of wave 1 interviewed)**
Sample approached	4,831	2,551 (100%)	2,234 (87.6%)	1,932 (75.7%)
Interviews	2,551 (52.8% of approached)	2,222 (87.1%)	1,973 (77.3%)	1,645 (64.5%)
Not interviewed*	2,280 (47.2% of approached)	329 (12.9%)	578 (22.7%)	906 (35.5%)
Wave to wave, net attrition		329 (12.9%)	249 (11.2% of Wave 2 interviews)	328 (16.6% of Wave 3 interviews)

*Note: * Not interviewed* figures are net totals of additional people approached from a previous wave, refusals, deaths, and cannot be found".

Table 4.4.
Frequencies by Wave: Participants found Cognitively Healthy at Baseline

Sample	***n*** **Wave 1**	***n*** **Wave 2**	***n*** **Wave 3**	***n*** **Wave 4**
Valid	2,390 *	2117	1891	1582
Total Unavailable to follow-up (% of W1)	0	273 (11.4%)	499 (20.9%)	808 (33.8%)

Note: * 161 participants were excluded with cognitive impairment.

Table 4.5.
Wave 1 Characteristics for Cognitively Healthy Participants

Wave 1 Variables	Statistics
Age years: mean (SD)	62.51 (1.51)
Alcohol: hazardous or harmful consumption n (%):	143 (6.0%)
Anxiolytics: n (%)	125 (5.2%)
APOE e4 carrier: Sub-study sample size; e4/e4 number (%) [Homozygous]; single e4 carrier (%) [Heterozygous].	526; 9 (1.7%); 132 (25.1%)
Benzodiazepines: n (%)	62 (2.6%)
BMI: mean (SD)	26.80 (5.30)
Caucasian: n (%)	2303 (96.4%)
Cognitively healthy [MMSE > 26]: n, mean (SD)	2390, 29.37 (0.83)
Delayed Recall: mean (SD)	6.33 (2.41)
Digit Span Backwards	5.03 (2.20)
Education years: mean (SD)	13.97 (2.70)
EPQ Neuroticism	3.28 (3.00)
Female: *n* (%)	1,176 (49.2%)
General Health: mean (SD)	2.34 (0.97)
Physical Health: mean (SD)	48.96 (9.82)
Goldberg Anxiety Scale: mean (SD), median, mode	2.20 (2.30), 1.00, 0.00
Goldberg Depression Scale: mean (SD), median, mode	1.63 (1.84), 1.00, 0.00
Immediate Recall: mean (SD)	7.28 (2.19)
Life events: mean (SD)	0.81 (1.07)
Mastery: mean (SD)	21.98 (3.55)
Negative Affect: mean (SD)	13.88 (4.86)
Psychological Distress (PsDM) by multiplication of GAS & GDS mean (SD), median, mode.	6.36 (11.862), 1.00, 0.00
Psychological Distress (PsDA) by addition of GAS & GDS mean (SD), median, mode.	3.82 (3.78), 3.00, 0.00

Wave 1 Variables	Statistics
Physical Activity: mild; moderate; vigorous: mean (SD) for each.	Mild: 1.48 (0.84) Moderate: 2.15 (1.00) Vigorous: 3.33 (0.98)
Positive Affect: mean (SD)	31.49 (7.16)
Present Smoker: n (%)	249 (10.4%)
Purdue Pegboard (both hands): mean (SD)	10.47 (1.72)
Social Support general (negative): mean (SD)	18.18 (3.02)
Social Support general (positive): mean (SD)	5.36 (1.86)
Social Support partner relationship (negative): n (%); mean (SD)	15.14 (3.16)
Social Support partner relationship (positive): n (%); mean (SD)	6.64 (2.59)
Spot the Word: mean (SD)	52.26 (5.4)
Symbol Digit Modalities Test: Mean (SD)	50.40 (9.13)

Note. MMSE = Mini Mental State Examination; BMI = Body mass index; EPQ = Eysenck Personality Questionnaire.

4.3.2 Distributions

Figures 4.1 to 4.9 illustrate the baseline distributions of each of the following key variables: GAS; GDS; MMSE; *Immediate Recall* (IR); *Delayed Recall* (DR); *Symbol Digit Modality Test* (SDMT); *Purdue Pegboard both hands* (PPb); *Digit Span Backwards* (DSB); and *Spot the Word* (StW). Each figure illustrates a normal curve overlay and quantile-quantile (QQ; sample versus theoretical distributions) plot, illustrating variation from the normal curve. These Wave 1 distributions are typical also of distributions in the remaining waves.

Acceptable normality is demonstrated in these figures, for: IR, DR, SDMT, PPB, and DSB. StW was normally distributed but truncated at its maximum scale score of 60 points (1.43 SD above the mean). GAS, GDS and MMSE were not normally distributed. GAS and

GDS both had their modal scores at zero and were approximately distributed exponentially (with negative exponent). Both had modal scores at zero and were truncated at zero.

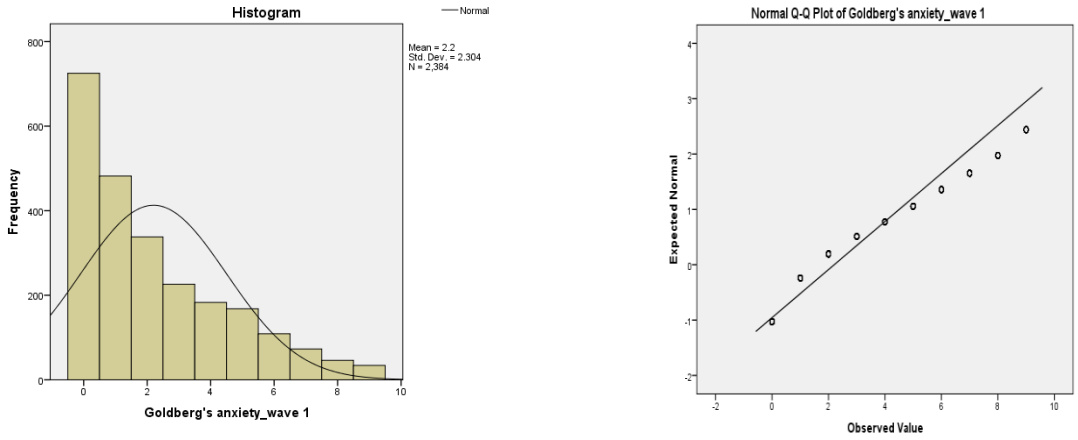


Figure 4.1. Wave 1 Goldberg Anxiety Scale (GAS)

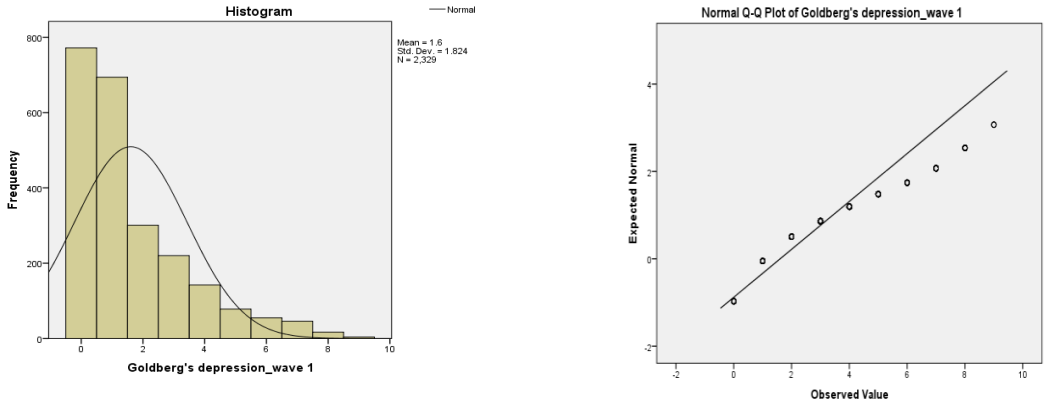


Figure 4.2. Wave 1 Goldberg Depression Scale (GDS)

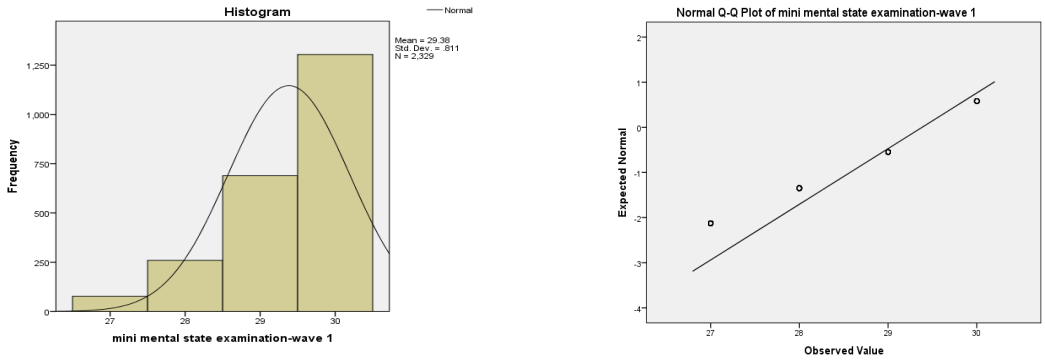


Figure 4.3. Wave 1 Mini Mental State Examination (MMSE)

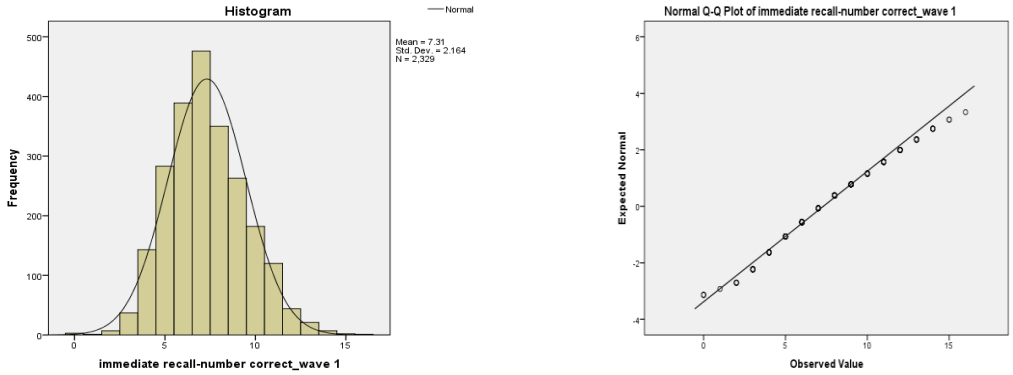


Figure 4.4. Wave 1 Immediate Recall (IR)

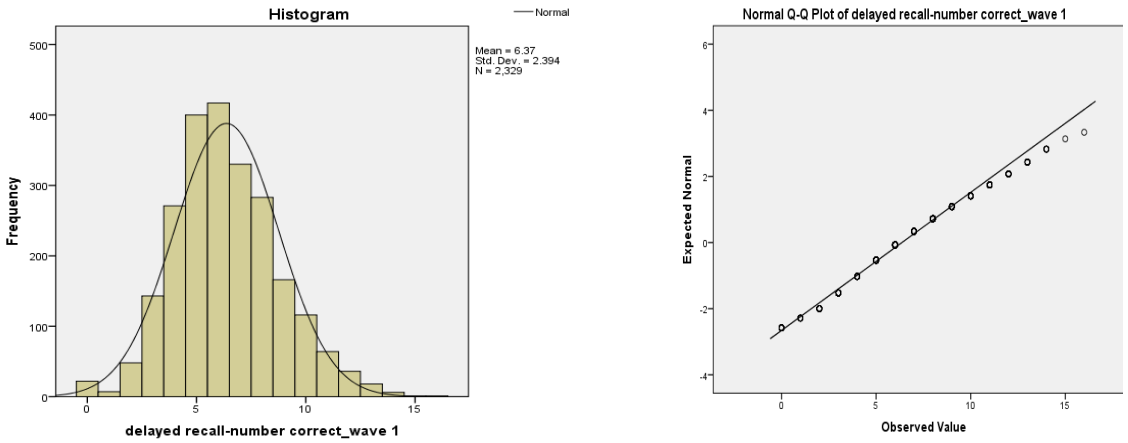


Figure 4.5. Wave 1 Delayed Recall (DR)

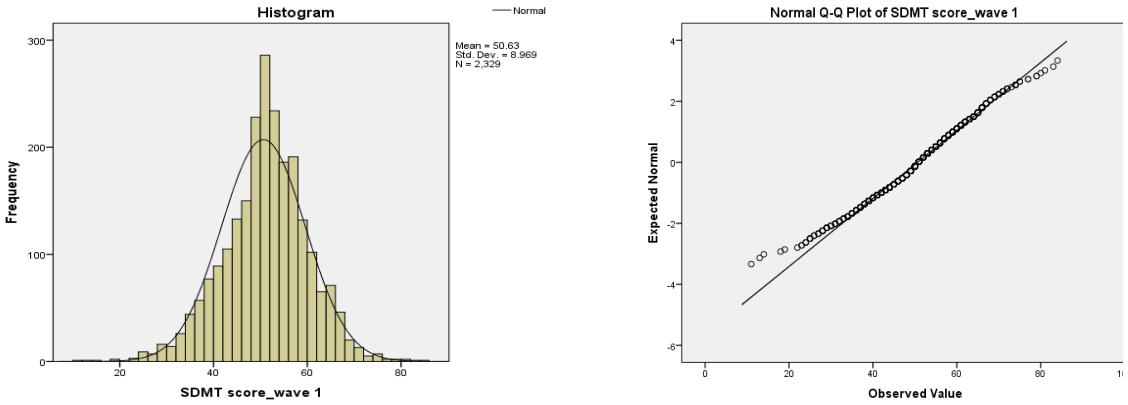


Figure 4.6. Wave 1 Symbol Digit Modality Test (SDMT)

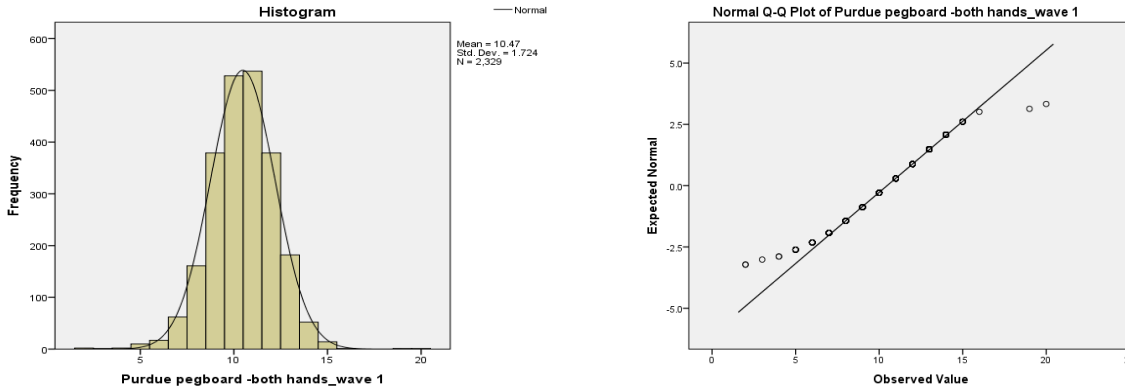


Figure 4.7. Wave 1 Purdue Pegboard both hands (PDPP-bh)

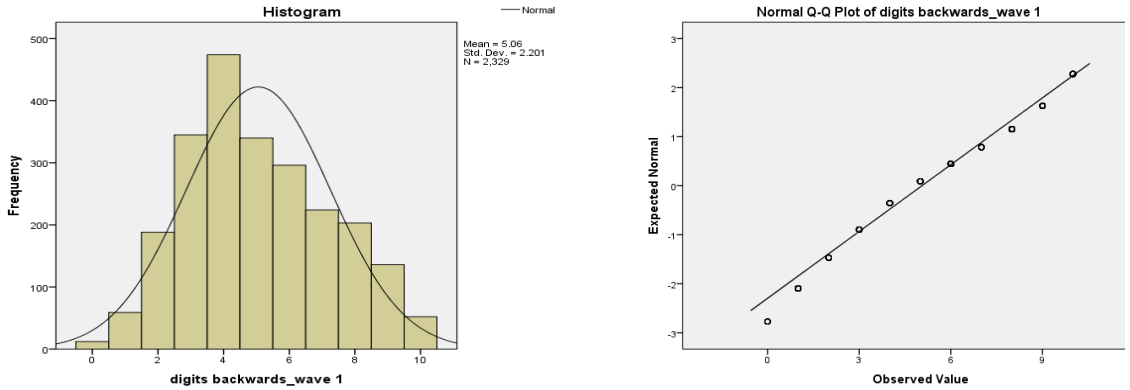


Figure 4.8. Wave 1 Digit Span Backwards (DSB)

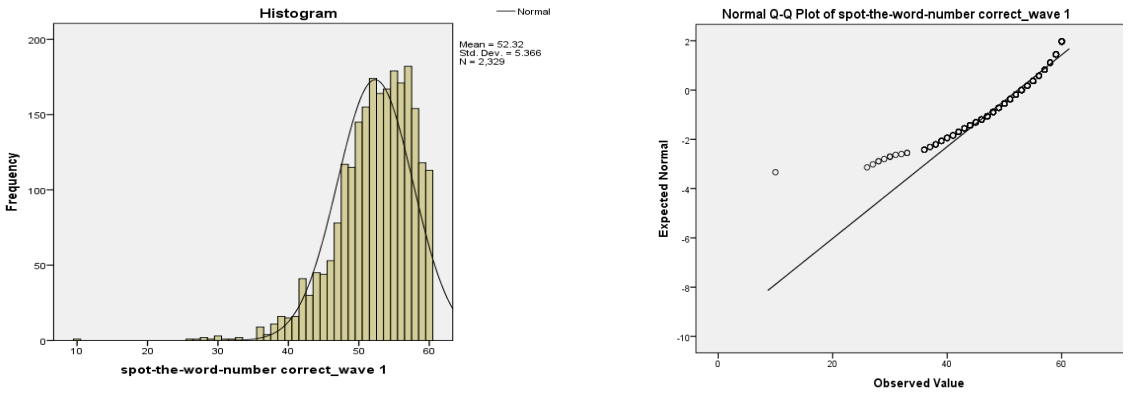


Figure 4.9. Wave 1 Spot the Word (StW)

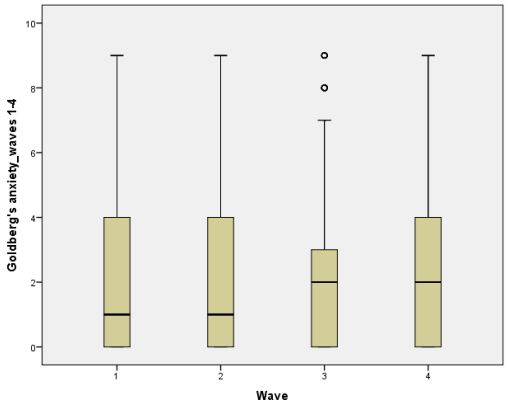
4.3.3 Key Variables by Wave

For an overview of trends in the nonparametric variables, Figure 4.10 compares box plots for all four waves, for GAS, GDS, MMSE, and StW. Figure 4.11 demonstrates trends, using error bars, for remaining cognitive variables. These parametric variables are SDMT, MMSE, IR, DR, DSB, and PPb. StW is presented both as box plots and error bars, because it is marginally parametric in distribution.

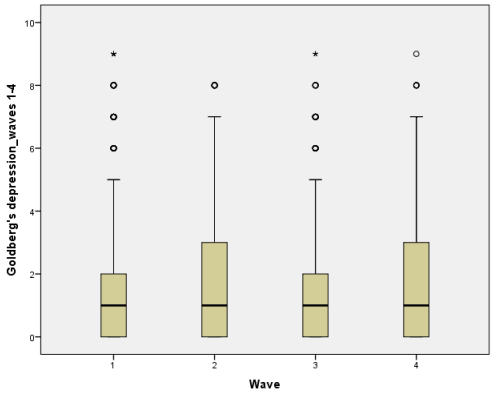
The box plots at Figure 4.10, indicate outliers, some of which may appear extreme. However, the outliers here, and in other variables not graphically displayed, are within testing parameters and should not be excluded.

At Figures 4.10 and 4.11, the only upward trend is for StW, but this information is of marginal value because of its mentioned, truncated distribution. Trends were roughly constant for: GAS, GDS, MMSE, StW, & DSB. Trending downward, were: SDMT, IR, DR and PPb. Lower scores for the cognitive measures represent poorer performance.

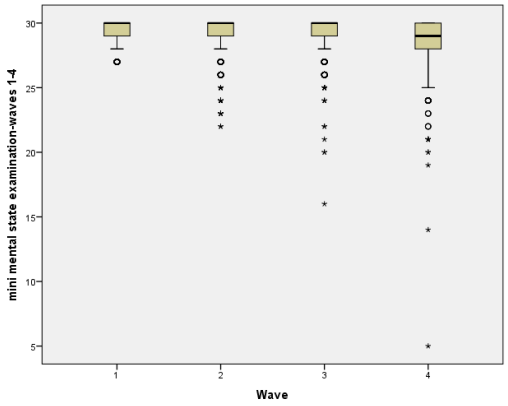
GAS



GDS



MMSE



StW

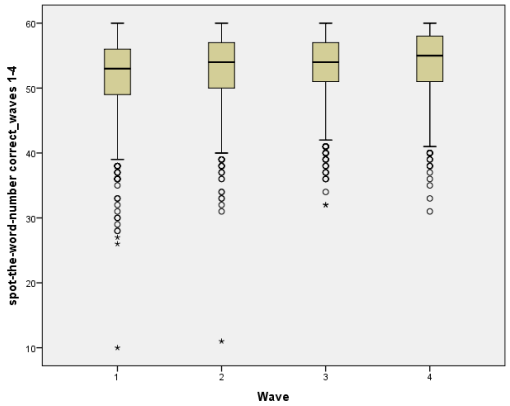
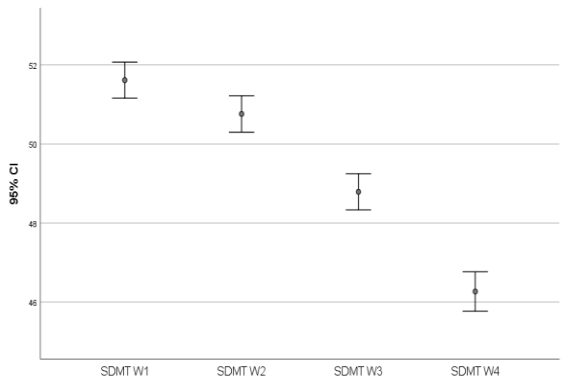


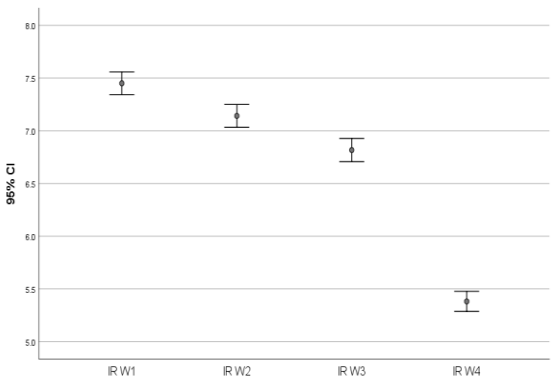
Figure 4.10.
Box plots of Anxiety, Depression, Mini Mental State Examination (MMSE), and Spot the Word (StW) across four Waves of data for the cognitively healthy cases.

Note: Vertical axes are raw scores.

SDMT



IR



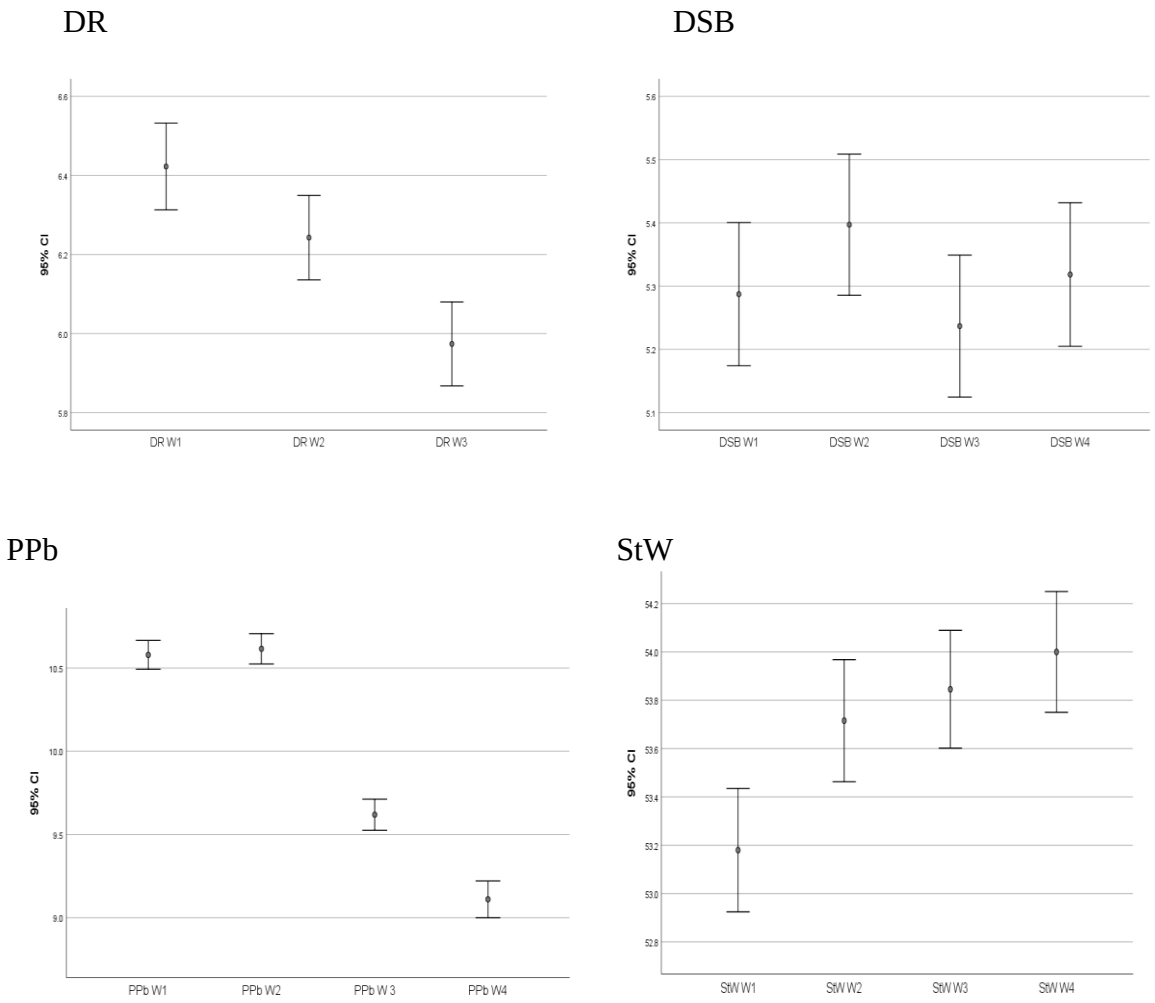


Figure 4.11.
Error bars of cognitive variables by wave across four Waves of data for the cognitively healthy full sample, for Symbol Digit Modality Test (SDMT), Immediate Recall (IR), Delayed Recall (DR; DR data were unavailable for Wave 4), and Digit Span Backwards (DSB), Purdue Pegboard Both hands (PPb; representative of the trend also for dominant hand and non-dominant hand).

Note: Error bars are for 95% confidence intervals of the means.

4.3.4 Participants Unavailable for Follow-Up

Table 4.3 above, provided frequencies by wave of cases accepted at baseline, as well as numbers (and percentages), unavailable to follow-up. Unavailability was due to: death, moved out of area, illness, dementia, and a small number of refusals.

Comparisons were made between participants available and unavailable for follow-up at either wave 3 or 4, as two separate analyses. Analyses were performed to determine whether such cases reflected different anxiety, depression, or cognitive scores at baseline and at either Wave 2 (for participants unavailable at Wave 3), or Wave 3 (for participants unavailable at Wave 4). The Mann-Whitney U-test and T-test for differences between groups, were compared for MMSE, GAS, and GDS. The Mann Whitney U-test for significance takes precedence over the T-test, for nonparametric variables. Therefore, significance reported by T-tests for GAS, GDS, and MMSE, at Tables 4.8 and 4.9, are irrelevant, unless corroborating significance reported by the Mann Whitney U-tests.

Results are at Table 4.6 (for Mann-Whitney U-tests), and Table 4.8 (for T-tests) for cases becoming unavailable at wave 3, and Table 4.7 (for Mann-Whitney U-tests) and Table 4.9 (for T-tests), for cases becoming unavailable at wave 4. Tables 4.25 and 4.26 also provide results of T-tests for differences between groups, for the parametrically distributed cognitive variables.

By comparing these results within and between tables, the following points emerge:

- For participants unavailable at Wave 3: From the U-tests, there are no differences between groups for their scores in GAS, GDS, or MMSE at Wave 2, and only a difference in GDS at Wave 1, indicating a higher GDS score for the *unavailable* group.
- For participants unavailable at Wave 4: There are no differences at Waves 1 or 3 in MMSE. For GDS, there are differences at Waves 1 and 3, confirmed by both types of test. For GAS, there are confirmed (by T-test) differences at Wave 3 but unconfirmed (by T-test) differences at Wave 1. The confirmed differences (at either Waves 1 or 3) indicate that GAS and GDS were higher, and MMSE were scores were lower, for the *unavailable* group.

- Remaining cognitive differences between groups are simpler to ascertain because they rely on T-tests alone. See Tables 4.8 and 4.9.
    - For participants unavailable at Wave 3 (Table 4.8), there were significantly lower scores at Wave 1 in all these cognitive variables. At Wave 2, there were significantly lower scores in SDMT, PPb, and DB.
    - For participants unavailable at Wave 4, the baseline cognitive scores were lower for SDMT and StW. And, at Wave 3, all cognitive scores were significantly lower for the *unavailable* group.
- In Sum:
    - GAS was higher at Wave 3 for participants unavailable at Wave 4, but otherwise there was no difference in GAS among these tests;
    - GDS was higher at baseline for participants unavailable either at Wave 3 or 4, and higher at Wave 3 (but not Wave 1) for participants unavailable at Wave 4;
    - With some exceptions, there was a predominance of lower cognitive scores at Wave 1, and Waves 2 or 3 for participants becoming unavailable respectively at Waves 3 or 4.

Sections 4.3.10 and 4.3.11 below offer further insights into predictors of unavailability to follow-up, by examining associations respectively, with *persistently-high-GAS* and *Chronic GAS*.

Table 4.6.
Mann-Whitney U-test: Differences between two groups, in medians for GAS, GDS, and MMSE at waves 1 & 2. Group1: cases present at wave 3; Group 2: cases missing at wave 3 but previously present.

Measure	Asymptotic Significance (at .05 level) of difference between medians of two groups: present or missing at wave 3	
	Medians at Wave 1	**Medians at Wave 2**
GAS	.023	not significant
GDS	**.001^**	.047
MMSE	not significant	not significant

^Remains significant after Bonferroni correction
(at $p < .05$; two-tailed) for 3 comparisons.

Table 4.7.
Mann-Whitney U-test: Differences between two groups, in medians for GAS, GDS, and MMSE at waves 1 & 3. Group1: cases present at wave 4; Group 2: cases absent at wave 4 but previously present.

Measure	Asymptotic Significance of difference (at .05) level between medians of two groups: present or missing at wave 4	
	Median at Wave 1	**Median at Wave 3**
GAS	**.014^**	**.010^**
GDS	**.000^**	**.001^**
MMSE	not significant	not significant

^Remains significant after Bonferroni correction
(at $p < .05$; two tailed) for 3 comparisons.

Table 4.8

T-test: Standardised differences between means (at waves 1 & 2 for GAS, GDS and cognitive measures) for two groups: available, or unavailable at wave 3 (and previously present).

	Standardised difference between means of two groups: available and unavailable at wave 3 (and previously present).			
	Standardised difference between means at wave 1		**Standardised difference between means at wave 2**	
Measure	**Difference between means (S.E.)**	**95% CI (*p*)**	**Difference between means (S.E.)**	**95% CI (*p*)**
GAS	.195 (.051)	**.095 – .295 (.000) ^**	.064 (.071)	-.075 – .203 (.373)
GDS	.253 (.051)	**.153 – .352 (.000) ^**	.179 (.072)	.038 – .320 (.013)
MMSE	-.160 (.028)	**-.216 – -.104 (.000) ^**	-.358 (.079)	**-.512 – -.203 (.000) ^**
SDMT	-.404 (.051)	**-.503 – -.305 (.000) ^**	-.421 (.072)	**-.562 – -.279 (.000) ^**
PPB	-.167 (.051)	**-.268 – -.066 (.001) ^**	-.236 (.071)	**-.375 – -.096 (.001) ^**
IR	-.246 (.051)	**-.345 – -.146 (.000) ^**	-.141 (.073)	-.284 – .002 (.050)
DR	-.186 (.052)	**-.289 – -.084 (.000) ^**	-.108 (0.080)	-.265 – .050 (.180)
DB	-. 255 (.051)	**-.355 – -.155 (.000) ^**	-.238 (.072)	**-.379 – -.097 (.001) ^**
StW	-.381 (.051)	**-.481 – -.282 (.000) ^**	-.198 (.077)	-.350 – -.046 (.011)

Notes: (1) A positive difference between groups implies cases not continuing at wave 3 had a higher mean (than continuing cases); (2) Refer to table 4.1 for meanings of abbreviates of measures; (3) ^ Remains significant (at $p < .05$; two-tailed) after Bonferroni correction for 11 comparisons.

Table 4.9
T-test: Standardised differences between means (at waves 1 & 3 for GAS, GDS and cognitive measures) for two groups: available, or unavailable at wave 4.

	Standardised difference between means of two groups: available and unavailable at wave 4 (and previously present)			
	Standardised difference between means at wave 1		**Standardised difference between means at wave 3**	
Measure	**Difference between means (S.E.)**	**95% CI (p)**	**Difference between means (S.E.)**	**95% CI (p)**
GAS	.111 (.058)	-.003 – .225 (.056)	.187 (.060)	**.068 – .304 (.002) ^**
GDS	.166 (.057)	**.055 – .278 (.004) ^**	.287 (.060)	**.170 – .405 (.000) ^**
MMSE	-.164 (.339)	-.227 – 1.102 (.641)	-.359 (.061)	**-.479 – -.240 (.000) ^**
SDMT	-.281 (.058)	**-.396 – -.166 (.000) ^**	-.429 (.061)	**-.548 – -.311 (.000) ^**
PPb	-.161 (.060)	-.280 – -.043 (.007)	-.271 (.062)	**-.393 – -.149 (.000) ^**
IR	-.154 (.059)	-.270 – -.038 (.009)	-.235 (.061)	**-.354 – -.117 (.000) ^**
StW	-.298 (.057)	**-.410 – -.187 (.000) ^**	-.333 (.062)	**-.455 – -.211 (.000) ^**

Notes:
(1) A positive difference between means refers to cases unavailable at wave 4 as having a higher mean (than available cases);
(2) Refer to table 4.1 for meanings of abbreviates of measures; and
(3) DR data were unavailable for wave 4.
(4) ^ Remains significant (at $p < .05$; two-tailed) after Bonferroni correction for 9 comparisons.

4.3.5 Prevalence

Prevalence estimates are at Table 4.10 for: clinical levels of anxiety (estimated by GAS); depression (estimated by GDS); and *comorbid anxiety and depression* (estimated by clinical levels of both measures). Also included in Table 4.10, is an equivalent set of results for

psychological distress, notionally also at clinical levels, and calculated by two alternative methods, multiplication and addition of scores for each, as described in the Methods Section. The trends in prevalence of all five variables over the four waves, are slightly downward.

Table 4.10.
Prevalence Estimates of Clinical Anxiety (GAS≥7), Depression (GDS≥5), Comorbid anxiety and Depression, plus Psychological Distress, for the 60+ Cohort from PATH, Cognitively Healthy Participants at Baseline.

Clinical Disorders	Wave 1 N, n, % prevalence, (95% CI % prevalence)	Wave 2 N, n, % prevalence, (95% CI % prevalence)	Wave 3 N, n, % prevalence, (95% CI % prevalence)	Wave 4 N, n, % prevalence, (95% CI % prevalence)
GAS	2385, 152, 6.4%, (2.5%-10.3%)	2098, 114, 5.4%, (1.3%-9.6%)	1876, 88, 4.7%, (0.3%-9.1%)	1575, 69, 4.4%, (-.04%-9.2%)
GDS	2382, 211, 8.9%, (5.0%-12.7%)	2097, 195, 9.3%, (5.2%-13.4%)	1875, 158, 3.1%, (-1.4%-7.5%)	1573, 133, 8.5%, (3.7%-13.2%)
Comorbid GAS & GDS	2385, 84, 3.5%, (-0. 4%-7.5%)	2100, 65, 3.1%, (-1.1%-7.3%)	1876, 41, 2.2%, (-2.3%-6.7%)	1574, 34, 2.2%, (-2.7%-7.0%)
Psychological Distress (PsDM) by multiplication of GAS & GDS	2382, 114, 4.8%, (0.9%-8.7%)	2095, 94, 4.5%, (0.3%-8.7%)	1875, 55, 2.9%, (-1.5%-7.4%)	1573, 49, 3.1%, (-1.7%-8.0%)
Psychological Distress (PsDA) by addition of GAS & GDS	2382, 125, 5.2%, (1.3%-9.2%)	2095, 100, 4.8% (0.6%-9.0%)	1875, 65, 3.5% (-1.0%-7.9%)	1573, 55, 3.5% (-1.4%-8.4%)

Notes:
N is sample size after discounting cases either unavailable for follow-up or with missing data;
n is the number of cases with clinical level score.
% prevalence is the percentage of n/N.
The 95% CI is for the % prevalence.
PsD cutpoints: by multiplication ≥ 35; by addition ≥12.
PsDM = PsD derived by multiplication.
PsDA = PsD derived by addition.

From Table 4.10, it is notable that comorbid GAS and GDS have prevalence, wave-by-wave, more like psychological distress calculated by the product of the GAS and GDS scores than by their sum. Such comparisons are more meaningful when accounting for the 95% confidence intervals. However, these confidence intervals indicate all the comorbidity

prevalence percentages, and most of the Waves 3 & 4 percentages for all measures, are not statistically significant estimates of the general population.

4.3.6 Scales

4.3.5.1 Internal consistency.

For GAS and GDS, internal consistency and basic descriptions at Wave 1 are listed in Table 4.11. GAS and GDS both have acceptable Lambda values for internal consistency.

Table 4.11.
Consistency for GAS and GDS at Wave 1(cognitively normal cases).

Measure/Scale	Number of Items	Maximum Guttman's Lambda	Score Mean (SD)	Notes
GAS	9	λ_2 = .783	2.2 (2.308)	
GDS	9	λ_2 = .761	1.64 (1.805)	If item 7 (dealing with waking early) were removed, λ_2 = .802

4.3.5.2 Exploratory factor analyses.

4.3.5.2.1 Goldberg Anxiety Scale.

The nine items of the GAS were analysed using data for Wave 1. Other Waves were also analysed (results not shown) and were found to be approximately consistent with Wave 1. Details of the analysis, including factor loadings, are described at chapter Appendix 4.A. Three factors were identified: Factor 1 – *Worry*: Drawing on items for: keyed-up, worrying, irritable, difficulty relaxing, and worried about health; Factor 2 – *Sleep*: Drawing on items for: difficulty relaxing, sleeping poorly, difficulty falling asleep; and Factor 3 – *Somatic*: Drawing on items for: headaches, trembling, and worried about health. 'Difficulty relaxing' was represented in Factors 1 and 2, and 'worried about health' was represented in factors 1 and 3. No symptoms of anxiety were unrepresented in the factor loadings.

4.3.5.2.2 Goldberg Depression Scale.

The nine items of the GDS were analysed using data from Wave 1. Exploratory factor analysis using Mplus options for binary data were used to ascertain whether there were latent factors underlying the scale. Details of the analysis, including factor loadings, are described at chapter Appendix 4.B. A two-factor solution was found suggesting: Factor 1 – Low energy: Drawing on items for: *Felt slowed up*, and *Lacking energy*; and, Factor 2 – Hopeless: Drawing on items for: *Lost confidence*, *Felt hopeless*, and *Lost interest*. *Waking early* and *Lost weight* were unrepresented in these factors.

4.3.7 Cross-Sectional Correlations with GAS

4.3.7.1 Associations between GAS, age, sex, and education.

Demographic covariates that may influence associations between anxiety and cognitive performance include *age*, *sex*, and *education*. Table 4.12 reports nonparametric correlations between GAS scores and the demographic covariates. At each wave, GAS was positively associated with female *sex*, and negatively associated with years of *education*. There was no association between GAS and *age*.

Table 4.12.
Nonparametric, Cross-Sectional Correlations between GAS (by Wave) and Age, Sex, & Baseline Education

	GAS score correlated with:		
Wave	**Age**	**Female**	**Education**
1	.019	**.131****	**-.072****
2	.023	**.135****	**-.068****
3	.031	**.117****	**-.049***
4	.040	**.092****	**-.051***

Note: * Correlation is significant at the 0.05 level; and, ** at the .01 level, (2-tailed)

4.3.7.2 Cross-Sectional associations between GAS, GDS, and cognitive measures.

For cognitively healthy individuals, nonparametric correlations between anxiety, depression and cognitive measures, by wave, are presented in Tables 4.13 to 4.16. These tables present a pattern of significant correlations between the cognitive measures at each wave. At Wave 1, GAS was positively correlated only with GDS and negatively with SDMT. These two correlations were sustained at all waves, and as time progressed, cross-sectional correlations with GAS included more of the cognitive measures so that by Wave 4, GAS was correlated with all cognitive measures except DB and StW. Most associations between cognition and GAS were weak. Between cognition and GDS, correlations were either medium or weak. Notably, associations between GAS and GDS were at a moderate level throughout all waves.

Table 4.13.
Nonparametric Correlations for Wave 1: Anxiety, depression, and cognitive performance.

Variable	GAS	GDS	SDMT	PPd	PPn	PPb	IR	DR	DSB	StW
GAS	1									
GDS	**.612****	1								
SDMT	**-.073***	**-.112****	1							
PPd	-.030	**-.065****	**.231****	1						
PPn	-.023	**-.065****	**.220****	**.478****	1					
PPb	-.029	**-.063****	**.261****	**.542****	**.564****	1				
IR	-.011	**-.060****	**.265****	**.167****	**.114****	**.146****	1			
DR	.000	**-.041***	**.287****	**.159****	**.116****	**.136****	**.819****	1		
DSB	-.037	**-.071****	**.338****	**.091****	**.078****	**.105****	**.239****	**.223****	1	
StW	-.006	**-.002**	**.329****	**.048***	**.072****	**.077****	**.270****	**.245****	**.313****	1

Notes:
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 4.14

Nonparametric Correlations for Wave 2: Anxiety, depression, and cognitive performance.

Variable	GAS	GDS	SDMT	PPd	PPn	PPb	IR	DR	DSB	StW
GAS	1									
GDS	**.654****	1								
SDMT	**-.063****	**-.104****	1							
PPd	-.021	**-.061****	**.240****	1						
PPn	**-.059****	**-.091****	**.250****	**.553****	1					
PPb	-.014	**-.064****	**.233****	**.599****	**.609****	1				
IR	**-.043***	**-.086****	**.233****	**.153****	**.109****	**.141****	1			
DR	-.030	**-.085****	**.231****	**.162****	**.115****	**.151****	**.812****	1		
DSB	-.038	-.027	**.345****	**.073****	**.081****	**.089****	**.229****	**.188****	1	
StW	.001	.006	**.278****	**.051***	**.084****	**.070****	**.239****	**.239****	**.335****	1

Notes:

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 4.15
Nonparametric Correlations for Wave 3: Anxiety, depression, and cognitive performance.

Variable	GAS	GDS	SDMT	PPd	PPn	PPb	IR	DR	DSB	StW
GAS	1									
GDS	**.595****	1								
SDMT	**-.115****	**-.166****	1							
PPd	**-.087****	**-.137****	**.271****	1						
PPn	**-.078****	**-.109****	**.263****	**.537****	1					
PPb	**-.095****	**-.120****	**.300****	**.583****	**.631****	1				
IR	-.037	**-.068****	**.282****	**.191****	**.162****	**.187****	1			
DR	**-.045***	**-.063****	**.290****	**.189****	**.150****	**.189****	**.819****	1		
DSB	-.030	**-.056***	**.311****	**.090****	**.098****	**.112****	**.224****	**.198****	1	
StW	-.012	-.043	**.269****	**.056***	**.055***	**.081****	**.228****	**.222****	**.338****	1

Notes:
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 4.16
Nonparametric Correlations for Wave 4: Anxiety, depression, and cognitive performance.

Variable	GAS	GDS	SDMT	PPd	PPn	PPb	IR	DSB	StW
GAS	1								
GDS	**.605****	1							
SDMT	**-.096****	**-.142****	1						
PPd	**-.073****	**-.162****	**.282****	1					
PPn	**-.086****	**-.155****	**.307****	**.591****	1				
PPb	**-.083****	**-.140****	**.288****	**.623****	**.648****	1			
IR	**-.056***	**-.082****	**.277****	**.141****	**.131****	**.107****	1		
DSB	-.041	**-.064***	**.311***	**.123***	**.142***	**.167***	**.217***	1	
StW	.008	.024	**.268****	.024	.050	**.061***	**.253****	**.313****	1

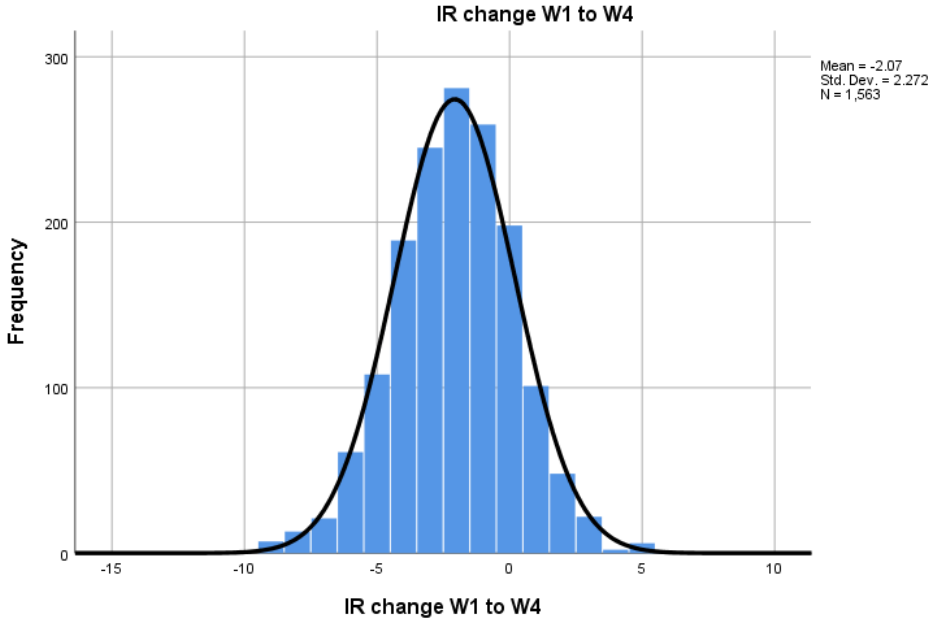
Notes: ** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
DR data were unavailable for wave 4.

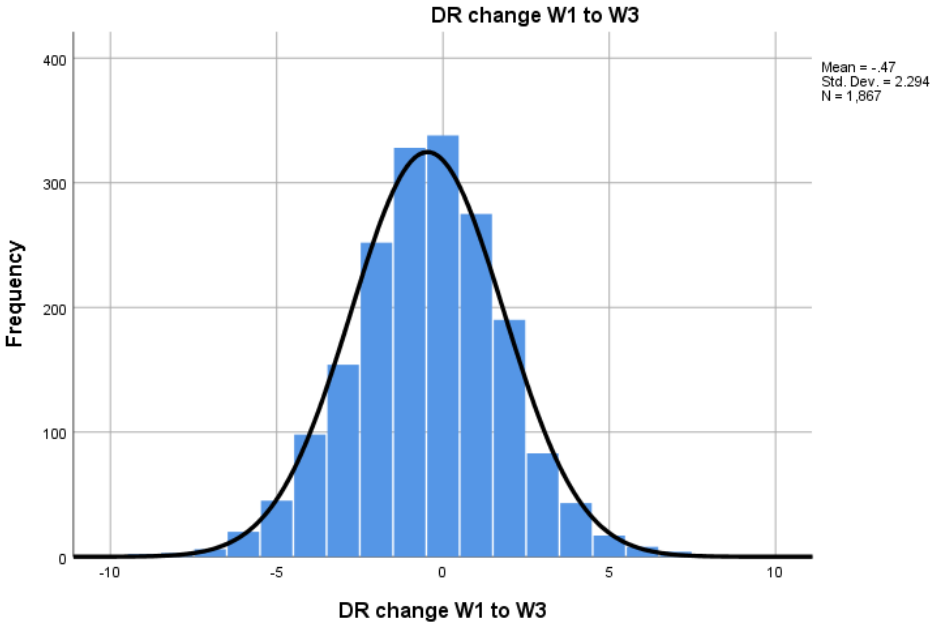
4.3.8 Cognitive Change

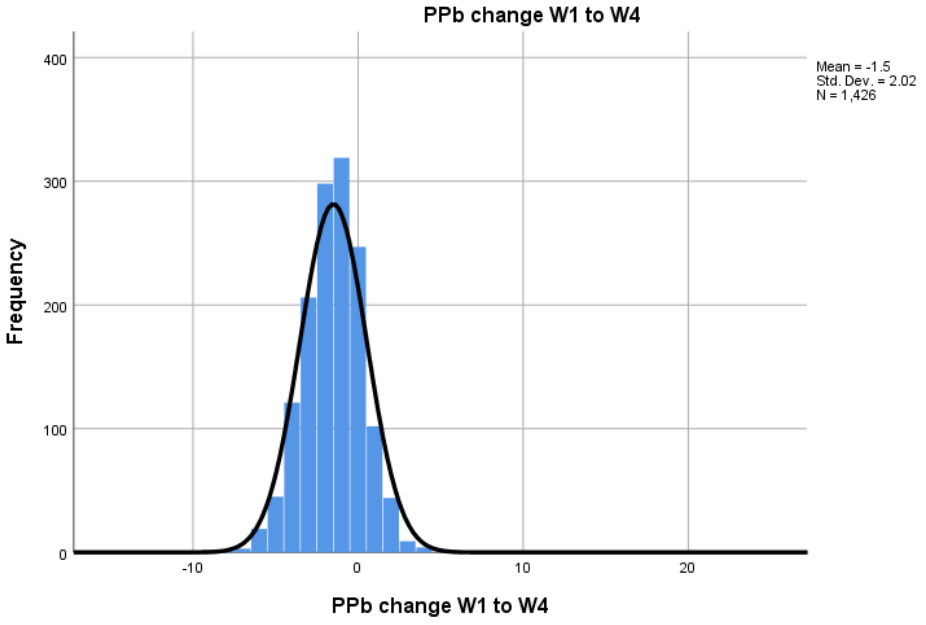
For the key variables, the wave-by-wave change in average cognitive performance was illustrated at Section 4.3.3, and at Figures 4.10 and 4.11, above.

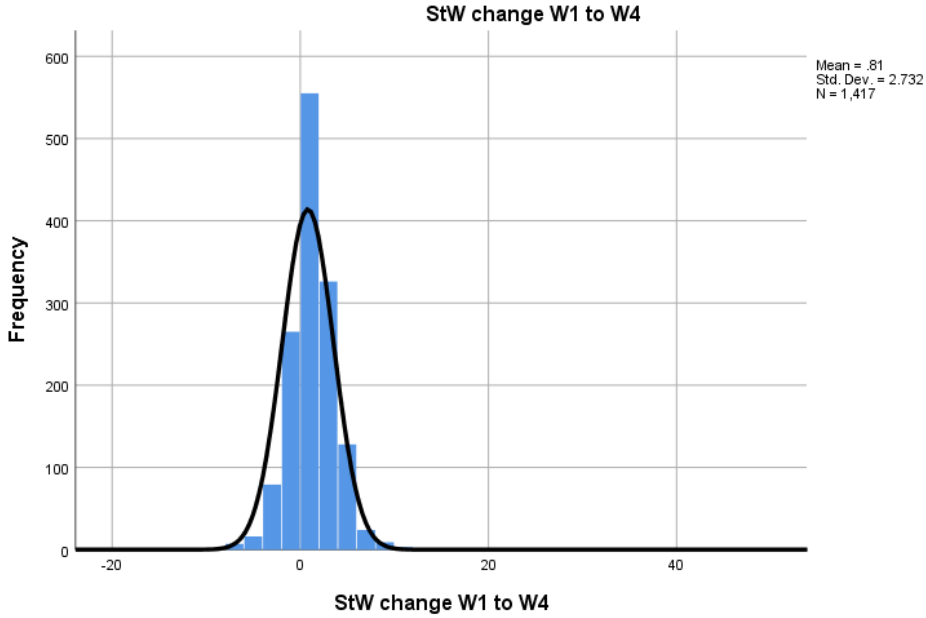
A different perspective on change between Waves 1 and 4 is provided by Figure 4.12 below, which shows frequency distributions of *cognitive change,* calculated as the difference in score (between Waves 1 and 4) for each cognitive variable and for each individual, then graphed as a frequency distribution of these *changes* over time. In each case, the spread of *cognitive change* is roughly, normally distributed. There is a clear shift to lower scores for IR, PPb, and SDMT; and to higher scores for StW; and, remaining cognitive measures were not clearly different after the four waves.

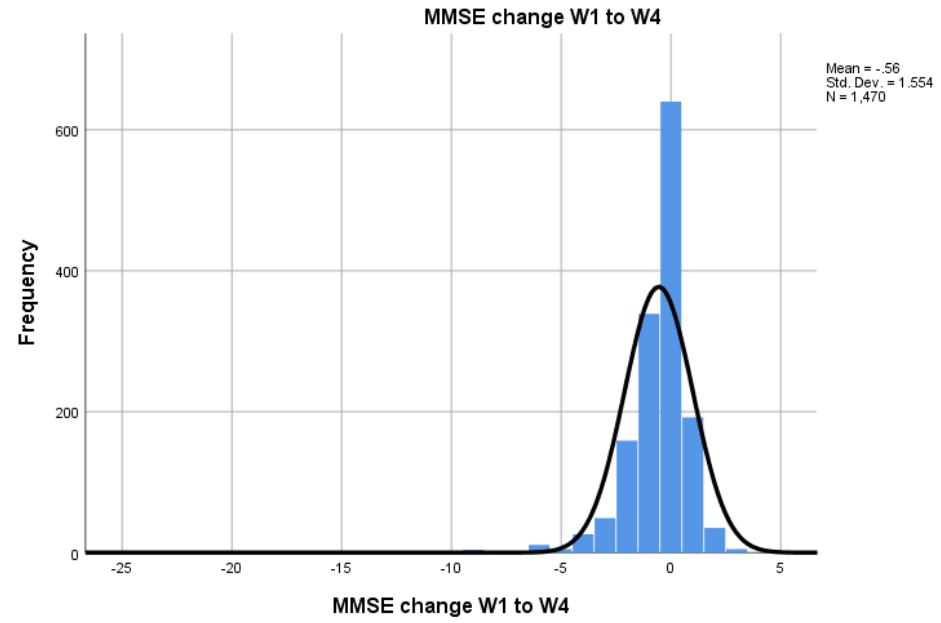
At Figure 4.13 and Table 4.17, trends for incident cognitive impairment indicate a sharp increase in both MCI and, dementia, toward the end of the study time frame.

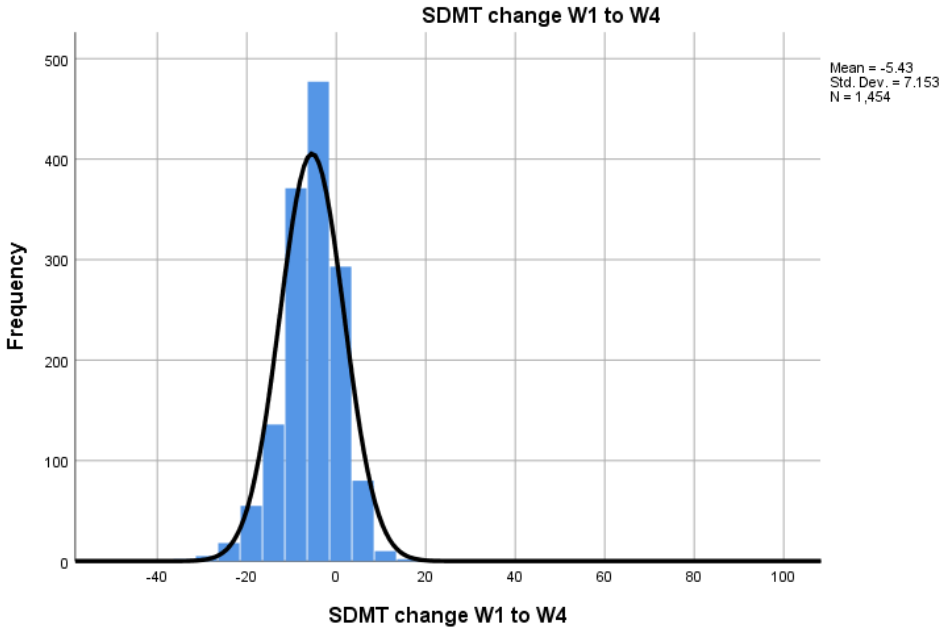

IR change W1 to W4
Mean = -2.07
Std. Dev. = 2.272
N = 1,563
Frequency
300
200
100
0
-15
-10
-5
0
5
10
IR change W1 to W4


DR change W1 to W3
Mean = -.47
Std. Dev. = 2.294
N = 1,867
Frequency
400
300
200
100
0
-10
-5
0
5
10
DR change W1 to W3


PPb change W1 to W4
Mean = -1.5
Std. Dev. = 2.02
N = 1,426
Frequency
400
300
200
100
0
-10
0
10
20
PPb change W1 to W4


StW change W1 to W4
Mean = ,81
Std. Dev. = 2.732
N = 1,417
Frequency
600
500
400
300
200
100
0
-20
0
20
40
StW change W1 to W4


MMSE change W1 to W4
Mean = -.56
Std. Dev. = 1.554
N = 1,470
Frequency
600
400
200
0
-25
-20
-15
-10
-5
0
5
MMSE change W1 to W4


SDMT change W1 to W4
Mean = -5.43
Std. Dev. = 7.153
N = 1,454
Frequency
500
400
300
200
100
0
-40
-20
0
20
40
60
80
100
SDMT change W1 to W4

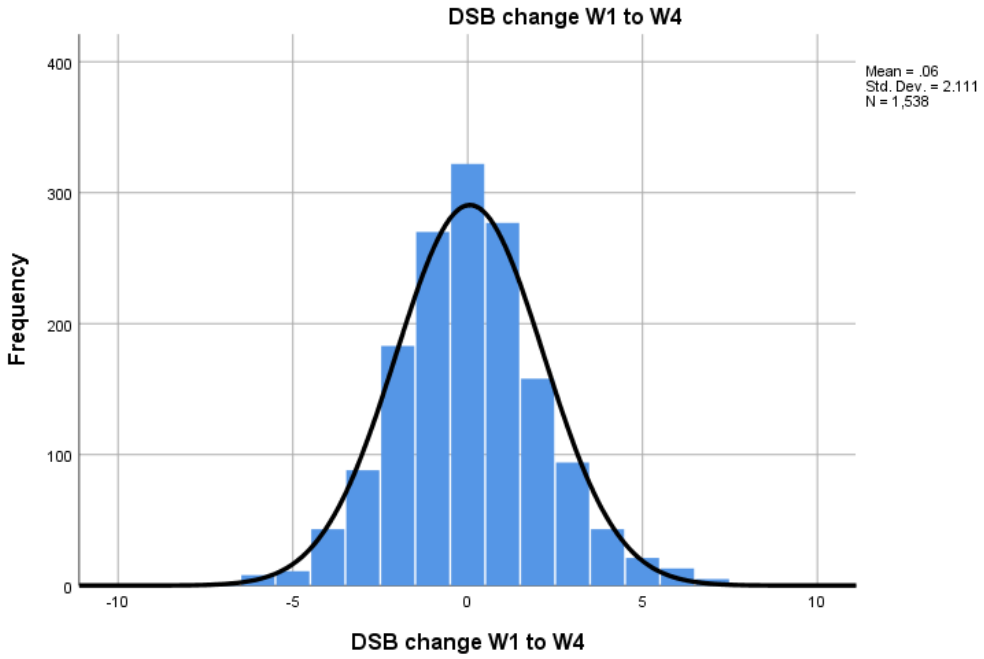


Figure 4.12.
Frequencies of score-changes from Wave 1 to Wave 4, for immediate recall (IR), delayed recall (DR), Purdue Pegboard – both hands (PPb), spot the word (StW), mini mental state examination (MMSE0, symbol digit modalities test (SDMT), and digit span backwards (DSB). Score-changes for DR were from Wave 1 to Wave 3 (Wave 4 data unavailable). For each graph, the normal curve is overlayed for comparison.

In addition to the above measures of cognitive ability, there are also to be considered the incidence of MCI and dementia. Figure 4.13 illustrates the frequencies by wave, of MCI and dementia, for which frequencies are presented at Table 4.17.

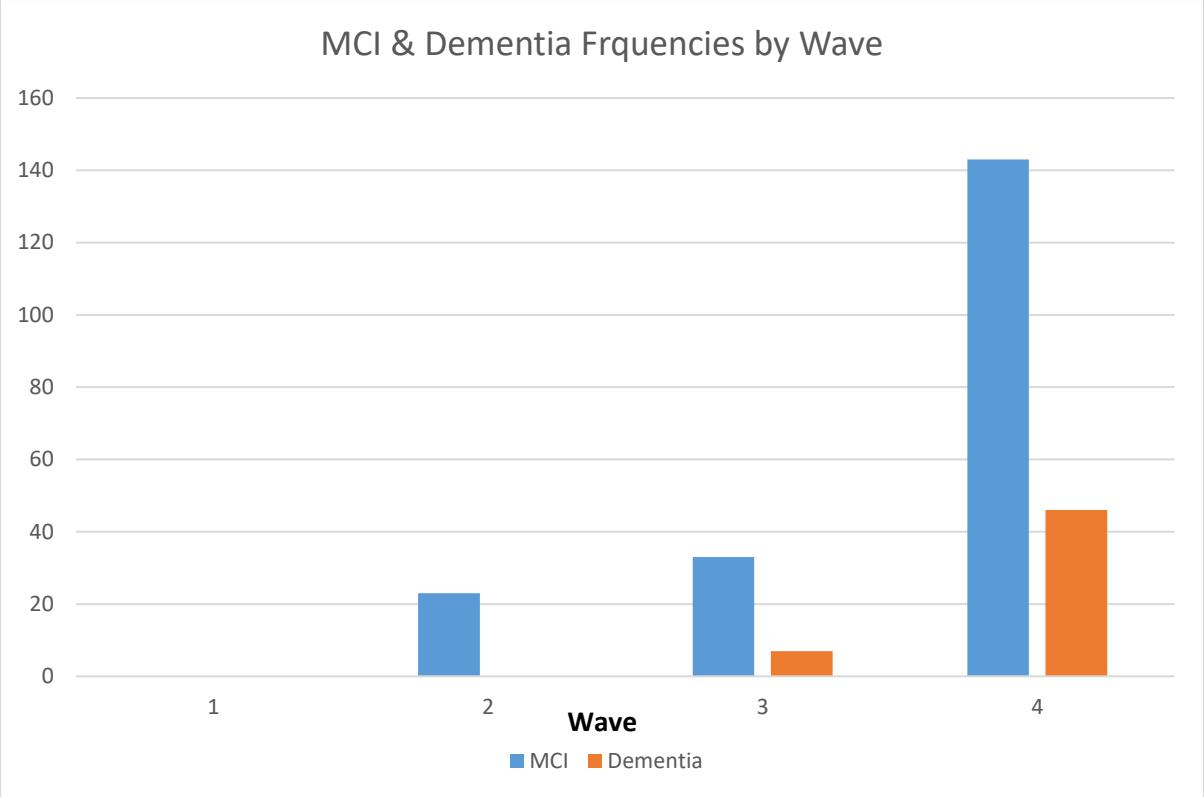


Figure 4.13. Frequencies of MCI and Dementia by Wave

Table 4.17
Frequencies by Wave, Illustrated at Figure 4.13, for MCI and Dementia

	Wave 1	Wave 2	Wave 3	Wave 4
MCI	0	23	33	143
Dementia	0	0	7	46

4.3.9 Confounding Variables

From Table 4.18, there were 14 variables which were associated with both the predictor and the prognostic outcomes (cognitive change), as indicated in the final column, thus indicating potential for confounding effects on associations between anxiety and cognitive change. These are in addition to depression, which has already been established in the literature as a confounder. These additional 15 variables were: *anxiolytics*; *education*; *sex*; *general health*; *physical health*; *mastery*; *physical activity* (at three levels); *positive affect*; *smoker status*; *sleeping problems*; *consulted doctor Re memory*; and *resilience*.

Table 4.18

Nonparametric Correlations of Possible Confounding Variables at Baseline, with GAS and Change (Wave 1 to Wave 4) in Cognitive Functions.

Variable	Baseline Anxiety (GAS)	IR	DR	PPb	StW	MMSE	SDMT	DSB	Correlated with both GAS and any Cognitive Decline? (Y)es or (N)o
Age	.020	**-.087****	**-.077****	**-.053***	-.001	-.030	-.037	-.026	N
Alcohol: hazardous or harmful consumption:	**-.050***	.012	-.014	.034	-.037	.024	.002	.004	N
Anxiolytics	**-.219****	.033	-.023	.022	.036	**.081****	.060*	.005	Y
Benzodiazepines	**.126****	.026	-.006	-.023	.001	-.003	-.010	-.032	N
Education years	**-.073****	.019	-.032	.004	-.046	**.067***	.011	-.012	Y
EPQ Neuroticism	**.498****	.009	.026	-.013	.002	.011	.008	-.030	N
Female	**.130****	**-.052***	.015	**-.058***	.035	**.125****	.009	.015	Y
General Health	**-.370****	.029	.026	**-.099****	.002	**.052***	.051	.022	Y
Physical Health	**-.435****	.035	.021	**.109****	-.005	.043	.053	.025	Y
Life events	**.200****	-.028	-.043	-.026	-.009	.025	-.041	.028	N
Mastery (Wave 4)	**-.380****	.027	.022	.004	.041	**.058***	.021	.031	Y
Negative Affect	**.579****	-.035	-.033	.002	-.030	-.001	-.007	-.026	N
Physical Activity: mild; moderate; vigorous.	**.129****	.049	-.003	-.034	-.014	**-.071****	.014	.000	Y
	.177**	.003	-.005	**-.060***	-.002	-.001	-.042	-.015	Y
	.133**	.005	.038	**-.072****	.032	-.007	-.035	.016	Y
Positive Affect	**-.280****	.031	.013	.006	.035	**.073****	.051	-.017	Y
Smoker: current - n (%); Mean all (SD) never=0; past=1; current=2	**.043***	.007	-.014	.023	-.029	**-.054***	**-.066***	-.030	Y
Social Support general (negative)	**.311****	.0004	-.029	-.030	.009	.-.008	-.038	.063	N

Variable	Baseline Anxiety (GAS)	IR	DR	PPb	StW	MMSE	SDMT	DSB	Correlated with both GAS and any Cognitive Decline? (Y)es or (N)o
Social Support general (positive)	**-.113****	-.016	-.007	-.044	.026	.031	.023	-.002	N
Social Support partner relationship (negative)	**.247****	-.022	-.020	.044	-.030	.006	-.018	-.010	N
Social Support partner relationship (positive)	**-.194****	.000	-.015	-.017	.009	-.058	-.012	-.007	N
Sleep medications Wave 1	**-.277****	.029	.040	.043	.009	-.024	.039	.037	N
Goldberg Wave 1, sleeping poorly	**.611****	-.033	-.028	-.033	.020	.034	-.018	-.020	N
BPH Wave 1, Trouble sleeping	**.543****	-.041	**-.054***	**-.056***	-.001	.014	-.034	-.024	Y
Subjective memory complaint	**-.196****	.016	-.001	-.028	.856	-.022	-.007	-.004	N
Consulted Doctor Re Memory W1	**.221****	.011	-.011	-.026	-.023	-.020	**-.065***	-.005	Y
Resilience Wave 3^	**-.130****	-.018	-.006	**-.079****	.025	.030	.026	-.001	Y
GDS Depression W1	**.613****	-.001	-.028	-.047	-.005	-.049	-.051	-.014	N

Notes. ^Resilience data were unavailable for Wave1; Wave 3 data were used here as a proxy.
* = significant at the p < .05 level; ** = significant at the p < .01 level (2-tail).

4.3.10 Persistently-high-GAS

Table 4.19 reports frequencies by wave, of *persistently-high-GAS* sub-groups from PATH. For the group with high GAS for at least three waves, the numbers of participants at

each wave were constant (at 140) until a reduction in wave 4. For the group with high GAS for at least two waves, the numbers of participants at each wave were constant (at 332) only in Waves 1 and 2, before a reduction in Wave 3. Notable is that by either definition of *persistently-high-GAS* (high for two or more, or for three or more, waves of the four), the group of participants represents only a small subset of the PATH sample. For example, 140 represented just 5.9% of the cognitively healthy, baseline sample.

The associations between persistently-high-anxiety and unavailability at Wave 4 follow-up, is reported at Table 4.20. The positive correlations infer that persistently-high-GAS (for either 2 or 3 waves) is weakly associated with loss to follow-up in Wave 4.

Table 4.19
Frequencies by wave, of cognitively healthy cases at baseline, for which there was a persistently-high-GAS score.

	Present at Wave 1	**Present at Wave 2**	**Present at Wave 3**	**Present at Wave 4**
High GAS for 3 or more Waves	140	140	140	122
High GAS for 2 or more waves	332	332	311	263

Notes: (1) GAS score is defined here as *persistently high* if ≥5 symptoms, present for ≥3 or ≥2 waves; (2) GAS is Goldberg Anxiety Score.

Table 4.20
Nonparametric Correlations between Persistently-high-GAS and Unavailability for Follow-up at Wave 4.

	Persistently-high-GAS for ≥ 2 waves	**Persistently-high-GAS for 3 waves**
Available until Wave 3 only (Unavailable at Wave 4)	.117**	.090**

Notes. The was no significant correlation for the group *Unavailable at Wave 3*.
** Correlation is significant at the 0.01 level (2-tailed).

4.3.11 Chronic GAS

Chronic anxiety, as measured by GAS, is similar to the above explanation of persistently-high-GAS but using the *clinical* cutpoint (symptom count ≥ 7) in place of the *high* cutpoint (≥ 5). Clinical levels of GAS, and its cutpoint, have been previously explained (Section 4.2.4.4).

Table 4.21 reports frequencies by wave, of chronic GAS. For the group with chronic GAS for at least three waves, and for the group with chronic GAS for at least two waves. The cell sizes are small, particularly for the group that exhibited chronic GAS for at least three of the four waves.

The associations between chronic GAS and unavailability at Wave 4 follow-up, is reported at Table 4.22. Chronic GAS was not correlated with unavailability for follow-up.

Table 4.21
Frequencies by Wave, of Cognitively Healthy Cases at Baseline, for which there was a Chronic GAS Score Observed for ≥3 or ≥2 Waves.

	Present at Wave 1	Present at Wave 2	Present at Wave 3	Present at Wave 4
Chronic GAS for 3 or more Waves	31	31	31	27
Chronic GAS for 2 or more waves	86	85	83	70

Notes:
(1) GAS score is defined here as *persistently high* if ≥5 symptoms, present for ≥3 or ≥2 waves;
(2) GAS is Goldberg Anxiety Score.

Table 4.22
Nonparametric Correlations between Chronic GAS and Availability for Follow-up at Wave 4.

	Chronic GAS for ≥ 2 waves	Chronic GAS for 3 waves
Available until Wave 3 only (Unavailable at Wave 4)	-.002	-.002

Notes. There was no significant correlation for the group Unavailable at Wave 3 (data not shown); and, no correlation with Available until Wave 3 (but unavailable at Wave 4) – data shown in table.

4.3.12 Associations with Cognitive Change, for GAS, GAS Items, Derivatives, and Proxies

Table 4.2 described the GAS derivatives and other proxies which are referred to here, in analyses of correlations. Table 4.23 provides Spearman (nonparametric) correlation between GAS and each of the derivatives and proxies at baseline.

From Table 4.23, most correlations were positive and significant at the $p < .01$ level. Exceptions were: the correlation between *BPHQ-anxiety-W2* and BIS (not significant), *and GAS Trichotomised Mild* with most other variables for which correlations were small, or negative, or not significant.

Apart from associations with *GAS Trichotomised Mild*, correlations ranged from .138 (between BIS and GAS-Sleep) to .801 (between GAS and GAS-Worry). The highest correlation between GAS and proxies other than GAS derivatives, was between GAS and *negative affect* (at .579). The proxy, *BPHQ-anxiety-W2* is described at Table 4.2, and is included in these analyses because it represents potentially valuable data even though the measurement was not taken at baseline. The correlation, not shown in the table, between *BPHQ-anxiety-W2* and GAS at Wave 2, was .607 ($p < .001$).

Table 4.24 presents nonparametric correlations between GAS (plus derivatives and proxies), and cognitive change between Waves 1 and 4, for each of the cognitive measures. The table demonstrates only a small number of correlations. The significant correlations appear only for GAS derivatives: (1) *Clinical GAS*, with decline in PPb; (2) *Persistently-high-GAS* subgroup (≥2waves) with decline in PPb; (3) *Persistently-high-GAS* subgroup (≥3waves), with decline in both IR and SDMT; (4) *Chronic GAS* (≥3 waves) with decline in DR; (5) *Trichotomised GAS*, in the low range, with improved PPb, and in the moderate to

severe range, with decline in both PPb and SDMT; and (6) *GAS-Somatic*, with decline in PPb.

Considering this same table (4.24) from the perspective of which cognitive measures were influenced by the GAS derivatives: StW, MMSE, and DSB were not associated with any of the GAS derivatives; IR was associated (negatively) only with *Persistently-High-GAS Subgroup (≥3waves)*; DR was associated (negatively) only with *Chronic GAS* (≥3 waves); PPb was correlated with five GAS derivatives [*Clinical GAS, Persistently-High GAS-subgroup (≥2waves*), *Trichotomised GAS moderate to severe, Trichotomised GAS Low*, and *GAS-somatic*] — these were all negative associations except for *Trichotomised GAS-low range*; and, decline in SDMT was associated with *Persistently-high-GAS subgroup (≥3waves)* and *Trichotomised GAS Moderate* to *Severe*. Effect sizes reflected by the correlations in Table 4.24 were all small.

Table 4.25 reports correlations of baseline GAS, derivatives, and proxies, with Wave 4 incident MCI and dementia plus their sub-categories. Positive correlations were: *Persistently-high-GAS* subgroup (≥3waves) and *Trichotomised GAS* mod*erate to severe*, with *amnestic* and *total* MCI. Various negative correlations are reported in the table. All correlations were with small effect size.

Tables 4.24 and 4.25 are also convenient places to demonstrate correlations between baseline PsD and cognitive change. PsD derived by multiplication was negatively correlated with PPb. Otherwise, there was no association found.

Table 4.26 reports only significant correlations between individual, baseline, GAS items and cognitive change. Decline in PPb over the four waves, was associated with the highest number of GAS items (item numbers: 5, 6, & 9). *Difficulty falling asleep* (GAS item 9) was associated with three measures of cognitive decline, (PPb, SDMT, & DSB). Only GAS item

number 1 (*Keyed up*), was (positively) correlated with MCI at Wave 4. Only GAS item 2, *Worrying*, was correlated with dementia at Wave 4.

There were no substantive correlations (results not displayed) between GAS (or proxies) and cognitive change, for the subgroups of participants who became unavailable for follow-up.

Table 4.23

Nonparametric Correlations between Baseline GAS, Derivatives, and Proxies..

Variable	GAS	Clinical GAS	Persistently-high-GAS subgroup (≥2 waves)	Persistently-high-GAS subgroup (≥3 waves)	Chronic GAS (≥2 waves)	Chronic GAS (≥3 waves)	GAS-Sleep	GAS-Somatic	GAS-Worry	GAS-Trichotomised Mild	GAS Trichotomised Moderate to Severe	BIS	Neuroticism	Negative Affect	Rumination	BPHQ-anxiety-W2^
GAS full sample	1															
Clinical GAS W1	.433**	1														
Persistently-high-GAS (≥2 waves)	.467**	.361**	1													
Persistently-high-GAS (≥3 waves)	.346**	.381**	.620**	1												
Chronic GAS (≥2 waves)	.282**	.495**	.482**	.585**	1											
Chronic GAS (≥3 waves)	.191**	.404**	.286**	.461**	.593**	1										
GAS-Sleep	.655**	.373**	.345**	.253**	.210**	.144**	1									
GAS-Somatic	.730**	.380**	.360**	.283**	.250**	.184**	.309**	1								
GAS-Worry	.801**	.433**	.437**	.437**	.275**	.194**	.370**	.377**	1							
GAS-Trichotomised Mild	.227**	-.269**	-.220**	-.189**	-.141**	-.119**	.020	.180**	.013	1						

Variable	GAS	Clinical GAS	Persistently-high-GAS subgroup (≥2 waves)	Persistently-high-GAS subgroup (≥3 waves)	Chronic GAS (≥2 waves)	Chronic GAS (≥3 waves)	GAS-Sleep	GAS-Somatic	GAS-Worry	GAS-Trichotomised Mild	GAS Trichotomised Moderate to Severe	BIS	Neuroticism	Negative Affect	Rumination	BPHQ-anxiety-W2^
GAS Trichotomised Moderate to Severe	.680**	.557**	.557**	.443**	.337**	.245**	.513**	.503**	.652**	-.483**	1					
BIS	.276**	.150**	197**	.144**	.119**	.098**	.138**	.188**	.273**	.009	.224**	1				
Neuroticism	.498**	.303**	.346**	.283**	.236**	.178**	.259**	.336**	.495**	.010	.408**	.588**	1			
Negative Affect	.579**	.332**	.340**	.254*	.220**	.159**	.264**	.353**	.639**	.020	.467**	.293**	.510**	1		
Rumination	.492**	.283**	.336**	.252**	.215**	.172**	.273**	.359**	.449**	.049*	.384**	.400**	.582**	.509**	1	
BPHQ-anxiety-W2^	.386**	.306**	.439**	.327**	.344**	.245**	.302**	.298**	.281**	-.168**	.302**	.071	.271**	.269**	.286**	1
Cortisol W1	.022	.059	.075	.080	.020	-.002	.032	.003	-.025	-.014	.023	.075	.015	-.022	-.026	-.009

Note: ** = significant at the p < .01 level; GAS= Goldberg Anxiety Scale; BIS= Behavioural Inhibition Scale; GAS-Physical= physical symptoms from the GAS; GAS-Worry= worry item from the GAS. ^BPHQ-anxiety data were available only from Wave 2.

Table 4.24

Nonparametric Correlations of Baseline GAS, Derivatives, & Proxies, with cognitive change from Baseline to Wave 4

Variable	IR	DR	PPb	StW	MMSE	SDMT	DSB
GAS full sample	-.030	.028	-.048	.031	.037	-.039	-.022
Clinical GAS W1	.000	.028	**-.060***	.020	-.022	-.020	-.035
W1 GAS for Persistently-high-GAS Subgroup (≥2 waves)	-.051	-.007	-.095	.034	-.013	-.076	-.032
W1 GAS for Persistently-high-GAS subgroup (≥3 waves)	.017	-.039	-.043	.076	-.087	-.031	-.080
W1 GAS for Chronic GAS (≥2 waves)	.115	.006	.049	.056	-.022	.019	.040
W1 GAS for Chronic GAS (≥3 waves)	.177	**-.375***	.059	.130	-.389	-.171	.126
GAS-Sleep	-.032	-.018	-.045	.025	.033	-.040	-.040
GAS-Somatic	-.018	-.010	**-.054***	.009	.007	-.023	-.010
GAS-Worry	-.018	-.024	-.026	.025	.031	.237	-.010
W1 GAS for Trichotomised GAS Low	-..019	-.055	**-.096***	-.022	.041	.026	.018
W1 GAS for Trichotomised GAS Moderate to Severe	-.007	-.062	-.036	.009	-.096	-.055	-.018
PsDM	-.027	-.037	**-.053***	-.016	-.010	-.043	-.023
PsDA	-.017	-.027	-.048	-.008	-.004	-.049	-.019
BIS	-.015	-.003	-.016	.016	.019	.010	.004
Neuroticism	.009	.026	-.013	.002	.001	.008	-.030
Negative Affect	-.035	-.033	.002	-.030	-.001	-.007	-.026
Rumination	-.022	.001	.008	-.032	-.005	-.024	-.007
BPHQ-anxiety-W2^	-.064	-.047	-.079	.089	-.052	**-.098***	.557
Cortisol	-.018	-.039	-.037	.087	-.046	.005	.025

Note. ^ This row of data was based on Wave 2 established as baseline with no cognitive impairment. BPHQ is approximately normally distributed so correlations are Pearson, parametric correlations.

Table 4.25
Nonparametric correlations of Baseline GAS, Derivatives, and Proxies, with Wave 4 MCI and Dementia

Anxiety or Proxy W1	MCI W4			Dementia (new at) W4		
	Amnestic	Non-amnestic	Total MCI	Alzheimer's disease	Other than Alzheimer's disease	Total Dementia
GAS full sample	-.022	..083	.030	-.096	.000	-.068
Clinical GAS	.086	.023	.090	-.072	-.024	-.071
W1 GAS for Persistently-high-GAS (≥2waves)	.179	-.067	.110	No cases	.018	.018
W1 GAS for Persistently-high-GAS (≥3waves)	.027	-.455*	-.364*	No cases	No cases	No cases
W1 GAS for Chronic GAS (≥2 waves)	-.206	-.086	-.406	No cases	No cases	No cases
W1 GAS for Chronic GAS (≥3 waves)	-.073	-.133	-.387	No cases	No cases	No cases
Trichotomised GAS Low	.473	-.033	-.016	.032	.031	.091
Trichotomised GAS Moderate to severe	.402	.108	-.006	-.082	-.016	-.099
GAS-Sleep	.022	.079	.070	-.122*	.018	-.072
GAS-Somatic	-.033	.018	-.023	-.029	-.019	.000
GAS-Worry	.004	.101	.068	-.056	-.019	-.061
PsDM	.024	.069	.066	-.097	.024	-.062
PsDA	.011	.091	.066	-.094	.016	-.057
BIS	-.049	.068	-.005	-.083	.024	-.056
Neuroticism	.022	.102	.082	-.042	-.012	-.061
Negative Affect	-.010	.095	.049	-.035	0.030	-.027
Rumination	.005	.077	.048	.020	.047	.029
BPHQ-anxiety-W2^	.028	.032	.049	-.152	-.119	-.229
Cortisol	-.038	-.018	-.047	-.147	.041	-.132
GDS Depression	-.029	.082	.023	-.037	.039	.004

Note: Correlations of binary variables are not necessarily meaningful. The next chapter examines these relationships with logistic regression.

Table 4.26
Correlations between Baseline GAS Items and Cognitive Change (Waves 1 to 4) AND Cognitive Impairment Wave4: Showing only Significant Results.

GAS items	PPb	StW	SDMT	DSB	MCI	Dementia
1-Keyed up					.113*	
2-Worrying		.079**				-.118*
5-Sleeping Poorly	-.057*					
6-Head & Neck Aches	-.059*					
9-Difficulty Falling Asleep	-.072**		-.072**	-.055**		

* = significant at the p < .05 level; ** = significant at the p < .01 level (2-tail).

4.3.13 Additional Variables as Potential Moderators or Mediators

Table 4.27 provides the nonparametric correlations between GAS, derivatives, and proxies, on the one hand, and *APOE* e4 carrier status & BMI, on the other. Only BMI was correlated with anxiety proxies (BIS, GAS-Somatic, and rumination) as well as cognitive change (PPb, SDMT). BMI therefore, qualifies as a possible confounder of associations between anxiety and cognitive change. APOE carrier status e4/e4 (homozygous) was unrelated to anxiety measures but was associated with cognitive changes (decline in DR, and DSB, and incident dementia at wave 4).

Table 4.27
Nonparametric Correlations of Additional Variables with Anxiety (and Proxies), and Cognitive Change

Variable	*APOE* e4		BMI
	e4 single Heterozygous	e4/e4 Homozygous	
GAS full sample	-.035	-.005	.035
Clinical GAS	.047	-.028	.011
Persistently-high-GAS Subgroup (≥2waves)	.014	-.004	.031
Persistently-high-GAS subgroup (≥3waves)	.036	-.033	.017
Chronic GAS (≥2waves)	.014	-.027	.012
Chronic GAS (≥3waves)	.064	-.017	.005
Trichotomised GAS Low	-.030	.043	.016
Trichotomised GAS Moderate to Severe	.013	-.051	.013
GAS-Sleep	-.040	-.003	**.052***
GAS-Somatic	.012	-.022	**.053***
GAS-Worry	.005	-.023	-.009
BIS	-.017	.016	**-.058****
Neuroticism	-.004	-.039	-.025
Negative Affect	-.038	-.045	-.004
Rumination	-.064	.007	**.050***
BPHQ-anxiety-W2	.034	-.030	.044
Change in IR	-.030	-.055	-.019
Change in DR	-.025	**-.117***	-.022
Change in PPb	-.035	.048	**-.071***
Change in StW	-.053	-.010	.014
Change in MMSE	.002	-.030	-.024
Change in SDMT	-.043	.018	**-.054***
Change in DSB	.050	**-.106***	-.011
MCI W4	.212	-.095	.001
Dementia W4	.035	**.396****	-.052
Correlated with both anxiety (or proxies) and Cognitive Change.	No	No	Yes

Notes: "Change in" IR etc, refers to change from Wave 1 to Wave 4 in cognitive score. Positive change represents an increased score.

4.3.14 Summary of Results

4.3.14.1 The Sample.

Baseline PATH data for cognitively healthy participants from the 60+ cohort, were analysed over four waves, at four-yearly intervals (12 years).

4.3.14.2 Distributions.

Baseline distributions of key variables were examined for normality. Most were approximately normally distributed. Three variables were distributed nonparametrically. They were GAS, GDS and MMSE. StW was distributed approximately with normal distribution but truncated at the maximum scale score, 1.43 standard deviations above the mean.

4.3.14.3 Prevalence.

Prevalence of *clinical anxiety* (GAS score ≥ 7) at baseline was 6.4% at baseline. Prevalence of *clinical* levels of *depression* (GDS score ≥ 5) was 8.9% at baseline. Prevalence of comorbid *anxiety* and *depression*, by the same measures, was 3.5%. A level of *psychological distress*, described notionally as a "clinical" level, was calculated by two alternative methods for the interaction of GAS and GDS. *Clinical psychological distress* represented either 4.8% or 5.2% of the sample at baseline.

4.3.14.4 Key variables by wave.

By observation of error bars (for parametric data) or box plots (for non-parametric data) across all four waves, there was a downward trend in scores for SDMT, IR, DR, PPb, and no clear trend for GAS, GDS, MMSE, or DSB. StW appears to trend upwards but the baseline distribution of this variable was only marginally normal, so error bar indication of trend over time was not necessarily a valid result, and box plots indicate no trend. There were no other upward trends.

4.3.14.5 Participants unavailable for follow-up.

Comparative group analysis of participants, available and unavailable for follow-up at Waves 3 and 4, revealed unavailable individuals scored lower on most cognitive measures. There were mixed results for differences (between groups) in GAS and GDS scores, earlier in the sequence of four waves.

4.3.14.6 Scales.

GAS and GDS scales were internally consistent. Other variables were not suitable for examination of internal consistency.

Exploratory factor analyses of GAS and GDS revealed latent factors, able to represent both constructs. The latent factors for GAS were: Worry, Sleep, and Somatic. For GDS, latent factors were: Low energy, and Hopeless.

4.3.14.7 Cross-sectional correlations with GAS.

Cross-sectional correlations reported at Tables 4.12 to 4.16, indicated:

1. Wave-by-wave, GAS was positively correlated with female *sex*, and negatively correlated with years of *education*;
2. At Wave 1, the set of cognitive measures are mutually correlated, and correlated with GDS. GAS was not correlated with the cognitive measures except for SDMT. This pattern was repeated at subsequent waves except that GAS became cross-sectionally correlated with more of the cognitive measures, ultimately with all except DSB and StW.
3. GAS and GDS were moderately correlated at each wave.

4.3.14.8 Cognitive change.

For the cognitive measures, the distributions of changes in scores between Waves 1 and 4 indicated a shift, to lower scores for IR, PPb, and SDMT; and to higher scores for StW, and DR. Both incident MCI and dementia escalated sharply over the four waves.

4.3.14.9 Confounding variables.

Fourteen variables were identified as possible confounders to associations between baseline anxiety and cognitive change between Waves 1 and 4. These 14 variables were in addition to GDS (depression). GDS was not established as a confounder for PATH data, in the preliminary analyses at Tables 4.18 or 4.25, but has been identified in the literature as a common confounding variable for associations between anxiety and cognitive change (multiple references to confounding and comorbidity at Chapters One & Two). As a precaution GDS will be included as a potential confounder in PATH analyses. The other 14 confounders are: *anxiolytics*; *education*; *female sex*; *general health*; *physical health*; *mastery*; *physical activity* at three levels; *positive affect*; *smoker status*; *sleeping problems*; *consulted doctor Re memory*; and *resilience*. BMI was added to this list in a subsequent examination of possible, additional moderators and mediators (Section 4.3.13).

4.3.14.10 Persistently-High-GAS.

Participants with persistently high anxiety represented only a small subset of the PATH sample: at baseline there were 140 with high anxiety (using GAS) for at least three of the four waves. *Persistently-high-GAS* was associated with loss to follow-up at Wave 4.

4.3.14.11 Chronic GAS.

Chronic GAS was defined as a clinical level of GAS sustained alternatively for ≥ 2 or ≥ 3 waves of the available 4 waves. The number of cases with chronic GAS, by either definition, was small. Chronic GAS was not associated with unavailability for follow-up.

4.3.14.12 Associations with cognitive change, for GAS, GAS items, derivatives, and proxies.

GAS and all the selected proxies were moderately to highly correlated, cross-sectionally, with each other. GAS (full scale) was not correlated with cognitive change. However, three measures of cognitive decline were associated with six of the GAS derivatives. Notable

among these was that decline in PPb was correlated with four derivatives. The only correlations with Wave 4 dementia were negative, suggesting anxiety may be protective against dementia. Two derivatives [*persistently-high-GAS* subgroup (≥3waves), and *Trichotomised GAS Moderate to severe*] were positively correlated with Wave 4 MCI.

Five of the nine, individual GAS items (at baseline) were correlated with cognitive change. Of these, the most influential appear to be *Difficulty falling asleep* which was negatively correlated with PPb, SDMT, and DSB. Of the cognitive measures, PPb was (negatively) correlated with the most GAS items (*sleeping poorly*, *head & neck aches*, and *difficulty falling asleep*).

4.3.14.13 Additional variables as potential moderators or mediators.

BMI may be an additional confounder of associations between anxiety and cognitive change, and may also be a moderator or mediator.

4.4 Discussion

4.4.1 Main Results

This chapter describes the PATH data for the 60+ cohort and provides a basic analysis. The analyses were mainly by examining distributions and correlations which were cross-sectional (wave-by-wave), and longitudinal, comparing baseline anxiety with cognitive change over the duration of the study. The full GAS scale was not correlated with Wave 1 to 4 change in any of the cognitive scales, and was not correlated with Wave 4, incident MCI or dementia.

The derivatives and proxies for GAS were important to consider because GAS itself offers little prospect of association between anxiety and cognitive change. However, most permutations of these variables, also demonstrated no correlation. The only correlations were with small effect size ($r^2 < .1$). These correlations were mostly with derivatives of GAS (Tables 4.22 and 4.23) rather than with the proxies.

4.4.2 Prevalence

Referring to Table 4.10, prevalence of *clinical anxiety* and *clinical depression* were not directly available from the 60+ cohort of the PATH data because diagnoses were not obtained by the study. The table is based on dichotomised data, using cutpoints of GAS≥7, and GDS≥5. Diagnoses for anxiety and depression were, however, obtained for the middle cohort (aged 52 to 58), during the fourth wave of the PATH study. Kiely and Butterworth (2015) analysed this data for sensitivity and specificity, using Receiver Operating Characteristics curve (ROC) and Area Under Curve (AUC), to identify cut points at which depression and anxiety scores (on the Goldberg scales) would most likely indicate clinical diagnosis. Because their analysis (Kiely & Butterworth, 2015) was not applied to the older age cohort, the results do not necessarily apply to the current project. On the other hand, these authors found that within their sample the results for cut points were not related to the age of the participant. Additionally, the age range of their sample was close to that of the 60+ cohort at baseline).

The *Goldberg Anxiety* or *Depression Scales* are broadly based on symptoms for GAD and Major Depressive Disorder. Comparison of PATH based results with prevalence statistics from other Australian sources, needs to consider not only age and reference period (one month for PATH), but also whether the measures were based on any specific disorder and whether that was comparable with the Goldberg scales. Comparison may also vary, depending on the environment from which the sample was taken. For example, in their literature review on prevalence of anxiety in older adults, Bryant et al. (2008) reported quite different prevalence for *all anxiety disorders* for adults >60, in community samples (1.2% to 15%), and clinical settings (1% to 28%). They attributed these divergent statistics to methodological inconsistencies. They noted the prevalence of *any level of anxiety symptoms* ranged from 15% to 52.3% in community samples. For comparison, PATH cases recording

any GAS score above zero at wave 1, numbered 1,678 (69.42%). Hunt, Issakidis, and Andrews (2002) reported 12-month prevalence of Generalised Anxiety Disorder (GAD) in ≥65-year-old Australians at 3.6% which was based on the Australian National Survey of Mental Health and Well-being (ANSMHW). By comparison, the clinical GAS prevalence results reported in Table 4.10 are 6.4% (CI: 2.5%-10.3%) at Wave 1, reducing to 4.7% (CI: 0.3%-9.1%) at Wave 3. The prevalence of 3.6% from Hunt et al. is not directly comparable to the PATH study results in Table 4.10 because their reporting period was 12 months rather than the one month in PATH. Also, in Hunt et al., the age range started at 65 years and was open ended above that. For PATH, the age range was 60 to 72 years. Anxiety tends to be less prevalent with advancing age over 60 in community settings (Bryant et al., 2008; Hunt et al., 2002). This downward trend is reflected in Table 4.10. For further comparison, McEvoy et al. (2011) also analysed the ANSMHW dataset and concluded, for *any anxiety disorder*, the 12-month prevalence was 5.2% (S.E. 0.7) for 65-74-year-olds, and 2.3% (S.E. 0.7) for 75-85-year-olds. Considering these various results and qualifications, the anxiety prevalence results from PATH data appear plausible, although a precise comparison remains unavailable.

An additional distinction between datasets considered above is that baseline cognitively impaired cases were eliminated from the PATH data. Prevalence estimates from PATH, prior to elimination of cognitively impaired cases at wave 1, would have been 6.9% for anxiety (compared to 6.4% at Table 4.10). Although this is a small adjustment, it contributes to the differences between datasets for comparison purposes.

Australian prevalence of depression was reported by Anstey, von Sanden, Sargent-Cox, and Luszcz (2007), based on the Australian Longitudinal Study of Ageing (ALSA). They reported 14.4% of community-dwelling participants were depressed. Age groups reported included: for 65-69-year-olds, 13.0-13.6% depressed; and for 70-74-year-olds, 11.7-14.2% depressed. Depression was measured in ALSA using the Centre for Epidemiological Studies

Depression Scale (CES-D) which did not have an evaluated and accepted clinical cutpoint. The CES-D instrument was designed to capture symptoms defined for major depressive disorder. The ALSA data included individuals in residential care. Also, the reporting period was one week. Thus, comparison of PATH (8.9% CI: 5.0%-12.7% at baseline) with ALSA (13.0% to 14.2% prevalence) is approximate. By using original PATH data at baseline, not reduced to a cognitively healthy sample, these prevalence statistics are marginally greater at mean = 9.5% (CI: 5.8%-13.2%).

An example of a lower estimate of the prevalence of depression comes from the ANSMHW. Wilhelm, Mitchell, Slade, Brownhill, and Andrews (2003) found the 30-day prevalence was 3.7% (S.E. 0.9) by *DSM-IV* criteria, and 3.9% (S.E. 0.8) by the World Health Organisation, International Classification of Diseases, 10th edition (ICD-10) criteria, in 55-64-year-old Australians. For 65+ year-olds they reported 1.2% (S.E. 0.3) by *DSM-IV*, and 1.2% (S.E. 0.2) by ICD-10. These figures do not include affective disorders other than major depression, and so are directly comparable with both the ALSA and PATH results (PATH used the Goldberg scale which was constructed on the criteria for major depressive disorder). From the available, Australian data, the PATH results appear plausible.

Comorbid anxiety and depression was present at 3.5%, reducing to 2.2% to in the PATH data. Bryant et al. (2008) noted the comorbid condition was at lower prevalence in the aged community and in the Berlin study of 70- to 85-year-olds by Schaub and Linden (2000) ranged from 4.5% down to 2.3% for individuals over 85. In an Australian study, McEvoy et al. (2011) reported comorbidity between major depressive disorder and any 12-month anxiety disorder ranged from about 22% to 34% in age groups which, however, did not demonstrate a trend over age. These figures were drawn from a graphical representation and are approximate. These Australian figures were drawn from the 2007 National Survey of Mental Health and Wellbeing. They are not directly comparable with the PATH data for which

anxiety, measured by GAS, is intended to reflect GAD only (not the full spectrum of anxiety disorders). However, there is a strong contrast between the two sets of figures and, apparently, no unambiguous method to conclusively compare the PATH data, specifically on the comorbidity of GDS and GAS.

The prevalence estimates from PATH, at Table 4.10, include results for PsD, calculated in two ways, as the product and sum of GAS and GDS. Psychological distress has been presented here as the interaction of anxiety and depression. Interaction is ordinarily calculated as a product. So, this form of interaction is reported. However, the literature more typically interprets PsD as the *sum* of anxiety and depression symptoms (e.g., the Kessler Psychological Distress Scale [K10]; Andrews & Slade, 2001). Cutpoints for determining a clinical level of PsD are not published, most probably because clinical PsD is not formally a psychological disorder, as defined by the *DSM-5*. For the Kessler psychological distress scale, there are ten items which present a mixture of anxiety and depression related questions based on experiences in the previous 30 days. Each question was ranked by the participant on a 1 to 5 scale. The score range was 10–50, with mean=14.2, median=12.0. The distribution was heavily skewed (skew=2.2). Although there were no clinical cutpoints presented by Andrews and Slade (2001), they noted 68% or participants scored < 15. These figures are consistent with the additive version of PsD (from PATH) as described at Table 4.5, with similar (negative) exponential distributions.

The calculated prevalence results at Table 4.10, for PsD, are based upon reasonable constructs and are consistent with the literature, even though, as said, there are no published definitions of clinical levels of PsD, nor corresponding cutpoints on published scales.

4.4.3 Derivatives of GAS

Derivatives of GAS were explored here both because each derivative has a specific interest value in discovering relationships with cognitive data, and because the main measure

of GAS was found to be uncorrelated with cognitive change. It, therefore, became necessary to investigate more deeply to determine if these derivatives offered insights into associations with cognitive ageing. Comments on each derivative follow.

4.4.3.1 Persistently-high-GAS.

Table 2.2 listed 37 studies accepted into the literature review, and demonstrated that 33 of these 37 did not specify *trait* anxiety as the key variable for testing associations with cognitive decline or CI. Instead, these 33 studies used a measure of *state* or *temporary* anxiety, or did not specify the duration of anxiety. Cases with *persistently* high anxiety are theoretically more likely to be associated with cognitive decline (Chapter One).

In this context, persistent means continuing over a long period of time. Persistence is not necessarily about continuity, but if there were a short-term reduction in the severity of the condition then persistence would imply the return of the higher-level condition. The word "persistent" is used here in place of "trait" anxiety. The concepts are similar. However, trait anxiety has been operationalised in a specific way by the State-Trait Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970). By referring to ongoing anxiety as "persistent", I draw on a wider and more generalised interpretation, not limited by the rich history of literature on the single concept of trait anxiety.

Persistently high anxiety is also distinguished from chronic anxiety, which implies a persistent, clinical level of anxiety (See below, Section 4.4.3.2). The statistical analyses in this thesis benefit from drawing on both concepts of: high anxiety (cutpoint of five symptoms which is equivalent to ≥1 SD above the mean); and, clinical anxiety (seven symptoms). Clinical anxiety has the benefit of identifying a level of anxiety recognised as a category which can be compared with other research. However, as noted, the cell sizes in the PATH data for chronic anxiety (persistently, clinical level), were small. The slightly lower cutpoint for high anxiety allowed a more useful sub-sample for analysis.

The two alternative calculations of *persistently-high-GAS* identified individuals who had experienced five or more symptoms, for ≥ 2 waves, or for ≥3 waves of the data. These alternatives allowed larger cell sizes for the 2-wave version, and greater persistence for the 3-wave version which might (theoretically at least) have related more strongly to cognitive change.

Each measurement of GAS referred only to the previous four weeks and so it was possible that the participant would have lower levels or no anxiety at other times, but as a population average the likelihood that these individuals had more of a persistent condition, appeared plausible, provided the condition was repeatedly observed.

The persistence of the condition and the change in cognitive ability were measured over the same 12 years of the study. This might suggest the anxiety cannot be assumed to predict the cognitive change. However, baseline data have been established as clear of CI. If subsequent waves included causal effects in both directions (anxiety causes cognitive decline and CI, and decline or impairment triggers anxiety), then this is precisely what would be expected from the model at Figure 1.5. Identifying the class of individuals who have persistently high anxiety, by drawing on the data for all four waves, does not invalidate the possibility of predictive association between baseline GAS and cognitive change.

4.4.3.2 Clinical & Chronic GAS.

As described in Methods (Section 4.2.4.9.4), the clinical level of GAS was defined as a symptom score ≥7. Chronic GAS levels, means persistently, clinical levels of GAS. Baseline *clinical GAS* was examined and found to have no significant associations except with decline in DR between baseline and Wave 4 (Table 4.24). For *Chronic GAS*, the cell sizes for the correlations were small, as indicated by the frequencies for chronic GAS at Table 4.21. The only correlation with cognitive change was with DR (Table 4.24). These two correlations (for clinical and chronic GAS) with DR will be considered in later chapters. However, like

persistently-high-GAS (Section 4.4.2.1 above), any correlation between *chronic GAS* and cognitive decline would be calculated over the same period of time and therefore would not qualify as indicative of whether anxiety predicts cognitive change.

Prevalence of the clinical level of GAS is discussed below at Section 4.4.5.

4.4.3.3 Latent factors of GAS.

Exploratory factor analysis of the GAS scale was carried out to identify latent factors which may usefully represent GAS as derivatives, or help to explain effects of important components of GAS. Similar factor analyses for comparison in the literature appear to be unavailable. Published analyses have been for the full Goldberg Anxiety and Depression scale of 18 items, and which have been confirmatory factor analyses to investigate the validity of the anxiety and depression components as the dominant latent factors (e.g., Christensen et al., 1999; Goldberg et al., 1987). Details of the factor analysis (for this thesis) of the GAS scale are provided at the Appendix 4.A, and a summary follows here for each factor.

4.4.3.3.1 GAS-Sleep.

The sleep, latent factor was identified at Appendix 4.A as factor 2, comprising two items: 5 (*sleeping poorly*; loading: 0.764), and 9 (*difficulty falling asleep*; loading: 0.745). This factor was unrelated to cognitive change (Tables 4.24 & 4.25), although *sleeping poorly*, as an individual item, was related (weakly) to decline in PPb (Table 4.26). This last point is explored further below at Section 4.4.9.

4.4.3.3.2 GAS-Somatic and GAS-Worry.

These two factors are considered here together because of the earlier observation (Section 1.2.2) that the (relatively) recently developed, Geriatric Anxiety Inventory (Pachana et al., 2007) put more emphasis on physical symptoms than on worry, which was supported by Gonçalves, Pachana, and Byrne (2011) and Miloyan and Pachana (2015). Correlations at

Table 4.24 show GAS-somatic was indeed associated (weakly) with cognitive decline (PPb only), whereas GAS-Worry was not. But this is small evidence of association, and therefore, no conclusion is drawn here from the PATH data on these alternatives of *somatic* and *worry* symptoms.

GAS-Somatic was comprised of items: 6 (*head & neck aches*, loading: .312), 7 (*trembling, tingling, dizzy spells, sweating, diarrhoea, frequent urination*, loading: .671), and 8 (*worried about health*, loading: .421). As such it has a scattered content and although named here as "Somatic" it is not purely a physical construct. GAS-Worry was comprised of items: 1 (*Keyed up*, loading: .774), 2 (*Worrying a lot*, loading: .695), 3 (*Irritable*, loading: .568), and 4 (*Difficulty relaxing*, loading: .483). Again, this is not purely about "worry", although it is close. Among these individual items, 1. *Keyed-up*, 2. *Worrying*, 6. *Head & Neck Aches*, had individual associations (mostly weakly) with cognitive change (Table 4.24).

4.4.3.4 Trichotomised GAS.

Another derivative of GAS was *Trichotomised GAS* [*zero*, *low* (GAS=1 to4), and *moderate to high* (GAS≥5), (as referred to previously at Section 2.3.2.1, and citing Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, & Cauley, 2017; Kassem, Ganguli, Yaffe, Hanlon, Lopez, Wilson, Ensrud, et al., 2017)]. Kassem found low symptom levels of GAS had a stronger association with cognitive change than moderate to severe levels. The PATH data demonstrated the reverse result, with low range GAS positively correlated with PPb, and higher range GAS negatively associated with both PPb and SDMT (Table 4.22). These results inferred that low symptom levels were associated with *improved* PPb results after four waves, and higher symptom levels were associated with *decline* in both PPb and SDMT scores. Thus, the PATH data, contrary to Kassem's results, accord with dose-response expectations.

4.4.3.5 GAS items.

Other components of the GAS worthy of consideration are the individual items. Like the derivatives and proxies, the items were individually tested for correlation with cognitive change (Table 4.26). Five of the available nine items were correlated (all negatively) with at least one measure of cognitive change, implying that each of these items may be a predictor of cognitive decline. *Worry* and *difficulty falling asleep* predicted two and three measures of decline, respectively. The other items predicted only one measure of decline. Again, however, each correlation was with small effect.

4.4.4 Proxies for Anxiety

The derivatives of GAS reported above could serve as proxies. Other proxies (listed at Table 4.2) were found to correlate with GAS, its derivatives, and with each other. They appear prima facie, therefore, to represent similar constructs to GAS and serve as alternative measures for anxiety. Unlike the derivatives, however, the proxies were mostly uncorrelated with changes in cognitive ability or with incident cognitive impairment. This suggests that it may not be anxiety which is a predictor of cognitive change but instead some selective elements of the anxiety measures (as described by the derivatives).

4.4.5 Participants Unavailable for Follow-up

Individuals who did not remain available for the study to Wave 4, scored lower on most cognitive measures. In the two-group comparisons to derive these results, there were mixed findings regarding relative levels of anxiety and depression for these same individuals. However, there was indication that unavailability at Wave 4 was related to persistently-high-GAS (Table 4.20). Contrary to this last finding, in their investigation of comorbid anxiety and depression in late life, DeLuca et al. (2005) noted that anxious participants were less likely to discontinue from their longitudinal study than non-anxious participants. On the other hand, Bierman et al. (2008) reported individuals with higher symptom count for anxiety and lower

cognitive performance were more likely to discontinue, which was consistent with the PATH data, on both counts. Whether individuals are more or less likely to become unavailable for follow-up may be peculiar to the nature of the sample and the study.

4.4.6 Cognitive Change

Graphs at Figures 4.11 and 4.12 present in different ways, the changes over time in cognitive scores. Figure 4.11 presented error bars for the means at each wave; Figure 4.12 presented distribution of the changes from Waves 1 to 4. There is agreement between these methods that there was decline in IR, PPb, and SDMT; and average improvement to higher scores for StW. Change in DR is not apparent at Figure 4.12 but is clear at Figure 4.11. There is agreement that there was no change in DSB.

For the 60+ cohort, an average decline in cognitive abilities over the 12 years of the PATH study was to be expected. For StW, average improvement in scores may be because recognition of real words in contrast to made up words would be largely a reflection of knowledge, and not only a measure of cognitive processing (reasoning, processing speed etc.). Older individuals tend to preserve such knowledge based abilities, or even improve on them (Horn & Cattell, 1967).

4.4.7 Confounders

From Table 4.18, there were 14 confounders identified. Additional to these 14 variables, are depression and BMI which were identified elsewhere.

Significant correlations were small and in some instances not in the expected direction. For example, *subjective memory complaint* was negatively correlated with baseline GAS, implying that a lower level of *subjective memory complaint* was associated with greater level of anxiety. Contrary to this result was that *consulting a doctor regarding memory* (at Wave 1) was positively correlated with baseline GAS. From these results, *subjective memory complaint* could be in error.

4.4.8 Cross-sectional correlations with GAS

The main implications from cross-sectional correlations are:

- GAS was only weakly correlated with cognitive measures, with possible implications for GAS in association with change in cognition; and
- GAS and GDS were moderately correlated at each wave, implying potential for multicollinearity issues in regression analyses in the following chapter.

4.4.9 Associations with Cognitive Change, for GAS, GAS Items, Derivatives, and Proxies

Unadjusted associations identified between baseline anxiety measures and cognitive change were summarised at Section 4.3.14.12. These were all with small effect size. Notwithstanding these small effects, further investigation (in Chapter Five) is warranted to consider whether deeper analysis might eliminate or explain these associations.

There was a cluster of associations with decline in PPb, reported at Tables 4.24 and 4.26. Although all were with small effect and were unadjusted, they are worth noting. These associations were with baseline values for: *Clinical GAS, GAS-Somatic*; lowest level of *trichotomised GAS*; PsDM (Psychological distress); and, GAS items 5-*sleeping poorly*, 6-*head and Neck Aches*, and 9-*Difficulty Falling Asleep*. However, as noted in the following chapter, all of these, except GAS items 2 and 9, were eliminated at the next step of analysis by inclusion of adjustment for the basic confounding variables, *sex, age, education*, and *depression*. GAS items 2 and 9 were also eliminated by subsequent adjustments presented in Chapter Five. So, although there appears to be a pattern of associations with PPb, none of these apparently related variables was worth pursuing beyond the next steps in analysis.

4.4.9.1 Covariates warranting further investigation.

Sex, age, education, and GDS were the key covariates in previous related studies. If sufficient unexplained variance remains after regression models including these covariates,

then additional covariates of interest have been identified above which can be selectively evaluated. Relevant covariates, identified above, are: *anxiolytics*; *general health*; *tobacco use*; *alcohol consumption*; *life events*; *social support*; *resilience*; *positive affect*; *mastery*; *physical health*; *physical activity*; *consulted a doctor Re. memory*; APOE e4 carrier status; and, BMI. Of these, APOE e4 was unrelated to anxiety (in all its measures at Table 4.27), eliminating APOE as a confounder. Also, BMI was not related to the full GAS measure. BMI was, however, related to both GAS derivatives or proxies and cognitive change (Table 4.27). Therefore, BMI remains of interest as a possible confounder, but only temporarily so. At Chapter Five, all associations between GAS derivatives and proxies and cognitive change, will be eliminated from further examination as contributing to associations between anxiety and cognitive ageing. Thus BMI, as a potential confounder, becomes redundant. *Resilience* was measured only in Waves 3 and 4. Therefore, this variable was not considered relevant when adjusting regressions for baseline covariates.

4.5 Conclusion

The few correlations reported between baseline anxiety and cognitive change were with small effect size. The following chapter will examine these identified correlations more closely to determine if they are attenuated when adjusted for likely confounding variables and when repeated measures of the dependent variables are considered.

CHAPTER FIVE:

Is Anxiety a Baseline Predictor of Cognitive Ageing?

Abstract

Background: This chapter considers correlations identified at Chapter Four, between *baseline* anxiety, (including Goldberg Anxiety Scale (GAS) items, GAS derivatives, and anxiety proxies) and cognitive change.

Methods: For each such correlation found significant, adjusted regression analyses were applied. Then, adjusted Generalized Estimation Equations (GEE) were deployed for further analysis if significant results were reported from the regression models. For these GEE models, repeated measures were included for the outcome variables but not for predictors which were always included only at baseline values.

Results & Conclusion: No anxiety-related, fully adjusted, baseline predictor was associated with cognition or cognitive impairment.

5.1 Introduction

The goal of this chapter is to complete an analysis commenced in the previous chapter, to discover if *baseline* anxiety predicts age related cognitive change. This focus on baseline predictors was a common method of previous studies (e.g., Brodaty et al., 2012; DeLuca et al., 2005; Jessen et al., 2010; Palmer et al., 2007; Somme, Fernández-Martínez, Molano, & Jose Zarranz, 2013). Analytical methods using baseline predictors only, were principally multivariate, linear, and logistic regression. These studies typically examined cognitive change as either the difference in score between baseline and follow-up, or incidence of cognitive impairment. For explanation of variance, most studies also considered the effects of covariates: age, sex, education, and depression.

In this chapter, I will analyse the PATH data by similar methods. For significant associations found from these methods, I will also examine: (1) The effects of adjustment for additional covariates as identified in the previous chapter; and, (2) Whether modelling by General Estimating Equations (GEE) reveals a different association when repeated measures for cognitive change are considered, but the predictor variable is held constant at baseline value.

The focus on baseline anxiety is adopted here despite the strong theoretical argument in Chapter One that incident or state anxiety was not expected to be causative of cognitive ageing. The proposition, partly explained by the heuristic at Figure 1.5, was that *state* (or enduring) anxiety would be required to provide the necessary long term, neuropsychological effects. However, the baseline associations in the PATH data must still be known and understood. Also, because many past studies have been done this way, it will be necessary to determine these baseline associations from PATH, in order to make comparisons with the earlier studies.

At Chapter Four (Tables 4.24 to 4.26), baseline GAS and *proxies* for anxiety were found not to be correlated either with change in cognition or with incidence of cognitive impairment. The single exception (an alternative measure of anxiety) was BPHQ-Generalised Anxiety Disorder, which was measured only from Wave 2. *Derivatives* of GAS found to correlate with cognitive change were: Clinical GAS; Chronic GAS (≥3 waves); GAS-Somatic; GAS-Sleep; Persistently high GAS (≥3 waves); Trichotomised GAS (Low); and Psychological Distress (by multiplication of anxiety and depression scores). There were also GAS items (1, 2, 5, 6, & 9) which were individually correlated with cognitive change (Table 4.26). Only these associations are explored in this Chapter.

5.2 Methods

5.2.1 Research Questions

In context of the thesis overall, Chapter Three, delineated the research questions for this present chapter. Both primary research questions (Section 3.2.2.1), and Secondary Research Question A (Section 3.2.2.2.A), apply here. Collectively, these research questions required investigation of whether *baseline* anxiety predicts either the rate of cognitive decline or the incidence of cognitive impairment.

5.2.2 Statistical Analysis

More specifically, Table 3.1 required testing by multivariate linear and logistic regression, hierarchical multilevel modelling, structural equation modelling, and moderation and mediation analysis, where appropriate. However, as the results will demonstrate below, significant associations were limited to regression outcomes. Thus, the more advanced analyses were not attempted after associations were found to be attenuated.

Where results remained significant after adjustment for the basic list of covariates (*age, sex, education*, and *depression*), the model was tested with additional variables as covariates identified at Section 4.4.9.1, and their possible effect sizes were mooted by correlations at

Tables 4.18 and 4.27. Among these variables, and considering the effect sizes, the most likely covariates to influence the relevant associations appear to be *Physical health*, *Anxiolytics*, *Mastery*, *physical activity*, *consulted a doctor Re. memory*, and *smoking status*. Although this is not a complete list (from Section 4.4.9.1), it will be established below as sufficient to demonstrate attenuation of all the possible associations examined.

For analysis of the predictor variable BPHQ-Generalised Anxiety Disorder, Wave 2 data were reset as baseline and all cases with cognitive impairment were removed. "Baseline" covariates were selected from the Wave 2 data. Cognitive change was identified as the difference between baseline and Wave 4 scores for each variable representing cognitive performance by domain.

SPSS software version 25 was used throughout. Significance was determined by reference to 95% confidence intervals.

5.2.2.1 Multivariate linear regression.

For each of the significant correlations identified earlier (Chapter Four), multivariate linear regression was applied to baseline GAS and its proxies and derivatives, as predictors, and cognitive change within cognitive domains as outcome variables.

5.2.2.2 Logistic regression.

For regression analysis involving binary dependent variables, analysis was performed using SPSS binary logistic regression.

5.2.2.3 Generalized Estimating Equations.

For associations found significant upon adjusted multivariate linear regression, further testing was applied. SPSS Generalized Estimating Equations (GEE) were deployed, with repeated measures for the dependent variable only. Mixed models were not required for obtaining random effects because the models were attenuated at basic levels.

5.3 Results

Most regression models produced results indicating that *sex*, *age*, *education*, and baseline GDS (depression), attenuated any initial association. These non-significant results are not presented here. The remaining (significant) associations were only for individual GAS items and for BPHQ- Generalised Anxiety Disorder (Wave 2), and are listed at Table 5.1. After configuring Wave 2 as baseline (for this single special model (5) involving BPHQ-Generalised Anxiety Disorder) by removal of cases with cognitive impairment, the remaining sample size was 2005.

Table 5.1
Significant Results from Multivariate Linear Regression Models for possible Associations Implied by Correlations Reported at Tables 4.24 to 4.26. Adjusted for Sex, Age, Education, and Baseline Depression.

Model #	Source Table	IV (Baseline Predictor)	DV	Re-gression Type	Coeffic-ient (95% CI)	Signifi-cance *p* =	Beta	Exp(B) (95% CI)
1	4.26	GAS item 2: Worrying	StW change W1–W4	MVLR	**0.899 (0.808 – 1.238)**	**.000**	**.130**	
2	4.26	GAS item 2: Worrying	Dementia by Wave 4	LR	**1.290**	**.017**		**3.632 (1.254 – 10.524)**
3	4.26	GAS item 9: Difficulty falling asleep	SDMT change W1–W4	MVLR	**-1.026 (-2.027 – -0.025)**	**.045**	**-0.057**	
4	4.26	GAS item 9: Difficulty falling asleep	DSB change W1–W4	MVLR	**-0.334 (-0.109 – -0.041)**	**.026**	**-0.062**	
5	4.24	BPHQ_GAD W2^	SDMT change W2–W4	MVLR	**0.634 (0.243 – 1.025)**	**.002**	**0.207**	

Notes: MVLR = Multivariate, linear regression; LR = Logistic regression; IV = Independent Variable; DV = Dependent Variable; GAD = Generalised Anxiety Disorder. For Model 5, Wave 2 was redefined and reconfigured as baseline. Covariates were drawn from this new baseline.

SDMT is the only DV represented more than once in Table 5.1. Predictors for SDMT were GAS item 9 (difficulty falling asleep) and BPHQ-Generalised Anxiety Disorder, but these variables predicted change in opposite directions – decline for GAS item 9, and improvement for BPHQ-Generalised Anxiety Disorder. GAS item 9 (difficulty falling asleep) also predicted a decline in DSB. GAS item 2 (worrying) predicted an improved score for StW, and an increased incidence of dementia by Wave 4.

Adjustments for additional, relevant covariates, were applied to these models (1 to 5; at Table 5.1), providing the results at Table 5.2.

Table 5.2
Regression Applied to Models in Table 5.1; Adjusted for additional covariates

Model # (from Table 5.1)	IV (Predictor) Wave 1	DV	Adjusted for:	Coeffic-ient (95% CI)	Signifi-cance *p* =	Beta	Exp(B) (95% CI)
1	GAS item 2: Worrying	StW change W1–W4	Sex, Age, Education, **Depression**, Consulted doctor Re. memory, Physical health, Anxiolytics, Mastery, Physical Activity, and Smoking Status.	**2.447 (0.734 – 4.161)**	**.005**	**.277**	
2	GAS item 2: Worrying	Dementia by Wave 4	Sex, Age, Education, Depression.	.987	.060		2.683 (.959 – 7.504)
3	GAS item 9: Difficulty falling asleep	SDMT change W1–W4	Sex, Age, Education, Depression, Consulted doctor Re. memory,	.246 (-2.333– 2.825)	.851	.016	
4	GAS item 9: Difficulty falling asleep	DSB change W1–W4	Age, Sex, Education, Depression, Consulted doctor Re. memory.	.021 (-0.791 – 0.832)	.960	.004	
5	BPHQ_GAD W2	SDMT change W2–W4	Age, Sex, Education, Depression, Consulted doctor Re. memory.	.543 (-0.223 – 1.309)	.162	.220	

Notes: IV = Independent Variable; CV's = Covariates; DV = Dependent Variable; GAD = Generalised Anxiety Disorder; Significant variance was explained by the bolded covariates.

From Table 5.2, Model 1, GAS item 2 (Worry) remained associated with StW (score change between waves 1 and 4) after full adjustment. Worry was no longer associated with incident dementia (by Wave 4; Model 2). GAS item 9 (difficulty falling asleep) was no longer associated with decline in SDMT (Model 3) or DSB (model 4). BPHQ-Generalised Anxiety Disorder no longer predicted change in SDMT.

Model 1 was explored further to determine if repeated measures for dementia, rather than the simplified dementia by wave 4, would clarify whether the association between GAS item 2 and dementia was sustained. For this purpose, GEE was deployed, with outcome variable of incidence by-wave for dementia, but relaying only on baseline measures of GAS item 2.

Table 5.3
GEE Applied to Model 1 only, from Tables 5.1 & 5.2.

Model # (from Tables 5.1 & 5.2)	IV (Predictor) (Baseline value as a constant)	DV By repeated measures (Waves 1 to 4)	Adjusted for Additional CVs	B	SE	95% CI	*P* For Predictor
1	GAS item 2: Worrying	StW	Sex, **Age**, **Education**, Depression, **Consulted doctor Re. memory**.	.457	.636	-.790 – 1.705	.472

Notes: IV = Independent Variable; CV's = Covariates; DV = Dependent. Bolded variables in the adjustment column indicate significant effect on the DV.

From Table 5.3, Worrying (GAS item 2) was no longer a significant predictor.

5.4 Discussion

After correlation analysis (previous chapter) then fully adjusted, linear, and logistic regression, only one variable, an item of the GAS scale, remained associated with cognitive change. This was: GAS item 2 (worrying), associated with change in StW between Waves 1

and 4. However, this association was not sustained in GEE analysis, accounting for repeated measures of the dependent variable (Table 5.3).

Analysis reported at Table 5.3 adopted an unusual approach for analysis of repeated measures of the outcome variable while holding the predictors at baseline values. This was specifically to highlight the results obtained when referring to the baseline measures. Such method is not without precedent within the literature reviewed at Chapter Two. For example, Pietrzak et al. (2014) applied multilevel modelling using only a baseline measure of anxiety as the main predictor.

The analysis of associations with GAS items (for example, by accounting for repeated measures of the predictor variables) will be taken no further here for two reasons. Firstly, these individual items are of limited interest. They do not fully represent the construct of anxiety. And secondly, they are binary indicators, which, therefore, carry little information.

5.5 Conclusion

Possible associations of cognitive change with baseline anxiety, derivatives, and proxies, have been eliminated progressively by the series of analyses commencing with correlations in Chapter Four, then regression and GEE. Referring only to *baseline* measurements as predictors of cognitive change, there is no association (in the PATH data) with cognitive ageing. In the next chapter, I will investigate the time-varying influence of anxiety, referring to the repeated measures of the full GAS scale.

CHAPTER SIX:

As a Time-Varying Variable, Does the Goldberg Anxiety Scale Predict Cognitive Ageing?

Abstract

Background: Investigation of possible associations between *baseline* representations of anxiety, and age-associated cognitive change, were presented in earlier chapters. The current chapter reports investigation of *repeated measures* of the Goldberg Anxiety Scale (GAS), which is the primary representation of anxiety within the PATH data.

Methods: The primary analysis method was Generalized Estimating Equations (GEE), by SPSS. Four, temporal treatments of GEE were deployed, to test present and delayed influence of anxiety upon cognition, which was also treated as a time-varying variable. The alternative temporal treatments were *time-lagged*, *auto-regressive*, and *cognitive change*. These temporal treatments are described at Section 6.2.4.4. For significant effects, additional investigations were applied to test the results and to identify implications. These additional methods included graphical interpretation, and linear mixed models (LMM) to examine random effects.

Results: The only significant association was the interaction, *anxiolytics**GAS as predictor of digit span backwards (DSB), over four waves. *Anxiolytics* is a binary variable representing baseline consumption (yes or no) of these medications. The fully adjusted effect for the standard temporal treatment was OR = 1.382 (95% CI: 1.132 to 1.688), p = .002. For *time-lagged,* OR = 1.273 (CI: 1.082 to 1.498), p = .004; for *auto-regressive* OR = 1.122 (CI: 1.001 to 1.257), p = .047; and, for *cognitive change* OR = 0.953 (CI: 0.838 to 1.083), p = 0.457.

Discussion & Conclusion: Other than the significant interaction, associations investigated by GEE found no, fully adjusted association between GAS and cognition. For the interactions, analyses were limited by a strong content of missing data. Also, there appears to be no significant effect over time, only a difference in intercept between subgroups which were implied by the interaction including a binary variable. These are tentative findings, to be analysed further in the next chapter.

6.1 Introduction

A diverse range of regression models was examined in Chapters Four and Five, to investigate possible associations between *baseline* anxiety and cognitive change. Only unadjusted associations were found between anxiety and rates of cognitive decline or incident cognitive impairment. These findings embraced a variety of representations of anxiety, including the main variable GAS, its derivatives, and proxies. As foreshadowed in the methods strategy (Chapter Three), the following investigation is limited to the main anxiety measure, GAS. This chapter extends the analysis to *repeated measures* for both the main predictor (GAS) and outcome variables, thus extending the analyses in this thesis, for the first time, beyond the influence of *baseline* anxiety.

Repeated measures of both anxiety and cognition have been included in previous investigations reported in the literature, using *multilevel models* (e.g., Bierman et al., 2008; Petkus et al., 2016; Wadsworth et al., 2012). As another option for comprehensive longitudinal investigation, some researchers have adopted *survival analysis* for cognitive impairment outcomes (e.g., DeLuca et al., 2005; Petkus et al., 2016; Ramakers et al., 2010; Wadsworth et al., 2012). However, for the PATH data, *survival analysis* would not be a valid approach because incident cognitive impairment was recorded only at four-yearly intervals, and, therefore, not on a continuous timeline. Multilevel models (MLM) remain as the important option to consider here, for both continuous and binary outcomes. Against this background, generalised estimating equations (GEE) are deployed in this chapter as a close approximation of MLM (Twisk, 2013). The choice of GEE as the primary analytical tool is further discussed at Methods.

A central consideration in the following analyses is that Chapter One established on the theory, that if anxiety causes long-term decline in age-associated, cognitive performance then the psychological and neurological mechanisms are most likely to occur over long periods. It

is because of this that a standard approach to MLM may be insufficient as an analysis method. For Standard, longitudinal MLM, the influence of the predictors does not account for, or identify, the specific association between the DV measure at each time point, and the measure of the predictor at a previous time point, the *time-lagged effect* of the predictor. To identify and account specifically for delayed effects of predictors, Twisk (2013) recommended inclusion in MLM models of time-lagged effects of the time-variant predictor variable (as explained further at Section 6.2.4.4). Although not adopting Twisk's comprehensive approach requiring four, alternative, temporal treatments, Bierman et al. (2008) included time-lagged effects of the main predictor, and found no influence of *prior* anxiety upon current cognition. This was so even though a fully adjusted model, but excluding lagged effects, demonstrated *present "temporary" association between anxiety and cognition,* and which varied between positive and negative association, depending on the level of the anxiety. By contrast, Petkus et al. (2017) used structural equation modelling to account simultaneously for lagged and double-lagged effects of the predictor (over one and two waves of the data). They found different associations for each, with cognitive change. Thus, the literature offers alternative methods and contrasting results. The alternative temporal treatments are explored here with new data in order to extend the previously published research, which has so far been limited to just the two mentioned studies.

6.2 Methods

Here, I detail reasons for making certain choices in methods, to clarify and justify choices in analytical techniques based on the research questions, theory, and limitations of the standard methodology.

6.2.1 Research Questions

This chapter addresses both the primary research questions (Section 3.2.2.1) and secondary research question B (Section 3.2.2.2). Question B refers to the *time-varying* nature of the central predictor variable, anxiety, as measured by GAS.

6.2.2 Outcome Variables

The continuous outcome variables were repeated measures for cognitive ability, which were specifically: *Purdue Pegboard both hands* (PPb), *Symbol Digit Modality Test* (SDMT), *Digit Symbol Backwards* (DSB), *Immediate Recall* (IR), *Mini Mental State Examination* (MMSE), and *Spot the Word* (StW). The binary outcome variables were incident MCI and dementia. Subcategories such as Alzheimer's disease and amnestic MCI were unavailable before Wave 4. Therefore, this chapter does not attempt to analyse longitudinal data in these subcategories.

6.2.3 Regression Analysis for Time-Varying Variables

The software package for SPSS Version 25 (IBM Corp., Released 2017) was used throughout. From the SPSS online-manual, and from Twisk (2013), the following summarises the features of, and differences between, the options within SPSS, for regression analysis with time-varying variables. Reasons for the choices of methods in this chapter are drawn from these descriptions.

GEE models provide for continuous, binary, or ordinal outcome variables. Mixed Models are available as Linear Mixed Models (LMM) for continuous outcome variables only or Generalized Linear Mixed Models (GLMM) for binary, ordinal, categorical, or continuous outcome variables. These are progressively more complex and more flexible methods. GEE and mixed models calculate longitudinal associations appropriately with adjustment for dependence between repeated measures. GEE calculates fixed effects only. The two, mixed

models methods both calculate fixed and random effects. For a more comprehensive comparison between the methods, see Twisk (2013), chapters 4 to 8.

In the literature described at Chapter Two of this thesis, multilevel modelling has been typically based on mixed models. Here I have taken a different approach. For a parsimonious analysis, I have used the simplest and most direct methods available. Almost exclusively, I have explored fixed effects only, using GEE. This is because, as reported below, for the fully adjusted , fixed-effects models, there was attenuation of the association between the primary predictor (GAS) and the outcome variable. Random effects statistics from mixed models, presuppose a fixed effects association. Therefore, the more comprehensive analyses available from mixed models generally were not required. However, there were exceptions where significant fixed effects justified analysis by LMM to obtain information about random effects.

6.2.3.1 Settings in General Estimating Equations (GEE) and for linear mixed models (LMM).

Settings for GEE are described fully at Appendix 6.A. Settings for LMM are described fully at Appendix 7.A.

6.2.3.2 Goodness of fit.

Comparison of the goodness of fit of models (in GEE output) with similar DV (and on the same sample) can be approximated by the quasi likelihood estimator of minus two log-likelihood (-2LL). This statistic does not permit valid Chi-squared calculation of probability (and thus, significant difference between models), but does allow approximate estimates based on the criteria that “less-is-better”. All models evaluated by GEE only, were attenuated. Therefore, this “quasi likelihood” parameter was sufficient for purpose.

6.2.3.3 Variance explained by the model.

GEE by SPSS does not compute the proportion of variance in the DV, explained by the model. However, this can be calculated from other components of the output, using the equation:

$$R^2 = 1 - S_{model} / S^2_{DV} \quad \text{(Equation 6.1)}$$

Where R^2 is the proportion of variance explained by the model; S_{model} is the total variance of the model, indicated in the SPSS output as the parameter, "Scale"; and, S^2_{DV} is the variance of the DV (Twisk, 2013; Equation 4.5). It follows, $1 - R^2$ is the unexplained component of the variance.

6.2.4 Time

6.2.4.1 Temporal confounding.

Established in previous chapters, was the need to eliminate cases where cognitive impairment was recorded at Wave 1. For observational data, this is an important precaution to reduce the prospect of temporal confounding in the associations between anxiety and cognitive change as outcome. However, the possibility of temporal confounding remains because unmeasured cognitive decline may be the cause of anxiety. Although this confounding may be impossible to eliminate, adjustment for baseline subjective memory complaint is included here in order to identify and reduce this influence and, thus, to reduce the degree of confounding. This adjustment will take the form of controlling for *baseline* data on the variable: *consulted a doctor regarding memory*. This variable was introduced in Chapter Four and was used to refine regressions in Chapter Five. Although adjustment for subjective memory complaint has precedent in the literature, most studies have not considered it. Therefore, the adjustments included here will appear in the tables after the more standard adjustments (for *sex*, *age*, *education*, and GDS [depression]), to accommodate

direct comparisons with results for these standard adjustments in the main body of the literature.

6.2.4.2 Adjustment for time.

To compare effects, models were estimated with and without adjustment for *time*. As recommended by Twisk (2013), *time* was entered as a CV due to the potential misleading results caused by missing data when entering ordinal or categorical predictors as factors. Further, detailed description of adjustment for time is provided at Appendix 6.B.

6.2.4.3 Interactions with time.

Associations between GAS and the cognitive DV may be modified by *time*. For example, if the sign of the coefficient of the time interaction term were positive, the relationship between the two terms would become stronger over time (Twisk, 2006). Models were explored for these interactions by including the predictors: *time*, *time**GAS or *time**Lagged-GAS ("lagged-GAS" is explained at Section, 6.2.4.4). Quadratic time was similarly considered. See also Section 6.2.7 for a qualification on interpreting models which include interaction terms.

6.2.4.4 Alternative temporal treatments.

Recommended by Twisk (2013), was that longitudinal, multilevel models be considered with alternative temporal treatments of the data. As well as the standard model, illustrated here as Temporal Treatment 1 by Figure 6.1, Twisk recommended a time-lagged model (Temporal Treatment 2; Figure 6.2), an autoregressive model (Temporal Treatment 3; Figure 6.3), and a changes (in outcome, between measurements) model (Temporal Treatment 4; Figure 6.4). In each of these mentioned figures, I have included both the relevant matrix equation and a simplified diagram, notionally representing parts of the calculations that are unique to this temporal treatment. Therefore, these notional diagrams do not attempt fully to represent the model equation. More specifically, the diagrams do not represent the effects of

average slope (coefficient) of the predictor upon the DV, or the matrix algebra (summarised for multilevel modelling, for example, by Tabachnick & Fidell, 2007), or the adjustment to the covariance between repeated measures (accounting for the dependence between measures).

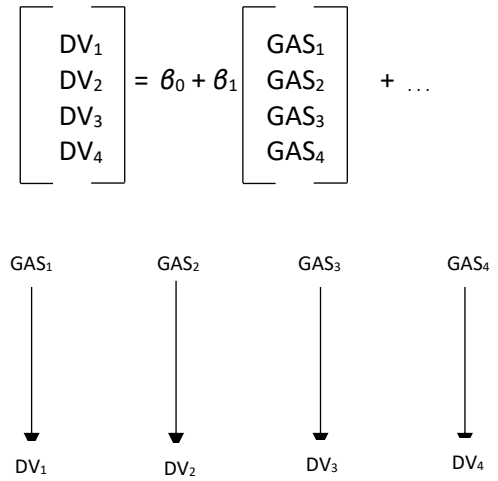


Figure 6.1. Temporal Treatment 1: Standard Multilevel Model.

DV_t = Dependent Variable (at time t) such as incident dementia or processing speed measured by SDMT; CV_t = covariate or predictor (at time t) such as anxiety (GAS); β_k represents the coefficient of the k^{th} term of the model, and, specifically, β_o represents the intercept.

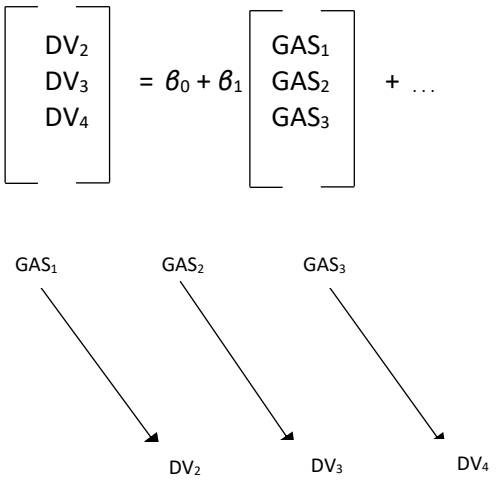


Figure 6.2. Temporal Treatment 2: Time-Lagged Model.

DV_t = Dependent Variable (at time t) such as incident dementia or processing speed measured by SDMT; CV_t = covariate or predictor (at time t) such as anxiety (GAS); β_k represents the coefficient of the k^{th} term of the model, and, specifically, β_o represents the intercept.

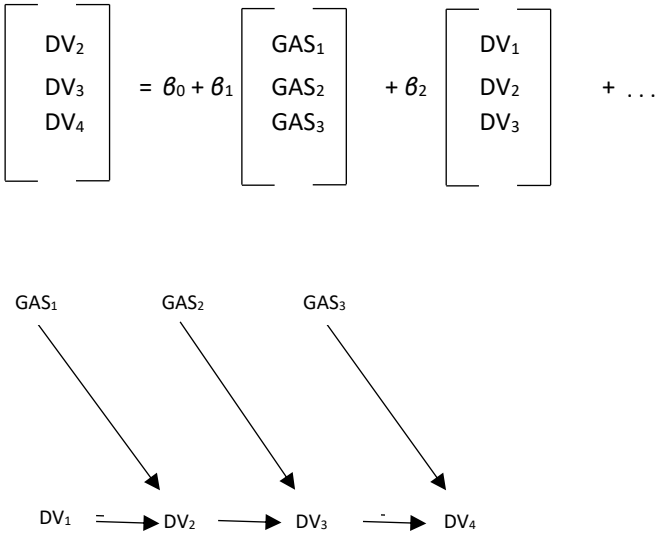


Figure 6.3. Temporal Treatment 4: Autoregressive Model: DV is a function of time-lagged GAS plus time-lagged DV.

DV_t = Dependent Variable (at time t) such as incident dementia or change in processing speed measured by SDMT; CV_t = covariate or predictor (at time t) such as anxiety (GAS); β_k represents the coefficient of the k^{th} term of the model, and, specifically, β_o represents the intercept.

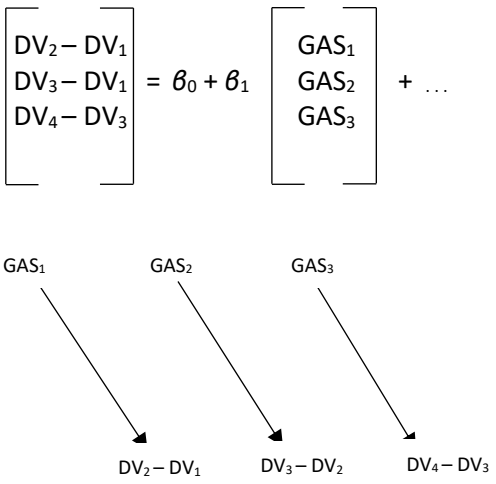


Figure 6.4. Temporal Treatment 3: Cognitive-Change Model.

DV_t = Dependent Variable (at time t) such as incident dementia or processing speed measured by SDMT; CV_t = covariate or predictor (at time t) such as anxiety (GAS); β_k represents the coefficient of the k^{th} term of the model, and, specifically, β_o represents the intercept.

Essentially, the differences between these temporal treatments are:

A. Treatment 2 (time-lagged) includes the predictor (GAS) from the *previous* wave of data (thus: lagged-GAS), in place of the current value of GAS (which was Treatment 1).
B. Treatment 3 (auto-regressive) similarly (to Treatment 2) draws on the lagged effect of the predictor. And, the DV is again the simple current measurement (current wave). However, this model introduces an additional CV, which is the previous wave's measurement for the DV.
C. Treatment 3 uses the same lagged effect of the predictor (GAS) as in Treatments 2 & 3, but the DV is changed from the raw measurements for the DV to the difference between the current and previous measurements of the DV.

Temporal treatments 2 to 4 have in common that they each include the time-lagged effect of GAS, in place of the immediate effect, or cross-sectional association, at each wave. The differences between treatments 2 to 4 are in the alternative arrangements of the DV.

Twisk (2013) advised against attempting to combine two or more of these temporal treatments into one model, on the basis that the result would be too complex to interpret. The better approach is to run the models separately but then to interpret each within the context of all results.

For the cognitive-change model (Figure 6.4), the change between waves for incident *cognitive impairment* was represented by the binary change: 0 = no change (between consecutive measures), and 1 = change (between consecutive measures from "not impaired" to "impaired"). For MCI this becomes a meaningless model because the data include a high frequency of reversion from MCI to normal cognition. So, this temporal treatment was excluded from the analyses for MCI.

6.2.5 Covariates

As in Chapter Five, the plan for controlling for covariates (CVs) was to include these sequentially, in four groups. Adjustments were made for: (1) the central covariates of *sex*, *age*, *education*; and, *depression*; (2) *consulted a doctor regarding memory* (Section 6.2.4.1); and (3) *anxiolytics*, *physical health*, *social support*, *mastery*, *physical activity*, *alcohol consumption*, *life events*, and *smoking status,* (Section 4.4.9.1). These groupings also accommodated a further requirement to adjust in correct sequence for temporally prior effects, where this criterion was relevant and determinable. Thus, adjustment for *sex* was prior to *age*. However, this criterion was mostly not a required consideration. Covariates were entered into models, using baseline values.

6.2.6 Models

Base models demonstrate the unadjusted association between the primary predictor (GAS or lagged-GAS) and the DV.

When sufficiently adjusted, all models demonstrated there was no association between GAS and the relevant DV. Therefore, *final models* are defined here as the simplest models for which the associations between the predictor (GAS or lagged-GAS) and the outcome variable, were attenuated. Thus, these *final models* excluded redundant CVs, those CVs that, by their removal from the model, did not alter the attenuated status of the association (for GAS or lagged-GAS).

Fully adjusted models included all CVs identified above (Section 6.2.5). These were designed to report which CVs remained significantly associated with the DV, when fully adjusted. These models also demonstrate the maximum variance explained when considering all known, relevant data. Fully adjusted models are presented here, with and without *time* and *time* interactions, in order to demonstrate the effects of such time adjustments. *Time* interactions were: *time**GAS, *time***time*; and, *time***time**GAS. Fully adjusted models are

also presented with interactions between GAS and the CVs that remained significant (in the fully adjusted models). Except where a significant association was found, investigation of fully adjusted models was limited to the standard temporal treatment. This was because all final (attenuated) models were identified at much simpler levels of adjustment and, therefore, alternative temporal treatments were unlikely to yield results.

6.2.7 Interactions

Interactions with *time* are described at Section 6.2.4.3. Interactions between GAS and CVs other than *time*, were considered only within the context of *fully adjusted models.* Fully adjusted models are presented here with and without interactions, because models containing interactions do not demonstrate main effects of the lower order terms, but rather effects conditional upon the value of the other term in the interaction, being set to zero (Field, 2013; Grace-Martin, 2018). Consider the equation:

$$Y = B_0 + B_1X_1 + B_2X_2 + B_3X_1*X_2 + \ldots \quad \text{(Equation 6.2)}$$

B_1 is conditional on $X_2 = 0$, and B_2 is conditional on $X_1 = 0$. For X_2 not equal to zero, the alternative effect of X_1, for which I will use the symbol β_1, is given by $\beta_1 = B_1 + B_3X_2$.

The reported significance of each term (X_1, X_2) is also conditional on the values of the terms in the interaction. Thus, models with and without interaction terms but which are otherwise equivalent, are not directly comparable in terms for either the effect size or significance of the lower level predictors (Grace-Martin, 2018).

6.2.8 Assumptions

As previously in this thesis, results for assumption testing would be reported here only upon violations. There were no such violations. Among the considered possibilities for assumption violations, were multicollinearity (especially between anxiety and depression measures), and normality of the distribution of residuals.

Regarding multicollinearity, the precaution was taken in the analyses, to centre the GAS (and lagged-GAS) data (all waves centred to the baseline mean). This has the effect of reducing multicollinearity, with any IV or DV but particularly of interest, with depression, which has been previously mentioned as prone to multicollinearity with anxiety measures.

Regarding the normal distribution of residuals, this can only be verified with continuous outcome variables. The binary outcomes, by definition, cannot produce residuals with a normal distribution. These residuals were, therefore, not required.

6.3 Results

6.3.1 Base, Final, and Intermediate Models

Appendix 6.C provides an analysis of detailed models for PPb. Tabulated results provide non-standardised results for multilevel models using GEE, for associations between GAS (by repeated measures) and cognitive scores (by repeated measures). Models include the four temporal treatments. Model interpretations at the appendix, describe the derivation of these models, and the effects of inclusion and exclusion of adjustments for time.

Appendix 6.D summarises *final models* and interpretations, for all DVs and all temporal treatments. In summary, no combination of DV and temporal treatment remained significant when sufficiently adjusted. The outcome variables, and temporal treatments requiring the most adjustment (before attenuation was reported), were: PPb – standard, auto-regressive, and cognitive change; SDMT – all temporal treatments; DSB – standard, auto-regress, and cognitive change; and StW, lagged-GAS. One covariate of interest in previous chapters, was *depression*. Adjustment for this variable resulted in attenuation of the association between GAS and the relevant DV, for: PPb, auto-regressive and cognitive change treatments; SDMT, all temporal treatments; and, DSB, cognitive change only.

6.3.2 Fully adjusted Models

Fully adjusted models are reported at Appendix 6.E. These include models for all DVs but only for the standard temporal treatment. There are three versions of each fully adjusted model. The first version reports the effects of all CVs but without adjustment for time, and excluding interactions. The second version is time-modified, meaning it includes effects of *time* adjustment and *time* interactions with GAS. The third version of the fully adjusted models investigates interactions between GAS and CVs (other than *time*), for CVs that were significantly associated with the DV in the first version of the model. Because a significant association was reported for the DSB models, the alternative temporal treatments also were examined for DSB. These are reported at Appendix 6.F. Here, models are reported only for the relevant (significant) interaction.

Also shown at these appendices 6.E and 6.F, are the "Quasi Likelihood under Independence Model Criterion (QIC) using the full log quasi-likelihood function", and the total variance explained by each model.

6.3.2.1 Two specific results.

From Appendix 6.E, two specific, fully adjusted results, are featured here for later reference. Chapter Eight will call on this information for the purpose of updating and evaluating previous meta-analyses. These results are:

- From Model S: Association between GAS and MCI:

  OR = 1.044 (0.871–1.251), $p = 0.216$.

- From Model N: Association between GAS and dementia was not determined in a fully adjusted model, which did not converge.

6.3.2.2 Effects of time.

For fully adjusted models, the *time* associations reported at Appendix new 6.E were:

a) *Time* was associated with: SDMT; and, StW.

b) *Time*time* was associated with: SDMT; StW; PPb; and, IR.

c) *Time**GAS, and *Time*time**GAS were not associated with any DVs.

Association with *time*, at a) implies that predicted values for these DVs changed significantly over the four waves of the study. Association with *time*time* at b) implies that changes in predicted values of the DVs changed quadratically over the four waves. For SDMT and StW, change over time was both linear and quadratic, implying both trends were present in data.

6.3.2.3 Interactions, other than with time.

The CVs tested for interactions with GAS were only those which were individually significant, in the fully adjusted models (Appendix 6.E). These selected CVs are summarised at Table 6.1. Models for dementia failed to converge when all CVs were introduced. The maximum list of CVs for which the dementia model ran successfully, was: *sex*, *age*, *education*, and GDS. Adjustment for *time* or any interaction term resulted in non-convergence of the model.

Table 6.1
Individually, Significant CVs in Fully adjusted Models. Each was tested for significant interaction with GAS.

Dependent Variable	Baseline Covariate								
	Sex	**Age**	**Edu-cation**	**Depression**	**Physical Health**	**Anxio-lytics**	**Alcohol**	**Smoker**	**Dr Re. Memory**
PPb	X				X				
SDMT		X	X						
DSB			X			X[a]			X
IR	X		X			X			
MMSE				X			X		
StW			X		X		X		
MCI								X	
Dementia		X[b]							

Notes:
a The interaction *anxiolytics**GAS was the only significant interaction.
b For Dementia, models failed to converge with more CVs than sex, age, education, & depression. Age was a significant CV but was not tested in interactions.

The interaction *anxiolytics**GAS was associated with DSB for the standard temporal model, with OR = 1.382 (CI: 1.132 to 1.688), p = .002; for *lagged-GAS,* OR = 1.270 (CI: 1.083 to 1.489), p = .003, for *auto-regressive,* OR = 1.122 (CI: 1.001 to 1.257), p = .047; and, for *cognitive change* OR = 0.953 (CI: 0.838 to 1.083), p = 0.457. See detailed GEE output at Appendix 6.E model I, and Appendix 6.F models A and B. No other significant interaction was observed.

6.3.2.3.1 Further investigation of significant interactions, in fully adjusted models.

Anxiolytics is a binary indicator with values 0 or 1, representing consumption of anxiolytics at baseline. GAS scores were centred at the baseline mean. The product of *anxiolytics* and GAS, therefore, produced values for the interaction component of the model, that were either zero (0*GAS), or the unaltered GAS score. For the centred GAS variable scores at or above the baseline mean were positive; scores below the mean were negative. The interaction effectively identified subgroups, with and without baseline consumption of anxiolytics. A further subgrouping is possible according to levels (low or high) of GAS scores. Subgroups will be examined more comprehensively at the next chapter. Here, I will provide only a preliminary analysis.

Firstly, LMM was used to reproduce the model. This was to determine *random effects* for the intercept and the slope of the interaction. This LMM model produced slightly different results for fixed effects, as was expected because LMM and GEE compute differently with respect to both missing values and the adjustment for dependence between measures (Twisk, 2013). However, when random effects were added, the LLM failed to converge, thus rendering random effects computations, invalid. Models for alternative temporal treatments produced similarly invalid analyses for random effects.

The remaining analyses here are mainly graphical in nature, with the aim of confirming and interpreting the significant effects. Figure 6.5 provides a graph of predicted DSB scores (from the fully adjusted model by LMM, without interactions). This is for the standard temporal model. The graph includes confidence intervals at each wave, calculated as 95% confidence for the sample means.

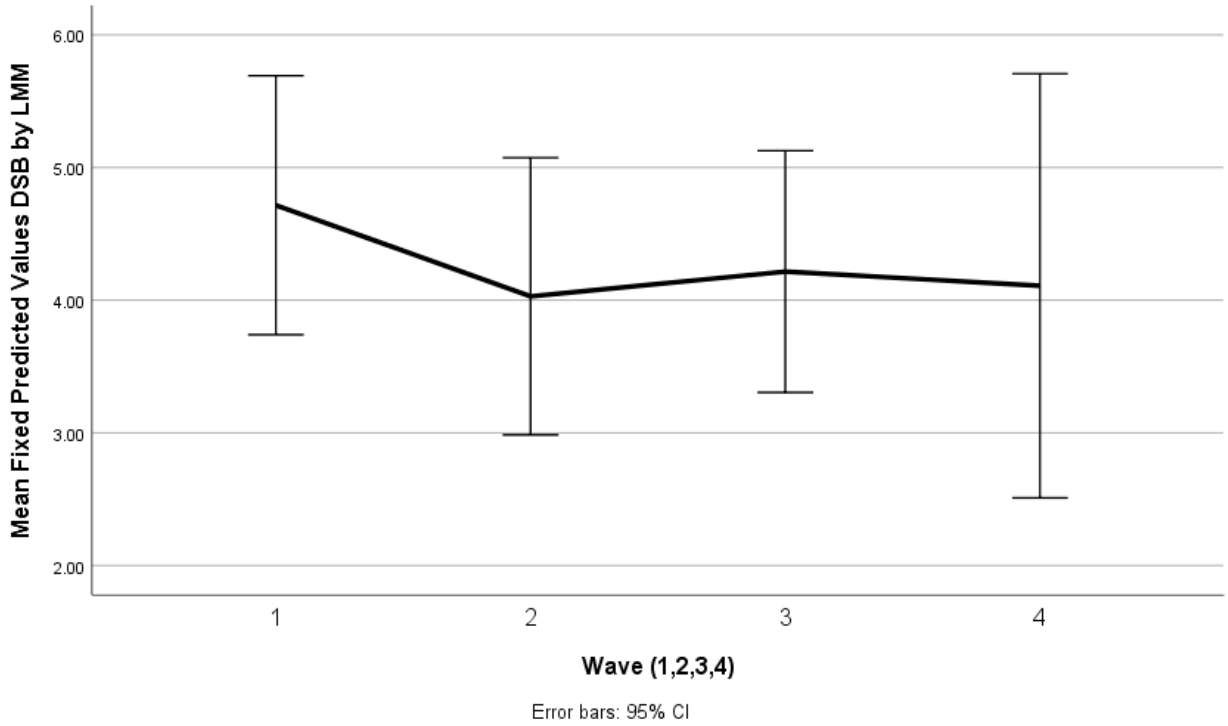


Figure 6.5. LMM predicted DSB over time, from Standard temporal, fully adjusted model; full sample.

From Figure 6.5, it may be concluded the fully adjusted model applied to the full sample, does not predict a trend over time, in the mean level of GEE predicted DSB.

Figure 6.6 divides the sample into two subgroups, for participants with and without baseline consumption of anxiolytics. Here the slopes are equivalent and imply no change over time, but the intercepts are different.

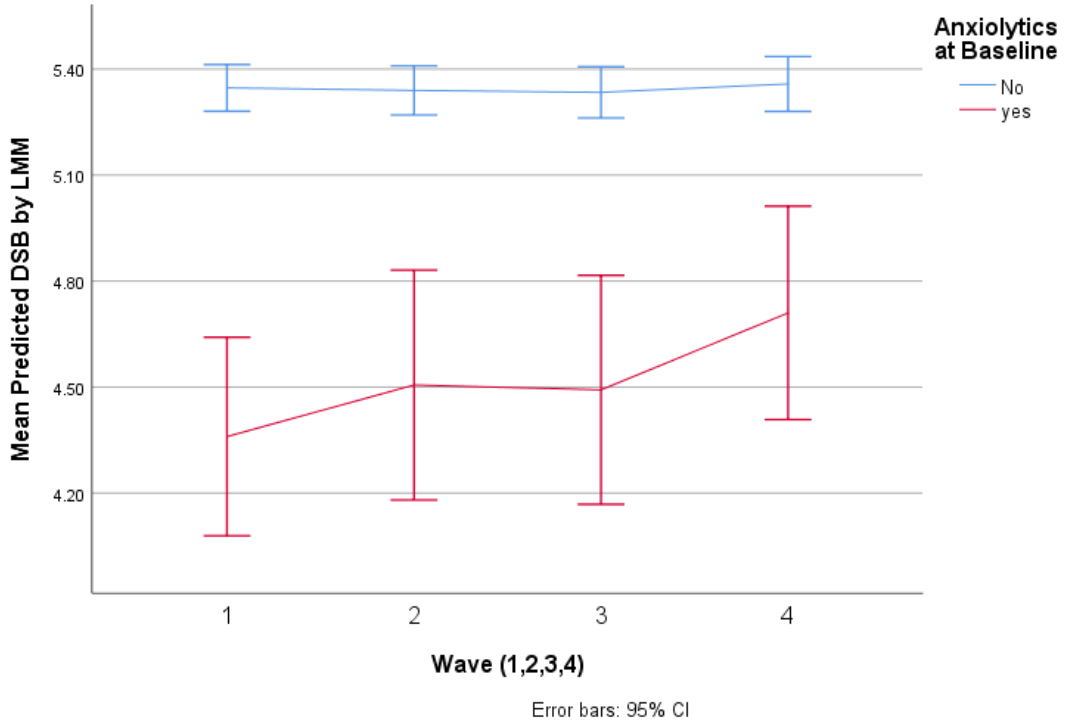


Figure 6.6. LMM predicted DSB over time, from Standard temporal, fully adjusted DSB model, for two subgroups, participants with and without consumption of anxiolytics at baseline.

Figures 6.7 and 6.8 show results for the sample divided into four subgroups: 1) no *anxiolytics* & negative GAS (blue line); 2) no *anxiolytics* & positive GAS (red line); 3) *anxiolytics* & negative GAS (green line); and, 4) *anxiolytics* & positive GAS (orange line). The graphic for confidence intervals at Figure 6.8 may be a little confusing, but they indicate the only subgroup different to the others is represented by the green line for participants who consumed anxiolytics and who had below mean GAS scores.

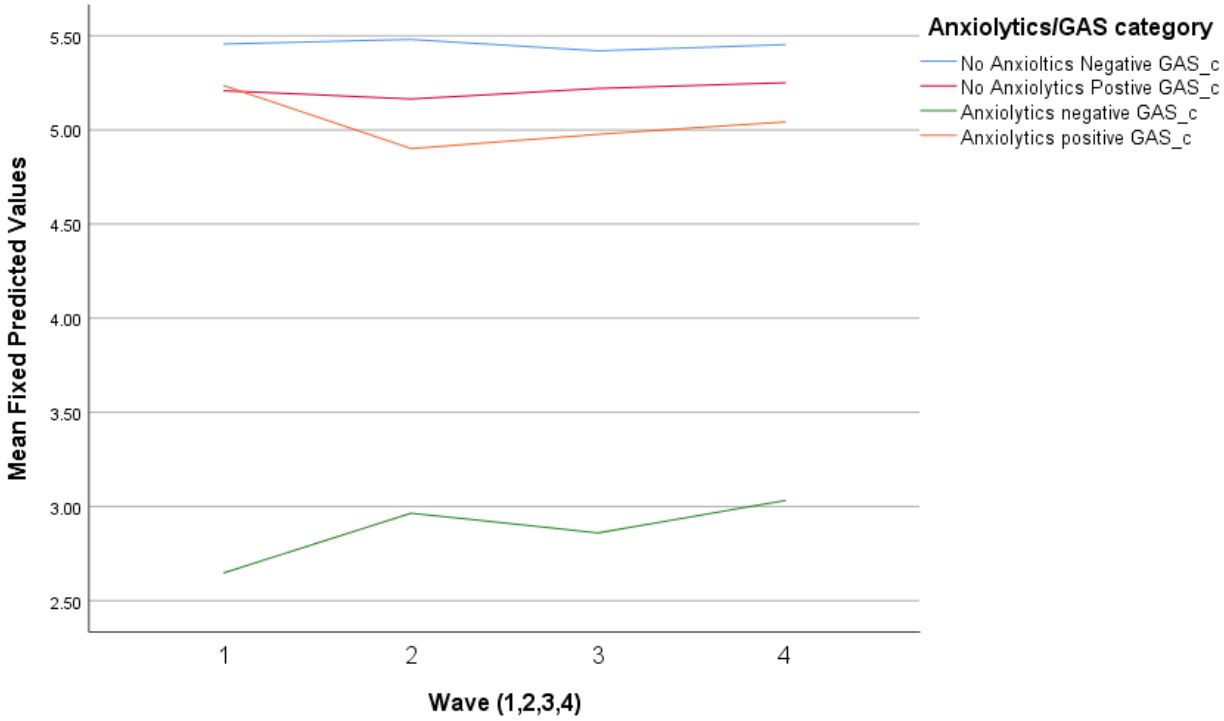


Figure 6.7. Predicted DSB over time, from Standard temporal, fully adjusted DSB model; full sample divided into four subgroups as indicated at the legend.

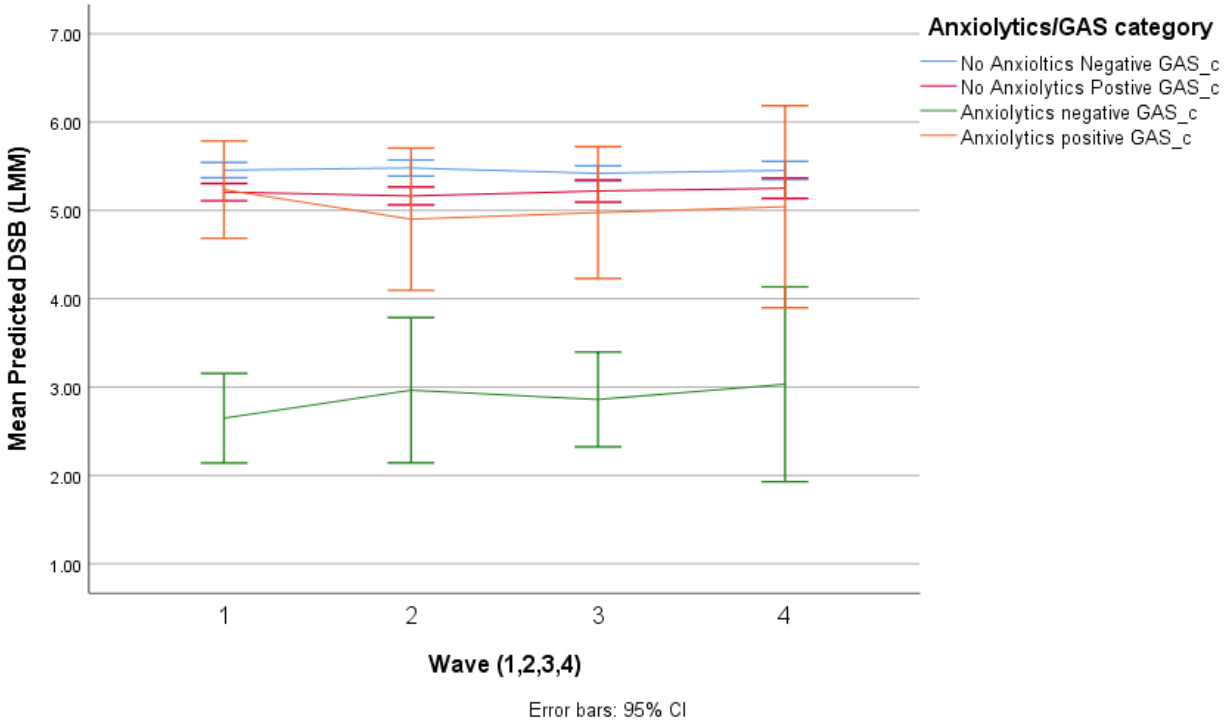


Figure 6.8. Predicted DSB over time, from Standard temporal, fully adjusted DSB model; full sample divided into four subgroups as indicated at the legend. This is the same as figure 6.7 except that confidence intervals (95% for the mean), are included. See Table 6.2 for means and CIs upon which this graph is base.

Table 6.2 provides the mean predicted DSB results of LMM analysis, with CIs, equivalent to the graph at Figure 6.8. The table is colour coded to match the graph. Cell sizes are small because of missing data. The small cell sizes (particularly for the green and orange subgroups) have also reduced accuracy for CI calculations. It is likely to be the missing data which has caused the LMM models for random effects, not to converge.

Table 6.2
Subgroup Means for predicted DSB (by LMM), with CI and Cell Sizes, corresponding to Figure 6.8.

	Subgroup Mean (CI) for Predicted DSB, n (cases missing)			
	No Anxiolytics & Negative GAS	**No Anxiolytics & Positive GAS**	**Anxiolytics & Negative GAS**	**Anxiolytics & Positive GAS**
Wave 1	5.46 (5.37–5.54), 175 (1355)	5.21 (5.11–5.31), 148 (605)	2.65 (2.14–3.15), 4 (27)	5.23 (4.68–5.79), 16 (78)
Wave 2	5.48 (5.39–5.57), 162 (1163)	5.16 (5.06–5.27), 124 (567)	2.96 (2.14–3.79), 5 (23)	4.90 (4.09–5.71), 11 (63)
Wave 3	5.42 (5.33–5.51), 157 (1035)	5.22 (5.09–5.35), 105 (507)	2.86 (2.32–3.40), 4 (25)	4.98 (4.23–5.72), 12 (49)
Wave 4	5.45 (5.35–5.56), 114 (843)	5.25 (5.14–5.37), 102 (456)	3.03 (1.93–4.13), 4 (26)	5.04 (3.90–6.19), 7 (36)

Although the analyses represented by Table 6.2 and Figures 6.5 to 6.8 are limited and not entirely equivalent to multilevel analysis, they *are* based on the LMM output for mean, predicted DSB. Therefore, they do provide some insight into the parameters which distinguish these four subgroups from each other.

Based on these graphs and Table 6.2, there was no change reported in predicted DSB over time, for any subgroup. All slopes were equivalent. The only difference between subgroups was the intercept for participants who consumed anxiolytics and had lower than

average GAS scores. The difference in DSB scores between this one subgroup and the remainder of the sample was roughly 2 points on the DSB scale ranging from 0 to 10. At Figure 6.8, Wave 4, the green and orange CI markers overlap, therefore, statistically, there was ambiguity at this one time point between the subgroups.

When the multilevel modelling of the interaction was extended to include *time* as a CV and *time* was included in the interaction: *time***anxiolytics**GAS, the results from GEE and LMM analyses were contradictory. For GEE analysis, this three-way interaction was not significant (p = .892). For LMM analysis, the interaction, fixed effects were: coefficient = .151 (.038–.263), p = .009. The opposing results between GEE and LMM methods, are most likely due to the different treatments by each for the considerable component of missing data. The goodness of fit for the LMM results was worse for the model including *time* (-2LL = 5030.520 compared to 5013.728 without *time*). Therefore, without the need to compute Chi-square probabilities, the model including time does not provide additional, significant information.

The meaning and the direction of change implied by the significant association of the *anxiolytics**GAS interaction, reported above, remains unclear. If there is no change over time, the moderately sized odds ratio (1.382) and its positive sign may mean only that there was a difference between subgroups, based on different intercepts.

Similar analyses to the above were applied to the significant interaction effects for the two alternative temporal treatments (lagged-GAS and autoregressive), with similar results.

These significant interactions will be further examined in Chapter Seven.

6.3.3 Variance Explained

Variances explained by all models were small. For example, consider the *final model* for the standard temporal treatment for SDMT, at Appendix 6.D, Table 1. By the method at Section 6.2.3.3, the variance explained by this model was 6.7%. The explained variance for

the *fully adjusted model* for SDMT, standard temporal treatment, was 12.2%. See this at Appendix 6.E, Model D. This small improvement in the variance explained was typical of most *fully adjusted models* compared to *final models*.

6.4 Discussion

6.4.1 Summary of Findings

The interaction of *anxiolytics* and GAS was associated with DSB in fully adjusted models for standard, lagged-GAS, and autoregressive models, with full adjustment. For these interactions, there was only a difference in intercept between subgroups of participants. Although considerable missing data limited the possible analyses, there appeared to be no effect over time and no difference in slope between these subgroups. Subgroups will be examined more comprehensively in the next chapter. Other than these results, extensive analysis by multilevel modelling has not demonstrated any fully adjusted association between GAS and any of the nominated dependent variables (Section 6.2.2).

6.4.2 Comparisons with the Literature

There is no known report in the literature, of significant association between the interaction of anxiolytics consumption and anxiety, with a cognitive outcome variable. The finding here of no association (other than for the *anxiolytics* interaction) is consistent with about a quarter of past research (Chapter Two).

The main difference between the present and previous studies is in the analytical methods. Multilevel modelling methods reported in the literature, have rarely investigated the time-lagged effects of anxiety. An exception was Bierman et al. (2008), which was mentioned above and is discussed further below. Bierman et al. introduced “previous” or lagged measures of anxiety. Structural equation modelling was also used to demonstrate lagged effects (Petkus et al., 2017). The more prominent alternative to MLM, for identifying the effects of *prior anxiety*, has been the regression studies drawing only upon a *baseline*

measure of the predictor and its association with subsequent cognitive change. Such study design does test "prior" (or time-lagged) anxiety effects, and removes most unintended temporal confounding. However, this method also contains less information than those which contend with the trends in anxiety over time. For example, if as expected, persistence of anxiety was critical to the processes of cognitive ageing then this association would remain hidden to such baseline studies.

6.4.2.1 Standard temporal treatment.

Notwithstanding the importance of the analyses for alternative temporal treatments, the standard temporal models, for all DVs, are the most comparable with the literature. Final models reported above, using PATH data, and deploying *standard, temporal treatment* for anxiety as a predictor, were attenuated for the DVs: PPb, SDMT, and DSB. For the remaining DVs: IR, MMSE, StW, MCI, and dementia, adjustment was not required; the base models were not significant. These results from PATH (finding no association) are aligned with three of 16 previous studies looking at cognitive decline, and six of 24 studies examining incident cognitive impairment. See Tables 2.3 and 2.4, respectively. Some research (Gulpers et al., 2016) has suggested there is no evidence of publication bias for the cognitive impairment research, but there is no comparable analysis of bias for the investigations of cognitive decline.

6.4.2.2 Alternative temporal treatments.

Two previous studies (Bierman et al., 2008; Petkus et al., 2017) featured time-lagged effects. Bierman et al. (2008) used MLM with models comparing lagged-anxiety (over three years) with standard temporal treatment, or, as they termed it, the effects of "present anxiety". For the standard treatment, Bierman et al. found (as previously described at Chapter One), an inverted U-shaped curve for which cognitive performance was highest when anxiety was moderate and lowest when anxiety was low or high. They found that lagged-anxiety had no

significant effect on association with a variety of outcome variables, including MMSE, Raven's Coloured Progressive Matrices (RCPM), Coding test (for processing speed), Auditory Verbal Learning Test (AVLT) learning and memory, AVLT recall, and AVLT retention. Models were adjusted for age, sex, education, alcohol consumption, benzodiazepine use, number of chronic diseases, and depression symptoms. With different results, Petkus et al. (2017), using SEM, found significant anxiety effects were those time-lagged by three years (one wave) for association with decline in attention, and, lagged by six years (two waves of data), for association with decline in processing speed. Reported SEM results were unadjusted but described as substantially equivalent to results adjusted for sex, depressive symptoms, and physical health. Both Bierman et al. and Petkus et al. tested processing speed but otherwise, their cognitive tests were different. Although the results of these two studies disagree, it may be that more options for time-lagging (one, two, and three waves), and options for cognitive measures, may have identified some agreement.

The results in this chapter for significant interactions, included the time-lagged and autoregressive temporal treatments. If the further investigation at Chapter Seven confirms these findings, the time-lagged and autoregressive results are likely to have important implications.

6.4.3 Interpretation of the Results

6.4.3.1 Small effect size and insufficient variance.

Small effect size is illustrated by Model B (the base model) from Table 1 at Appendix 6.C, which yielded a significant coefficient for GAS, as an *unadjusted* predictor for PPb. The coefficient was -0.034, meaning that if there were a unit increase in the score for GAS, the predicted score for PPb would be reduced by 0.034. Here, PPb was on an effective scale of 0 to 30 (30 being the maximum score achieved throughout the study). Therefore, to obtain a predicted, unit decrease in this scale of zero to 30, would require an increase in GAS score of

1/0.034 = 29.4 points. This 29.4 points exceeds the entire GAS scale of 0 to 9, which would, therefore, be an impossibility at an individual level. The coefficient could become meaningful only as an average result so that, in a sample, some individuals might change over time more than others, but on average only a small fraction of one point on the PPb scale would be observed as the difference.

This small effect is consistent with the observations above, that models typically explained only small proportions of variances in the outcome variables. For example, on this same model (Model B from Table 1 at Appendix 6.C), the variance explained was just 0.24%.

As small as this explained variance is, and as small as the predicted change in cognitive outcome might be, a further level of analysis renders the effect of even smaller impact. Twisk (2013) noted that in models for time-variant CVs and DVs, the variance is ambiguously distributed *within*- and *between*-subjects, and that the components cannot be separated. If each type of change (*within* and *between*) applied individually then for the example above (a GAS coefficient of -0.34), for the *within*-subject change, it would mean that over the 12 years of the study, for the average individual, a unit change in GAS would predict a decline in PPb score of 0.34 points. Therefore, at this rate, a unit change in PPB would take 35.3 years. For *between*-subject it would mean that a unit difference in GAS score between any two individuals, at any time point, would predict an average -0.34 difference in PPb score *between* these two individuals. Therefore, within any one model, the total variance explained would be divided between the *within*- and *between*-subject variance, and with insubstantial effect in either category. Such small effects are consistent with the result that all models were attenuated when adjusted by short lists of CVs.

An exception was noted in the results for the auto-regressive model for Model C, at Table 3, Appendix 6.C, for associations with PPb. Here, there was a larger proportion of

variance explained (29.86%) by the model which introduced lagged-PPb as a CV. It was noted at Appendix 6.C, this relatively large figure suggested the dominant part of the variance in PPb could be attributed to the auto-regressive effect, and, therefore, was not related to the influence of the primary predictor, GAS.

Notwithstanding this exception, the pattern of results points to small effect sizes for associations between anxiety and cognitive ageing. Such results are not a consequence of low power of the PATH data. For example, Appendix 6.G provides a table of projected power ratios for future waves of the PATH project. (This table was reproduced from a grant proposal, as specified at the appendix.) It demonstrates the dataset has sufficient power to "detect a wide range of associations".

6.4.3.2 Attenuated lagged-GAS models.

Results implied lagged-GAS models (temporal treatment 2), were occasionally less indicative of association than the standard temporal treatment. For example, at Table 1, Appendix 6.D, for PPb, the final model for the standard treatment required adjustment by five CVs before attenuation was reported, while the time-lagged treatment was non-significant, without adjustment. This is only an approximate comparison. The standard and lagged treatments cannot strictly be compared because they are based on a different number of waves of data and a different sample size due to loss to follow-up of participants. However, it may be that any effect of time-lagging has been disguised or distorted by the small variance explained within any one model. More importantly, such comparison of effect between GAS and lagged-GAS, does not imply that one is more relevant or more valid than the other; the two methods attempt to identify different relationships as described above at Methods. It is necessary to discover only whether the fully adjusted , time-lagged effect was established, in order to determine whether it was relevant. Because all final models were attenuated, and

these were adjusted by fewer CVs than the fully adjusted models, the time-lagged association between GAS and cognitive change was not established.

The remaining temporal treatments (autoregressive and cognitive change) were similarly unhelpful in supporting conclusions about the effects of time-lagged associations between GAS and any of the outcome variables. As mentioned, only the significant interactions may provide further insight into the alternative temporal treatments.

6.4.3.3 Attenuation reported with inclusion of *depression* in models.

Depression has been identified earlier as an important, potential confounder. For example, at Chapter One, I noted that,

> "Depression is highly comorbid with anxiety (Burton et al., 2013) and predicts cognitive ageing (Diniz et al., 2013), so may be a confounding variable . . ."

I also noted that anxiety and depression share a genetic aetiology (Zimmerman & Chelminski, 2003). Depression was described in Chapter One as possibly ambiguously identified with anxiety, particularly by the Spielberger State-Trait Anxiety Inventory. In the PATH data, the comorbidity (anxiety and depression) varied over time between 3.5% and 2.2%. Chapter Four noted depression was strongly correlated cross-sectionally with GAS at all waves. GDS is also a candidate for confounding multilevel models because it was correlated with both GAS and most measures of cognition for all waves (Tables 4.13 to 4.16). The case for confounding by depression was not confirmed by association with cognitive change from Wave 1 to 4 (Tables 4.18 and 4.25) but considering the weight of evidence elsewhere, provision must be made for the prospect that GDS is a confounder in PATH.

Considering these many connections between anxiety and depression, in the present investigation of the associations of anxiety with cognition, the effects of depression are important to identify.

In the present analyses of MLM, models for outcome variables, PPb, SDMT, and DSB, required adjustment for *depression* before attenuation was reported. Of these, only SDMT required the adjustment across all temporal treatments. The results in this chapter confirm the importance of *depression* in testing the associations, but only for the outcome variables: PPb, SDMT, and DSB. *Depression* was not a critical covariate for the outcome variables, IR, MMSE, StW, MCI, or dementia.

6.4.3.4 Effects of time.

A feature of the results was that in all models, there was insufficient effect by *time* to alter which model was identified as the final model. From the fully adjusted models, it is noteworthy that linear *time* was significant only for the DVs, SDMT and StW, although quadratic time was associated with these two DVs as well as PPb and IR. Association of linear time means only that the DV was changing over time. Association of quadratic time means there was a quadratic trend in the DV, which may or may not have also overlayed a linear trend. *Time* interactions with GAS were not associated with the DVs in any fully adjusted or final models. Therefore, no association between GAS and a DV, was observed in these models, to vary over the duration of the study. This is most likely a consequence of the fact that associations between GAS and DVs were observed to be limited to *base models* or models with elementary adjustments, and that such associations were with inconsequential effect size.

Twisk (2013) had recommended investigating models with and without adjustment for *time* but noted adjustment removes variance associated with change in the DV over time and could, therefore, confound the results. The outcome here that *time* made little or no difference to the models, places doubt on whether there was enough variance due to *time*, to change the results for other predictors.

In the literature on anxiety and cognitive ageing, *time* has been entered into most models but without comparison of effects with and without this inclusion. Twisk (2013) observed generally in the literature that often the inclusion of *time* into multilevel models was unspecified.

6.4.3.5 Attenuation reported with inclusion in models of subjective memory complaint, and physical health.

At Chapter Four, subjective memory complaint (as represented by *Consulted Dr Re memory*) at baseline, was noted as a probable confounder. In Tables at Appendix 6.D for final models, *consulting Dr Re memory* was a critical attenuating covariate only for PPb standard temporal treatment. Although it was important for clarifying this specific model, in general it was not as influential as expected. Similarly, *physical health* (another confounder identified at Chapter Four) was required only for PPb standard temporal treatment models before attenuation was reported.

6.4.5.6 GAS interactions other than with time.

As mentioned, the only significant interactions in fully adjusted models were for *anxiolytics**GAS (or lagged-GAS). The significant effect of the interaction was a consequence only of the difference between subgroups (described at Section 6.3.2.2.1) and their predicted DSB outcomes. These different outcomes appear to have been driven not by different slopes in the fully adjusted models, but only by different intercepts, meaning there was no difference in effect (on DSB) over time, only in the attributes of the participants in each subgroup. What these differences between groups are, and their implications, will be examined in the next chapter.

6.4.4 Methods

In this chapter I have examined both present effects and time-lagged effects of the main predictor, GAS. Lagged effects were structured to test the association between GAS at one

wave with the DV measurement at the following wave. It is possible also to consider effects that were lagged by two or more measurements (waves) instead of one. Petkus et al. (2017) included, lagged and double-lagged effects of the anxiety predictor into one model. However, this was using SEM rather than multilevel modelling, and the results were complex. For the analyses in this chapter, because of the low variance available and the dearth of significant results, examination of time-lagged effects by two or more measures were not presented in the results. Nonetheless, a representative sample of models were tested for the double-lagged GAS predictor, and all results were non-significant (for base models) or were attenuated.

6.5 Conclusions

There was no fully adjusted association between GAS and cognitive change except that an interaction with GAS was significantly in association with DSB. The interaction was *anxiolytics**GAS, and was significant in standard, lagged-GAS, and autoregressive, fully adjusted models. Because of missing data, analyses were limited and at times contradictory. However, it appears the significant interaction may reflect only different intercepts between categories of participants, rather than a change over time. The following chapter will investigate subgroups in greater depth.

There were interesting observations revealed by these analyses. Inclusion of *Time* and *time*-interaction terms made no difference to the identification of final models. Depression was confirmed as an important confounder for some outcome variables. And, variance explained by most models was trivially small, implying the larger, unexplained proportion of variance in the DVs could be influenced by, as yet, unknown confounding effects.

From the literature, time-lagged models are rare. Had there been more comprehensive analyses in the past, using such methods, or if there are more such analyses in future, meta-analyses may have greater potential to identify and differentiate the present and lagged effects of anxiety upon cognitive ageing.

CHAPTER SEVEN:

Stratifications of Multilevel Models

Abstract

Background: This chapter investigates a scoped selection of stratifications (or subgroups) for possible associations between Goldberg Anxiety Scale (GAS) and cognition, and extends the analysis of the *anxiolytics* subgroup, identified in the previous chapter.

Methods: Subgrouping variables were those identified at Chapter Six as predictors which remained in significant association with cognition, in fully adjusted models. As foreshadowed at Chapter Three, additional subgrouping variables were those quantifying levels of persistent GAS. Models were analysed using SPSS Linear Mixed Models (LMM). Alternative temporal treatments, introduced in the previous chapter, were included in the analyses by subgroup.

Results: Only the mentioned *anxiolytics* subgroup was identified with significant association between GAS and cognition. For the *anxiolytics* subgroup the association was with working memory (digit span backwards), with coefficient = 0.215 (0.001–0.429), $p = .049$.

Discussion: Examination of these results included evaluation of credibility criteria for subgroup analysis, available in the literature. This examination placed doubt on the credibility of the result for the *anxiolytics* subgroup.

Conclusion: Within the PATH data, there remains only marginal, and possibly unreliable evidence for association between anxiety and age associated cognitive change.

7.1 Introduction

This chapter extends the analysis of Chapter Six, by investigating stratifications of the regression models for time-varying anxiety.

Here and in the literature, "stratifications" and "subgroups" are interchangeable terms. Subgroups within subgroups are referred to as "compounded". This is a similar concept to "layering" of stratifications.

Interactions (considered in the previous chapter) can be interpreted as subgroups when at least one of the variables is categorical (Baron & Kenny, 1986). Interactions were constructed in Chapter Six from the covariates (CVs) which remained in significant association with the dependent variables (DVs) in relevant, fully adjusted models (Table 6.1). This chapter deploys the same CVs as subgrouping variables, but only for models involving DVs selected for their relatively high level of variance explained by the fully adjusted models. The significant interaction reported at Chapter Six, for the categorical variable *anxiolytics*, remains relevant to the present chapter.

This scoping was because of the need to minimise the models to be analysed. A challenge with analysis by stratification is that there are endless permutations possible, which can lead to over analysis, yielding poor reliability of results because of the potential for highly situational specifics (Epstein, 1983). Additionally, Sun, Briel, Walter, and Guyatt (2010) recommended investigation of subgroups only upon a priori hypotheses. Interpreting Sun et al., such short-listing is a necessary precaution partly to confirm validity of the result (upon a priori criteria) and partly because of the prospect of Type One Error (false positive) arising by chance from a long list of similar tests. Thus, analyses in this chapter were limited by restricting subgroupings to prospective associations suggested by theory or previous results.

Stratifications have been limited to two categories: subgroups by variable identified at Table 6.1; and, subgroups by levels of persistent anxiety. These subgroups based on persistence of anxiety will be defined in Methods, consistently with previous chapters. Persistence of anxiety was described (Chapter One) as likely to be necessary for anxiety to be a risk factor for cognitive ageing.

Except to consider more deeply any significant findings, compound subgroups were limited to a depth of two levels (subgroups within subgroups), and not all level two permutations were investigated. Small cell sizes also, excluded some permutations. Alternative temporal treatments (Section 6.2.4.4) were not investigated except where significant findings in the standard temporal treatment suggested further investigation. This was considered reasonable, based on the results in Chapter Six which revealed no results from alternative temporal treatment that were not already apparent in the standard treatment for the similar model.

Because of these necessary constraints the analyses by stratification of multilevel models is intrinsically limited and does not attempt exhaustively to investigate all possibilities. However, within these limits, subgroup analysis is an important attempt to identify classes of participants for whom an association between anxiety and cognition might otherwise remain hidden.

7.2 Methods

7.2.1 Research Questions

This chapter addresses both primary research questions and secondary research question C, as defined at Chapter Three (Section 3.2.2). The primary questions were:

(5) Is anxiety a risk factor for the rate of age-associated cognitive decline?

(6) Is anxiety a risk factor for incident cognitive impairment?

The secondary question was:

"Are there subsets of participants for whom associations are different?

Firstly, comparisons will be performed between groups with and without chronic anxiety, defined by persistence of anxiety at various symptom levels, for two or more waves of data. Secondly, subsets may be identified by confounding variables (Section 3.2.1.d.iii)."

7.2.2 Scoping of Subgroups

Selections of DVs for investigation were drawn from Table 6.1 and based on the level of variance explained (the higher the better) in the relevant fully adjusted models at Appendix 6.E. These DVs were: *symbol digit modality test* (SDMT); *digit span backwards* (DSB); and, *spot the word* (StW). For these DVs, the variance explained by fully adjusted models were, respectively: 7.3%; 5.7%; and 17.1%. Models for remaining DVs at Appendix 6.E, explained less than 5%. The subgrouping variables were baseline CVs indicated at Table 6.1 for each of these selected DVs. These resulting subgrouping variables are listed at Appendix 7.B, Tables 1 to 3 respectively, for each of the DVs.

The CVs drawn from Table 6.1 for subgrouping, were supplemented by dichotomised variables for persistence of anxiety, which were configured to indicate whether the participant had at least two measurements (over the four waves) of a high level of anxiety (GAS≥5 symptoms) or a clinical level of anxiety (GAS≥7 symptoms). Persistent, clinical GAS is referred to here also as "chronic GAS". These additional grouping variables were foreshadowed at Chapter Three, and the cut-points were based on previous research (Chapter Two).

Relevant to the scoping of subgroups, was a set of principles identified in the literature. Sun et al. (2010) addressed the question of whether subgroup effects were believable. They placed some doubt on subgroup analysis and provided criteria for judging the credibility of

such effects. Based on these criteria, the authors recommended limiting the scope of subgroups. Their criteria are reproduced at Section 7.2.3.

There is need to take precautions with this analysis not only from the theoretical perspective offered by Sun et al. but also from consideration of the data. One of the characteristics of the PATH data for the variables considered here, is that there are data missing from one or more variables for a high proportion of cases and the level of missingness is exacerbated by the length of the list of covariates. Multilevel modelling can cope well with missing data but when subgrouping, and particularly compound subgrouping divides the data into small cells, such a heavy burden of missing data may yield many cells void or close to void of data. Results from stratified analysis may then be appropriately regarded as of limited validity, unless demonstrated otherwise.

Three layers of stratification often produced a preponderance of small and empty cells. Level 3 compounding was, therefore, not investigated beyond this finding. There was a further limitation placed on the permutations of StW models. Mean StW scores were demonstrated at Chapter Four to trend upwards over the four waves of data. This trend is different to other cognitive measures and may be explainable as a consequence of new learning by participants (see description at Table 4.1), but this DV is of less interest to investigation of anxiety as a predictor of cognitive ageing. StW was investigated only to the first level of subgrouping, with the open contingency to investigate more deeply if a significant association were found.

7.2.3 Credibility Criteria for Subgroup Analyses

Eleven criteria for assessing the credibility of subgroup analysis were recommended by Sun et al. (2010). These criteria, addressing the perspectives of design, analysis, and context, are reproduced below (with author permission).

Credibility Criteria for Results of Subgroup Analysis

Design

1. Is the subgroup variable a characteristic measured at baseline or after randomisation?
2. Is the effect suggested by comparisons within rather than between studies?
3. Was the hypothesis specified a priori?
4. Was the direction of the subgroup effect specified a priori?
5. Was the subgroup effect one of a small number of hypothesised effects tested?

Analysis

6. Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?
7. Is the significant subgroup effect independent?

Context

8. Is the size of the subgroup effect large?
9. Is the interaction consistent across studies?
10. Is the interaction consistent across closely related outcomes within the study?
11. Is there indirect evidence that supports the hypotheses interaction (biological rationale)?

7.2.4 Linear Mixed Models

General estimating equations (GEE), the main modelling method selected in the previous chapter, was vulnerable to small cell sizes. Linear mixed models (LMM) were adopted for the present chapter, as a more stable method for the analysis required for the greater, cell-size problem presented by the stratifications. LMM provides the additional advantage of allowing calculation of random effects, (provided fixed effects are demonstrated). LMM methods are detailed at Appendix 7.A.

7.3 Results

7.3.1 Subgroup Results

Results are reported at Appendix 7.B, Tables 1 to 3 respectively for the DVs: SDMT, DSB, and StW. Each table provides, for each subgroup and sub-subgroup, the unstandardised coefficient, 95% confidence interval (CI), and sample size, for the association

of GAS with the nominated DV. Following each table is a summary and interpretation of the key findings.

The single significant finding was for the baseline *anxiolytics* subgroup, for outcome variable, DSB: coefficient = 0.215 (0.001–0.429), $p = .049$, $n = 126$.

Layering of *anxiolytics* with *education* produced a mixture of invalid and non-significant models (results not shown). The only other DV at Table 6.1 with *anxiolytics* as a significant CV, was *immediate recall* (IR). Subgroup tests on IR did not yield any significant association between GAS and the DV (results not shown).

7.3.2 Further Investigation of Anxiolytics Subgroup

7.3.2.1 Effect size.

The effect size for the *anxiolytics* = Yes subgroup was 0.215 (.001–.429). This means, for a unit difference in predicted DSB, there would need to be a 1/0.215 (= 4.65) difference in GAS score (on a scale of 0 to 9). A unit difference in DSB (scale of 0 to 10) over 12 years represents a mean 2.5% change in score per wave, or 0.6% a year. Therefore, the effect on DSB was small, for large differences in GAS.

7.3.2.2 Random effects

For the *anxiolytics* (Yes) subgroup, upon introduction of random effects for GAS to the model, fixed effects were attenuated, and the random effects were non-significant or redundant (results not shown).

7.3.2.3 Graphical interpretations.

Table 7.1 provides the mean (centred) GAS score, by wave, for each of the *anxiolytics* subgroups. Figure 7.1 is a graph of the same figures. There is little significant change in GAS for the *anxiolytics* = Yes group, and no change over time for the anxiolytics = No group. There is a difference in intercept between the two subgroups. The Yes subgroup has a significantly higher level of GAS symptoms.

Table 7.1
Centred GAS Score for each Anxiolytics Subgroup

Baseline Anxiolytics Subgroup	GAS: centred on baseline mean Mean (95% CI), n for non-missing data			
	W1	**W2**	**W3**	**W4**
No	-.139 (-.229–-.049), *n* = 2289	-.176 (-.271–-.081), *n* =2016	-.184 (-.278–-.090), *n* = 1804	-.070 (-.174–.034), *n* = 1515
Yes	2.584 (2.10–3.07), *n* = 125	2.202 (1.671–2.733), *n* = 102	1.767 (1.240–2.293), *n* = 90	1.225 (0.639–1.810), *n* = 73

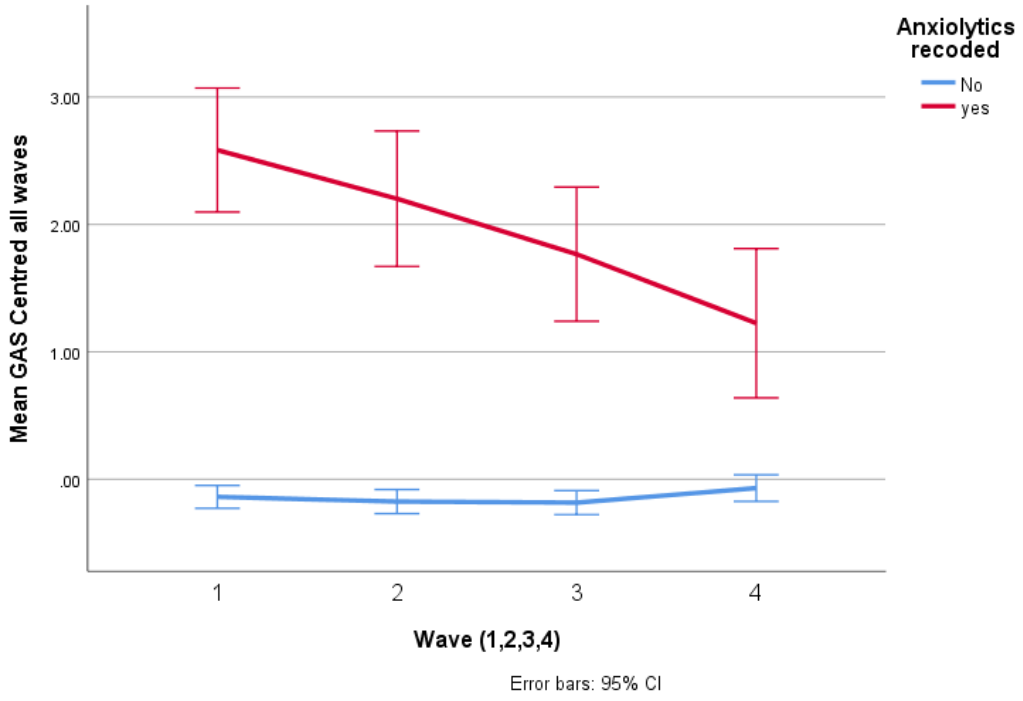


Figure 7.1. Centred GAS Score for each Anxiolytics Subgroup

At Table 7.2 and Figure 7.2, the DSB scores, predicted by LMM, are presented for the same *anxiolytics* subgroups (Yes & No), as in Table 7.1 and Figure 7.1. There is an apparent difference in intercept but not in slope. The predicted DSB for the Yes group at Table 7.2 indicates a small but non-significant, positive slope. This is in apparent contradiction to the mixed models result which was positive and significant (Section 7.3.1), although only

marginally so, with p = .049. Also, the mixed models effect size was small (Section 7.3.2.1). Table 7.2 and Figure 7.2 were both produced by different software (SPSS Explore & Line Graph by Legacy Dialogue) to the mixed model (SPSS Mixed Models; Appendix 7.A). The apparent contradiction between the two sets of results is possibly due to different treatment of small cell sizes and missing data.

Table 7.2
Predicted DSB Scores by Anxiolytics Subgroup

Baseline Anxiolytics Subgroup	DSB: predicted by LMM Mean (95% CI), n for non-missing data			
	W1	W2	W3	W4
No	5.348 (5.289–5.407), *n* = 323	5.346 (5.283–5.409), *n* = 286	5.338 (5.271–5.404) *n* = 262	5.350 (5.280–5.421) *n* = 216
Yes	4.390 (4.101–4.677), *n* = 20	4.516 (4.179–4.853), *n* = 16	4.504 (4.70–4.838), *n* = 16	4.685 (4.349–5.020), *n* = 11

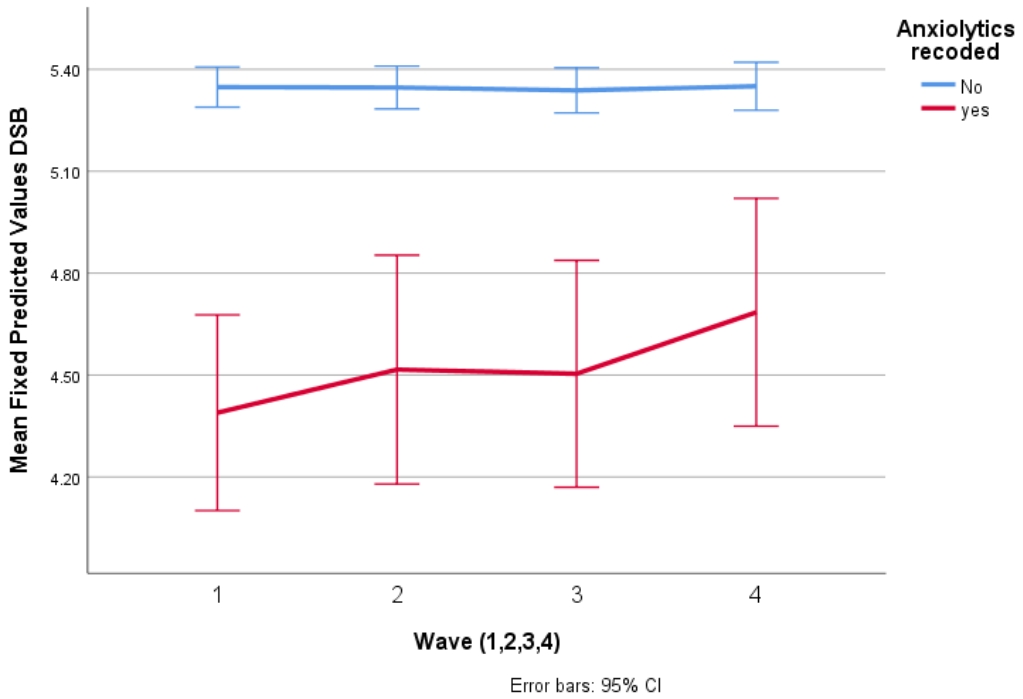


Figure 7.2. Predicted DSB Scores by Anxiolytics Subgroup

7.3.2.4 Credibility criteria.

For evaluations of the credibility criteria from Section 7.2.3, see Table 7.3.

Table 7.3
Evaluation of Credibility Criteria

Feature	Criterion Number	Criteria	Evaluation
Design	1	Is the subgroup variable a characteristic measured at baseline or after randomisation?	**Yes.** The subgrouping variable, *anxiolytics*, was measured at Baseline.
	2	Is the effect suggested by comparisons within rather than between studies?	No. This subgrouping has not been observed in other studies, and is not suggested by previous observations within PATH.
	3	Was the hypothesis specified a priori?	No.
	4	Was the direction of the subgroup effect specified a priori?	No.
	5	Was the subgroup effect one of a small number of hypothesised effects tested?	No. Considering the analyses here, and in the interactions examined in the previous chapter, a moderately large group of effects were tested.
Analysis	6	Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	**Yes.** The *interaction* reported at Chapter Six, found a highly significant effect $p = .002$.
	7	Is the significant subgroup effect independent?	**Yes.** The subgroup effect was determined within a fully adjusted model.
Context	8	Is the size of the subgroup effect large?	No. The subgroup effect size was moderate. The effect size of the subgroup was 0.215 (.001–.429), $p = .049$.
	9	Is the interaction consistent across studies?	No. There is no other known study on this subgroup effect.
	10	Is the interaction consistent across closely related outcomes within the study?	No. There was no closely related association.
	11	Is there indirect evidence that supports the hypotheses interaction (biological rationale)?	Marginal. See arguments regarding validity, at Section 7.4.3.2. There was no sustainable argument to support a predictive association between GAS and anxiety within this subgroup.

Regarding item 11 of Table 7.3, a relevant observation of the results is that study participants who consumed anxiolytics at baseline, had higher GAS scores at baseline (Table 7.1 and Figure 7.1) and these GAS scores declined over time. Also, they had lower DSB

scores at baseline, and these DSB scores improved slightly but not significantly (Table 7.2 and Figure 7.2).

7.3.3 Assumptions

Assumption tests were accepted. Notable, was that residuals produced by MLM models, often had only marginally normal distribution when cell sizes were small. However, no result was rejected on these grounds.

7.4 Discussion

7.4.1 Overview

One subgroup was identified, for which a significant association was found between GAS and cognition; in this case the outcome variable was working memory (DSB). The subgroup was for participants who reported, at baseline: consumption of *anxiolytics*. The result will be evaluated, but firstly it is useful to consider perspectives from the literature.

7.4.2 Literature

From Table 2.2, few previous studies (5 of 37) examining associations between anxiety and cognitive ageing, accounted either for anxiolytics or benzodiazepines. These analyses typically involved only controlling for such consumption, within models which were focussed on other results. None of these studies that I am aware of, performed moderation or stratification analysis to identify such a class of participants. More generally, subgroup analysis appears to be a rarely adopted method.

In the context of this thesis, and particularly after the results of Chapter Six, subgroup analysis was important to consider. However, Sun et al. (2010) offered insights into the credibility of subgroup analysis. Adopting the criteria of Sun et al., the evaluation below, of the results from this chapter, will serve to confirm their cautionary note.

Although not based on subgroup analysis, Cherbuin et al. (2009) considered anxiolytics within PATH data, and found baseline anxiolytics predicted progression to MCI at Wave 2. Their modelling method was logistic regression, and they adjusted for a long list of CVs, as I have here. The same study did not find an association between anxiety and cognitive change.

7.4.3 Interpretation and Evaluation of Results for the *Anxiolytics* Subgroup

7.4.3.1 Comparison with Cherbuin et al. (2009).

The result in this chapter, for the *anxiolytics* subgroup, implies that for these participants only, there was a marginally significant, positive association between GAS and DSB scores, over the four waves of the study. This is on a different time scale than the analysis by Cherbuin et al. (2009), which considered only two waves, the outcome variable was different (diagnosis of MCI, rather than DSB score), the result indicated an effect in the opposite direction, and importantly, the result by Cherbuin et al. was for association between anxiolytics and cognition, not between GAS and cognition. So, there appears little on which to make a comparison. However, if *anxiolytics* as a predictor in the Cherbuin et al. study were regarded as a proxy for anxiety then the apparently, opposite, cognitive effects would call for further evaluation of the results. This evaluation is presented next. But firstly, it should be noted from Appendix 6.E, Model S, that for the full four waves of the PATH data, in the fully adjusted model for MCI (the DV reported by Cherbuin et al) there was no association between either GAS or anxiolytics, and MCI. Thus, the association reported by Cherbuin et al. between waves 1 and 2, was attenuated over the full length of the study.

7.4.3.2 Validity of the *anxiolytics* subgroup results.

Following are alternative perspectives or rationales, for and against acceptance of the reported association between anxiety (GAS scores) and DSB for the subgroup which consumed anxiolytics at baseline:

A. Prescription for anxiolytics may be an alternative measure of anxiety. However, prescription of anxiolytics (reflecting a diagnosis of anxiety) is not the same as consumption of anxiolytics, which is a treatment, and as such would be expected to modify anxiety levels, and therefore, protect against the effects of anxiety upon cognition. Within the four-yearly Waves, the PATH data do not record the relative timing of GAS and cognition scores, and anxiolytics prescription by a doctor. Additionally, PATH does not provide data on the period of consumption of the medication. Therefore, there were insufficient data to analyse the effects of *anxiolytics* as though its administration were an element of a treatment intervention trial. Notwithstanding these limitations, an apparent protection against the effects of anxiety is indicated in the data. See Figures 7.1, for effects on anxiety, and Figure 7.2 for effects on DSB scores. In the anxiolytics subgroup, anxiety trends downward and DSB scores improve (although not significantly so in the graph, but according to the LMM result). This rationale supports the credibility of the PATH results, disposes of the interpretation of *anxiolytics* as a proxy for anxiety, and questions the plausibility of the results from Cherbuin et al. (2009) because of an effect in the reverse direction.

B. If the rationale at A were true, and anxiolytics successfully protected against anxiety, then two other effects might be expected: (1) Other cognitive scores for the same subgroup (*anxiolytics*), might be expected also to improve; and, (2) The harmful influence of anxiety should be visible elsewhere, so that there would be an indication of a predictive association between anxiety and cognitive decline, independently of anxiolytics. These other effects were not apparent in the data.

C. From Appendix 6.E, Model G for the fully adjusted model predicting DSB, *anxiolytics* predicted DSB with coefficient = -0.958 (-1.873 – -0.042), $p = .040$.

This is the reverse sign of the effect of GAS upon DSB within the *anxiolytics* = Yes, subgroup. Model G refers to the full sample, and the subgroup results refer only to a sample of 126, and which includes a burden of missing data. However, these results with opposite effect place doubt, each upon the other. If the rationale at A, were accepted then it would be unlikely for the independent effect of *anxiolytics* upon DSB to be negative. This apparent contradiction may be a consequence of the combination of the weak association (of GAS with DSB in the *anxiolytics* subgroup) as delineated below at rationale D. If, however, the negative effect, in the full model G, were accurate then this would align with the result from Cherbuin et al. (2009) for the effect of *anxiolytics* upon MCI.

D. As noted elsewhere but summarised here, the finding of association (between GAS and DSB) for the *anxiolytics* = Yes, subgroup, was weak in six respects: (1) Small cell sizes; (2) Missing data (Section 7.2.2); (3) Small effect size (Section 7.3.2.1); (4) Marginal significance (p = .049); (5) Entry of random effects into the mixed models, produced attenuation of the fixed effects (Section 7.3.2.2); and, (6) By different software, calculation of mean (predicted) DSB by wave, with confidence intervals, produced (predicted) slope which was not significant (Section 7.3.2.3).

Considering these arguments for and against the plausibility of the reported result, the *anxiolytics* subgroup association with DSB should be qualified as a marginal effect that may not be reliable. Additionally, the subgroup was defined upon a binary variable, with limited information. It is, therefore, correct and important to evaluate the effect by criteria established for subgroups. This follows.

7.4.3.3 Subgroup credibility criteria applied to *Anxiolytics* results.

At Table 7.3 there were affirmative responses (in support of acceptance of the validity of the anxiolytics subgrouping) only for criteria 1, 6, and 7. Eight other criteria were negative, or in one case (11), *marginal*. Sun et al. (2010) did not attempt to weight the criteria for relative importance. They explained acceptance of a subgroup result would rarely be a binary 'yes' or 'no' but would more accurately be placed on a continuum which reflected relative uncertainty. On these criteria, the result appears to be of doubtful credibility.

7.4.3.4 Implications of association between anxiety and working memory.

Notwithstanding this doubtful credibility of an association between anxiety with working memory within the anxiolytics subgroup, the prospect that the result indicates a valid association remains to be interpreted.

The result implied that for higher but subsequently declining GAS scores, DSB scores improved over time (Section 7.4.3.2 A). This was only for individuals who reported consumption of anxiolytics at baseline. Speculatively, if anxiolytics were protective against the cognitive effects of anxiety then cognitive scores might be expected either to improve (as only DSB did), or to decline less rapidly. There may have been additional effects, hidden within the noise, of improvement or reduced decline, in other cognitive measures. Such hidden effects might be revealed only by further research, perhaps when more waves of the PATH data become available.

Without the benefit of such additional research, and considering the effect (anxiety X anxiolytics upon DSB) in isolation, the question remains as to what this isolated result might mean. For example, could DSB, as a measure of working memory, be unusually sensitive both to the damaging effects of anxiety and the remedial effects of anxiolytics? Might this mean that when both conditions apply, a result emerges? Although arguable, this prospect must remain as conjecture until further research can clarify the many unresolved issues, such

as whether a range of working memory tests may explain the dynamics more fully. Ideally such research would include a larger sample, and complete information on the drugs involved, their dosage, duration of treatment, and repeated measures for any return to treatment.

It is worth being reminded at this point, that there appears to be no other study with a similar result. Notwithstanding speculation about meaning, the finding is likely to be only an artefact of the data and the statistical tests applied.

7.4.4 Interpretation and Evaluation of Results for *Consulting Dr Re. Memory* Subgroup

The subgrouping variable, *Dr Re Memory* reflected cognitive change reported at baseline, and thus introduced temporal confounding because cognitive change preceded or coincided with any reported anxiety. Ideally, either these participants should be excluded from the sample (as others were at Chapter Four, for diagnosis of cognitive impairment), or regression models should be controlled for these effects. All fully adjusted models were indeed controlled for *Dr Re Memory* and, therefore, there is neither a need for further adjustment of the data or the results, nor a meaningful result that the subgroup on *Dr Re memory* implies anything about anxiety as a predictor of cognitive change.

7.4.5 Limitations

Stratification by persistent GAS does not permit a strictly valid, longitudinal analysis. Establishing persistent GAS included examination of GAS scores across all waves of the data. This method introduced the possibility, for example, that a GAS score at Wave 4 would contribute to establishing the presence or absence of persistent GAS. However, cognitive change may have commenced before Wave 4. Therefore, outcome would have preceded the presumed cause. Nonetheless, the persistence of anxiety was a central factor in the theory for a causal connection (Chapter One), and therefore persistence needed to be considered, even if by such methods. Despite these limitations, it remains of value to establish even this

methodology identified no significant association. Alternatives are possible, such as establishing a degree of persistence (in GAS) based only on data from the early waves and establishing cognitive change from data based only in the later waves. However, this reduces the longitudinal time frame for each calculation. Nonetheless, such computations were undertaken, but without identifying significant results (results not shown).

An additional limitation was the high proportion of missing data, particularly for analyses requiring modelling within small cell sizes. Consequently, many models were inconclusive. They produced either no result or warning messages such as failure to converge.

7.5 Conclusions

The significant result for association between GAS and DSB for the *anxiolytics* subgroup has not been invalidated but it has been demonstrated to be a marginal effect that may not be reliable, and there remains doubt about its credibility.

CHAPTER EIGHT:

Overview of Statistical Analyses, and Revised Meta-Analysis Results

Abstract

Background: This chapter provides a Summary and interpretation of statistical results from PATH, plus revision of the meta-analysis from Chapter Two with results from the PATH analyses.

Results: Key results were: (1) Meta-analysis of association between anxiety and MCI, based on six studies (including PATH) with relative risk (RR) = 1.024 (0.944–1.112), $p = 0.565$, $I^2 = 63.9\%$; (2) Meta-analysis for association between anxiety and dementia, based on five studies (excluding PATH, from which a result was unavailable), with relative risk (RR) = 1.81 (1.22–2.70), $p = 0.003$, $I^2 = 78.6\%$; and, (3) For PATH participants who consumed anxiolytics at baseline ($n = 126$), an association of the Goldberg Anxiety Scale (GAS) with working memory (digit span backwards; DSB) over 4 waves and 12 years, was coefficient = 0.215 (0.001–.429), $p = .049$.

Discussion & Conclusion: All results were inconclusive. The meta-analyses were unreliable because of the diversity of sample characteristics and methodologies within the small samples of studies from which they were drawn, and the *anxiolytics* subgroup result was evaluated as unreliable because of the combination of small effect size, marginal significance, missing data & small cell sizes, and this being an isolated result without corroboration from other sources or closely related models.

8.1 Introduction

The methods strategy at Chapter Three, delineated the research questions for this thesis, and presented the plan for analysis of the PATH data (Table 3.1). These statistical analyses followed, in Chapters Four to Seven. This chapter briefly overviews the analyses and represents the results in summary form.

8.2 Overview of Analysis of PATH Data

8.2.1 Chapter Four: The Data

The PATH project was introduced in Chapter Four with extensive descriptive information, and unadjusted correlations, both cross-sectional and between various time points. From these correlations, a set of variables was identified (Section 4.4.9.1), representing potential confounders for longitudinal associations between anxiety and cognitive change. This set of variables was progressively refined in following chapters.

8.2.2 Chapter Five: Is Anxiety a Baseline Predictor of Cognitive Ageing?

Chapter Five provided the first, adjusted, regression analyses of the PATH data. All predictors were entered into models at baseline values only, and outcome variables represented change in cognitive performance (between Waves 1 and 4) or incident cognitive impairment (by Wave 4). Methods were linear and logistic regression, except for a single test by Generalized Estimation Equations (GEE) to challenge one significant result, by considering repeated measures of the outcome variable. Variables tested as predictors representing anxiety, were the Goldberg Anxiety Scale (GAS), its items, its derivatives, and its proxies. One fully adjusted association was found, between GAS, item 2 (*worry*) and change between waves 1 and 4 in *Spot the Word* (StW). The result was coefficient = 2.447 (0.734–4.161), $p = .005$. However, this association was attenuated within a fully adjusted, GEE model.

8.2.3 Chapter Six: As a Time-Varying Variable, Does the Goldberg Anxiety Scale Predict Cognitive Ageing?

This was the first analysis considering association based on repeated measures of both anxiety and outcome variables. Only GAS was examined, as the primary measure for anxiety. Multilevel models were examined for association with Purdue Pegboard both hands (PPb), Symbol Digit Modality Test (SDMT), Digit Symbol Backwards (DSB), Immediate Recall (IR), Mini Mental State Examination (MMSE), and Spot the Word (StW). Similarly, binary outcomes by wave, were incident MCI and dementia. Models were fully adjusted by the set of variables at Section 6.2.5. The exception was dementia, for which a fully adjusted model did not converge, possibly due to missing data and small cell sizes.

Models were examined also for alternative temporal treatments (Section 6.2.4.4), which were principally about investigating delayed effects of GAS upon the outcome variables. These alternative temporal treatments were: *time-lagged*; *autoregressive*; and, *cognitive change*.

No fully adjusted model was significant for association between GAS and any cognitive measure.

Covariates remaining in significant association with outcome variables in fully adjusted models, were tested also in interactions with GAS. One, such interaction remained significant when fully adjusted. This was *anxiolytics**GAS in association with DSB. *Anxiolytics* was a binary variable representing the consumption, or not, of prescribed anxiolytics at baseline. The result was, odds ratio (OR) = 1.382 (1.132 to 1.688), $p = .002$. Two, alternative, temporal models for the same interaction were also significant. They were for the *time-lagged* and *autoregressive* treatments. Investigation of this interaction, with all temporal treatments, demonstrated the association reflected different intercepts for the binary values of *anxiolytics*, but did not represent change over time. The interaction was identified as representing

subgroups of participants and further investigation was deferred to Chapter Seven, which was planned for the wider and specialised investigation of *stratifications*, or *subgroups* (interchangeable terms).

8.2.4 Chapter Seven: Stratifications of Multilevel Models

This was an extension of the analysis by models investigating time-varying anxiety, commenced in Chapter Six. Subgrouping variables were those identified at Table 6.1 as predictors which remained in significant association with cognition, in fully adjusted, multilevel models. As mentioned at Chapter Three, additional subgrouping variables were those quantifying levels of persistent GAS. The primary analytical method was linear mixed models (LMM). Alternative temporal treatments, introduced in the previous chapter, were included in the analyses by subgroup but only where the standard temporal treatment identified an association.

One subgroup was identified, with significant association between GAS and cognition. This was the *anxiolytics* subgroup with outcome variable, DSB. The result was: coefficient = 0.215 (0.001–0.429), $p = .049$. Upon analysis of the direction and size of the effect, and the marginal significance, the conclusion was the result was likely to be unreliable and may not be credible.

8.3 Summary & Revision of Meta-analysis

8.3.1 Summary of Meta-Analysis Results from Chapter Two

At Chapter Two, meta-analysis of results from the literature, for rate of cognitive *decline*, was not possible due to heterogeneity of methodology. For the association between anxiety and incident cognitive *impairment*, meta-analyses were presented at Chapter Two, in three parts: (1) from Gulpers et al. (2016), with a census date of January, 2015, and after removing studies which were not adjusted for *depression* (Section 2.4); and, (2) My updated meta-analysis based on a systematic review, and including studies published until the census date

of July, 2017 (Section 2.3.2). Both sets of results, which are re-presented here, excluded studies unadjusted for baseline cases with cognitive impairment. These results were:

(1) From Gulpers et al. after removing studies without adjustment for *depression*:

i. Progression from cognitively normal to MCI:

Relative risk (RR) = 1.92 (1.41–2.63), $p = 0.001$, $I^2 = 0.00\%$. Based on 3 studies; and

ii. Progression from cognitively normal to dementia:

RR = 1.68 (0.94–3.02), $p = 0.081$, $I^2 = 87.5\%$. Based on 2 studies.

(2) My updated meta-analysis at Chapter Two:

i. Progression from cognitively normal to MCI:

RR = 1.07 (0.90–1.26), $p = 0.440$, $I^2 = 70.8\%$. Based on 5 studies; and

ii. Progression from cognitively normal to dementia:

RR = 1.81 (1.22–2.70), $p = 0.003$, $I^2 = 78.6\%$. Based on 5 studies

Results at (1) and (2), are contradictory, with association demonstrated for MCI only, at (1), and for dementia only, at (2). Both sets of results were based on a small number of studies which are inadequate for meta-regression to determine if differences between studies were related to important parameters such as: age range of participants; sex distribution; method of measurement of anxiety by diagnosis or self-report; and, the set of covariates identified for adjustment. All these results were based on small samples of studies and may not be reliable.

8.3.2 Revision of Meta-Analysis

The only result available from PATH for updating the previous meta-analyses, was for GAS as a predictor of MCI. The result from Chapter Six, for the fully adjusted model for dementia, did not converge and was discarded. As mentioned earlier, meta-analysis for the rate of cognitive decline was not possible.

For MCI, the single-study result at Appendix 6.E, Model S, was equivalent to RR = 1.015 (0.950–1.077), $p = 0.642$. Including this result in my meta-analysis for MCI, yielded a new result of: RR = 1.024 (0.944–1.112), $p = 0.565$, $I^2 = 63.9\%$. This confirmed my previous result that no association with MCI was identified. The significant association for dementia, by my meta-analysis at Chapter Two, remained unrevised by the PATH data.

8.4 Discussion & Conclusion

A single, subgroup result indicating an association between GAS and DSB was marginally significant but of questionable reliability and credibility. The sequence of meta-analysis results also points to questionable reliability and credibility. The most recently published meta-analysis (until the census date for this thesis, of July 2017) was by Gulpers et al. (2016). When excluding studies for which there was no adjustment for depression, the single significant result from Gulpers et al., was for MCI (based on only three studies). Contrary to this, my updated meta-analysis at Chapter Two, including more recent studies than those in Gulpers et al., found no association with incident MCI and this (non-result) was confirmed after inclusion of results from PATH. For incident dementia, my updated meta-analysis (at Chapter Two) found an association, which was contrary to results from Gulpers et al. (2016). My updated result for dementia was not revised with results from PATH and remains as the only significant, meta-analysis finding from this thesis. However, this result for dementia may also be unreliable. As noted at Section 2.3.2.2, the high dispersion indicated real, methodological or sample differences between studies. These important differences were illustrated at Table 2.7.

From analysis of published results and PATH data, there was no, conclusive finding for a predictive association between anxiety and cognitive change.

CHAPTER NINE:

Conclusions and Recommendations

Abstract

This final chapter overviews the theoretical, methodological, and statistical findings of this PhD project, to describe the current state of research, its limitations, implications, and possible future. Chapter Eight summarised the statistical results from PATH and from the research literature. These results were evaluated as inconclusive. This chapter attributes these weak results to limitations, both in the PATH data and in data and methods reported in the literature. A longitudinal association between anxiety and cognitive ageing may not be possible to identify without strategic changes to the methodology, particularly for measuring anxiety and in the longitudinal analysis of associations with cognitive ability. Extending the research to investigate causality would require additionally a method for random control trials. Recommendations are provided for strategic development of research methods.

9.1 Introduction

The question was whether anxiety is a risk factor for cognitive ageing. This is an important question because it suggests an opportunity to mitigate risk of cognitive decline and dementia. This thesis has placed doubt on published results and highlighted important limitations in the published methodology. In this chapter, I discuss the strengths and limitations, and necessary changes in research methodologies.

9.2 Discussion

9.2.1 Results

Chapter Eight summarised the results from the analyses here of PATH data, and from the literature. Essentially, these outcomes were: (1) an unreliable result with small effect, that anxiety predicted improved working memory, based on a small subgroup within PATH of participants who consumed anxiolytics at baseline; and, (2) an unreliable meta-analysis result based on just five previous studies, that anxiety predicted incident dementia. All other results were either non-significant or dismissed as invalid. The necessary inquiry at this point is to determine why the results, from both PATH and the literature, were inconclusive.

9.2.2 Possible Reasons for Inconclusive Results

In addition to the insufficiency of studies to allow adequate meta-analysis, there are two possibilities to explain the results in this thesis: (1) There was no effect to be found; or (2) Measures deployed were inadequate to detect an association.

More specifically, within PATH, associations may have been undetected because of: missing data; small cell sizes; inadequacies of the anxiety measure (Sections 1.2 and 9.2.2.1); relatively young age of participants (60 to 76 years); unavailability of data to verify

persistence of anxiety (between four-yearly waves); unavailability to follow-up of some participants who, on average, were more anxious, more depressed and less cognitively able than participants who remained within the study; or any combination of these limitations.

Within the literature, as pointed out in the first two chapters of this thesis, there were many important limitations, some of which were:

1) A gap was apparent between the formal definition of anxiety, and the operationalisation of anxiety in self-report measures. There are also biological ambiguities. Without these distinctions in the operationalisations of anxiety measures, there is apparent risk of confusing stress and anxiety (Section 1.2.1.2).
2) The only alternative to self-report of anxiety was diagnosis, which has its own limitation of being a binary result, one implication of which is that sub-clinical levels of anxiety have been grouped with zero anxiety.
3) There is the possibility that anxiety instruments need to be reconfigured for the aged (Section 1.2.2) and may need to account for stages in development of anxiety disorders (Section 1.2.3.2).
4) There has been almost a complete absence in the various methodologies, of attempted identification of the persistence of anxiety levels and delayed effects of anxiety. Studies which have targeted "state" or acute anxiety as the central predictor, cannot have measured long-term effects of anxiety by this measure alone. Similarly, studies which have not distinguished between acute or chronic anxiety, have introduced unknown error. Studies which have targeted chronic anxiety by use of the Spielberger state-trait anxiety inventory (Section 1.2.3.1) have also introduced an unknown degree of ambiguity with the measure of depression (Section 1.2.1.3). If correctly measured, persistence of anxiety could be analysed by stratification of participants according to the persistence of their

symptom levels. Multilevel modelling can incorporate the longitudinal effects of anxiety, testing it as a time-varying variable, but such modelling does not distinguish between effects from short- and long-term exposure to anxiety without additional analysis (such as the suggested stratification) which has been absent from published studies. Additionally, standard multilevel modelling assumes only an immediate effect (Section 6.2.4.4) at each measure. Studies which look for delayed effects are rare (Section 6.4.2). If the theory presented at Chapter One is correct, that cognitive damage from anxiety is a long-term process (Section 1.4.3), then most research has not investigated the essential mechanisms. Finding a longitudinal effect without identifying the nature of the anxiety (persistence and delayed effects) which predicts the cognitive outcome, opens the potential for misinterpretation. For example, if it is true that only long-term, or chronic anxiety (and not acute anxiety) predicts cognitive ageing, but a statistical association were found (without distinguishing the nature of the anxiety), then the apparent association may have been produced not by anxiety but by other effects. These other effects could include symptoms interpreted as anxiety, but which may have been caused by underlying stress or depression (Section 1.2.1.3). Or, there may have been essential covariates overlooked. On this last point it is worth noting most published studies have not provided statistics on unexplained variance in their models. From the PATH data, I have noted the explained variance was small.

5) Prospective lists of covariates and modifiers need also to consider the possibly confounding biological measures such as cortisol and DHEAS (dehydroepiandrosterone sulphate) levels, key genetic predictors of dementia (particularly APOE e4), and hippocampal volume. These measures (except

DHEAS which was unavailable) were not indicated as confounding covariates in the PATH analysis (possibly due to data limitations). However, this biological information does need to be tested for confounding effects before excluding such covariates from regression models. Most studies have not considered these measures.

6) Covariates need also to consider the confounding effects of anxiolytics and the subset, benzodiazepines, which have been shown to modify anxiety and may be associated with long term cognitive decline (Section 1.4.4).
7) There have been relatively few studies which were acceptable for meta-analysis. Meta-analysis on five studies (for association with incident dementia) produced an unreliable result, as indicated at Chapter Eight by the dispersion parameter, I^2 = 78.6%, and as demonstrated by a diversity of sample and methods characteristics, at Table 2.7. Meta-regression was unavailable (for such a small sample of studies) to verify effects of major differences in methodology and effects of important covariates such as *sex*, *age*, *education*, and *depression*.

Without being able, categorically and definitively, to identify causes of the inconclusive results, these strong limitations in the methods would place doubt, even upon apparently stronger results.

9.2.3 Addressing Weaknesses in the Methodology

There is a manifest requirement for more studies which qualify for meta-analysis. However, before this happens it would be necessary to resolve methodological difficulties as described above. Chiefly, research is needed to establish improved measurement of anxiety, which:

1) distinguishes between anxiety and stress response;
2) Recognises all definitional elements of anxiety;

3) Recognises any different elements of anxiety experienced by the aged; and,

4) Provides a mechanism to record duration of anxiety symptoms.

Item 2) may not be possible within a self-report procedure. If this is so then self-report could be supplemented with diagnosis. Diagnosis alone, however, would need to be extended from a binary to a dimensional result, possibly with a symptom count.

Analytical methods need also to reflect the long term and delayed effects of anxiety, assuming the theory at Chapter One is a correct description of the neuropsychological mechanisms. Additionally, analysis should routinely consider a wide diversity of covariates and modifiers, as it was here.

9.2.4 The Neuropsychological Mechanisms

The Diathesis-Anxiety Heuristic of Cognitive Ageing, presented at Figure 1.5, remains hypothetical. Further research is required to verify the many links and effects, as well as the validity of the combined effects as represented by the overall model. The prospect of feedback loops needs to be investigated at both biological and psychological levels. Further research will be required to establish if these reciprocal paths function collectively as complex feedback loops, and if they do, whether anxiety and cognitive change might be modifiable through some form of intervention within such loops. If a feedback style of system-control is identified, then this will be key to much future research and clinical practice.

The causal paths suggested by Figure 1.5 are complex. An assumption of a simpler system of causal links may be incorrect and may lead to research which misses essential information. If this is so then conclusive evidence of whether anxiety predicts cognitive ageing, may continue to be illusive.

9.2.5 Establishing Causality

The title for this thesis introduced the phrase “risk factor”, implying not just prediction but causality. Investigating *prediction,* has been the sole objective of all prior research. To establish causality, it will be necessary to investigate further the neuropsychological mechanisms as suggested, and to introduce a form of randomised control trial (RCT). Although the random assignment of persistent anxiety would be neither practical nor ethical, RCT intervention studies would be feasible, by randomly assigning a variety of anxiety treatments including placebo treatment (Section 1.1.2.2.2).

Blind, placebo controlled, random intervention trials, would need to observe the same protocols as improved observational studies, by employing better measures of anxiety, establishing persistence of anxiety, and controlling for a well-developed and comprehensive set of covariates (Section 9.2.3). Such a study could evaluate both the efficacy of the treatment compared to placebo, and the changes in cognitive performance. Possible research questions might include:

1. Does treatment of anxiety change the experience of anxiety?
2. Does treatment of anxiety protect the individual from cognitive decline or cognitive impairment?
3. Are anxiety level and persistence associated with cognitive change, independently of anxiety treatment?
4. Which anxiety measures have strongest association with results for questions 1 to 3?

Each of these questions could be explored more deeply by looking at covariate effects, moderation, and mediation. For example, does age moderate answers to the above questions?

9.2.6 Strengths

The important limitations have been expressed above (particularly in Sections 9.2.2 & 9.2.4), both for the present study and for the published reports on associations between anxiety and cognitive ageing. It is important also to outline the strengths of this PhD investigation and report. These are principally:

1. The comprehensive overview in Chapter One, of the neuropsychological mechanisms for anxiety and for linking anxiety with cognitive ageing.
2. Figure 1.5 particularly, provided an important heuristic of the association between anxiety and cognitive ageing while also demonstrating the prospect for feedback control.
3. Identification in Chapters Two and Eight, of the inconclusive nature of the meta-analysis of published results. This provides fresh motivation of further research and improved methods.
4. Identification of the prospect for an RCT by introducing treatment interventions.
5. Identification of weaknesses in the measurement of anxiety.
6. Identification of weaknesses in the analytical methods applied in the literature to identifying association, when this is theoretically likely to depend on the influence of anxiety over extended time periods.
7. Analysis of PATH data included investigation of possible delayed effects of anxiety upon cognition, and the possible influence of trait, persistent, or chronic anxiety in contrast to acute or state anxiety. These methods were unusual and in part unique.
8. Analysis of the PATH data included a comprehensive set of potentially confounding covariates. This was not always the case in published studies.

9. The finding from PATH data was inconclusive. Because PATH is a moderately large, population-based study, the result that there may be no association provides important corroboration with the conclusion from meta-analysis which also indicated an inconclusive result.

9.3 Conclusions

Whether anxiety predicts cognitive ageing remains unknown and may be unknowable in the present state of development of the research methodology. However, a plausible, theoretical explanation is available for such association. This theory needs further research to develop a more complete explanation of the neuropsychological mechanisms, including the prospect of feedback loops which may influence the effects of anxiety upon cognitive change. The contrast between theory and empirical results underlines the need for clarity and refinement of the research methods as delineated above. Finally, to establish causality would require not only the necessary developments recommended for valid analysis of association, but also blind, placebo controlled, random intervention trials, testing a variety of anxiety treatments.

Appendices

Appendix 4.A:

Exploratory Factor Analysis: Goldberg Anxiety Scale: Wave 1

A principal axis factor analysis was applied with oblique rotation (direct oblimin). Oblique rotation was chosen because any latent factors were not expected to be independent within this well-defined, single construct. The Kaiser–Meyer–Olkin (KMO) measure reported the sampling adequacy with, KMO = .82 ('meritorious', according to Hutcheson & Sofroniou, 1999) and all KMO values for individual items were greater than .73 (from the diagonal of the anti-image correlation matrix at Table 1), which is above the acceptable limit of .5 (Field, 2013). For reference, a correlation matrix is presented at Table 2. Eigenvalues were obtained for each factor in the data. Three factors had eigenvalues over Kaiser's criterion of 1 and in combination explained 61.16% of the variance. The scree plot showed an inflexion justifying only one factor. See Figure 1. Three factors were retained in order to interpret these differing results conservatively. Table 3 shows the factor loadings after rotation, together with internal consistency (using Maximum Guttmann's Lambda) along with Eigenvalues, and percentage of variance for each factor. The consistency test on factor 3 indicated inadequate consistency. The items that cluster on the same factor suggest that: Factor 1 - WORRY: represents being keyed up, worried, irritable and difficulty in relaxing; Factor 2 - SLEEP: represents sleep issues; and Factor 3 - SOMATIC: represents somatic issues including worry about health.

Table 4.A.1:
Anti-image correlation matrix for Goldberg Anxiety Scale, Wave 1

	Keyed-up	Worrying	Irritable	Difficulty relaxing	Sleeping poorly	Headaches/ neckaches	Trembling, tingling etc.	Worried about health	Difficulty falling asleep
Keyed-up	.815[a]	-.344	-.228	-.169	-.001	-.020	-.051	-.025	.009
Worrying	-.344	.836[a]	-.147	-.173	-.077	-.028	-.025	-.105	-.008
Irritable	-.228	-.147	.868[a]	-.171	-.031	-.028	-.062	-.100	.018
Difficulty relaxing	-.169	-.173	-.171	.874[a]	-.175	-.099	-.015	-.074	-.128
Sleeping poorly	-.001	-.077	-.031	-.175	.745[a]	-.043	-.040	.003	-.488
Headaches/ neckaches	-.020	-.028	-.028	-.099	-.043	.888[a]	-.151	-.061	-.068
Trembling, tingling etc	-.051	-.025	-.062	-.015	-.040	-.151	.842[a]	-.208	-.044
Worried about health	-.025	-.105	-.100	-.074	.003	-.061	-.208	.866[a]	-.065
Difficulty falling asleep	.009	-.008	.018	-.128	-.488	-.068	-.044	-.065	.730[a]

Note: a. Measures of Sampling Adequacy (MSA)

Table 4.A.2:
Correlation Matrix

	Keyed-up	Worrying	Irritable	Difficulty relaxing	Sleeping poorly	Headaches/ neckaches	Trembling, tingling etc.	Worried about health	Difficulty falling asleep
Keyed-up	1.000	.528	.445	.430	.233	.180	.211	.243	.192
Worrying	.528	1.000	.415	.448	.293	.196	.212	.289	.236
Irritable	.445	.415	1.000	.407	.233	.180	.218	.273	.185
Difficulty relaxing	.430	.448	.407	1.000	.410	.257	.219	.280	.366
Sleeping poorly	.233	.293	.233	.410	1.000	.211	.194	.193	.578
Headaches/ neckaches	.180	.196	.180	.257	.211	1.000	.243	.193	.213
Trembling, tingling etc	.211	.212	.218	.219	.194	.243	1.000	.306	.191
Worried about health	.243	.289	.273	.280	.193	.193	.306	1.000	.208
Difficulty falling asleep	.192	.236	.185	.366	.578	.213	.191	.208	1.000

Notes:
Determinant = .133
All correlations are single tailed, $p < .001$

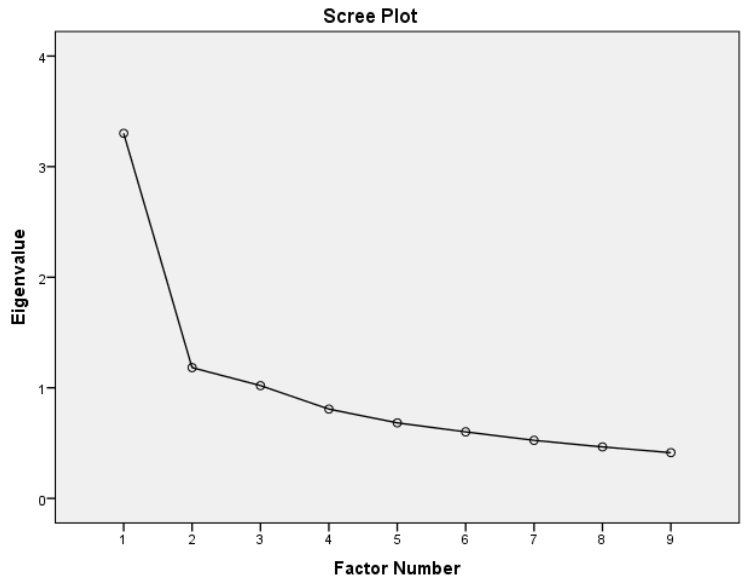


Figure 1. Scree plot from exploratory factor analysis of Goldberg Anxiety Scale for Wave 1 data of PATH, 60+ cohort (n = 2,409)

Table 3:
Summary of exploratory factor analysis of Goldberg Anxiety Scale for Wave 1 data of PATH, 60+ cohort (n = 2,409)

Items	Rotated Factor Loadings		
	1	2	3
Keyed-up	**.774**	-.058	-.035
Worrying	**.695**	.031	.000
Irritable	**.568**	-.023	.095
Difficulty relaxing	**.483**	.276	.043
Sleeping poorly	.052	**.764**	-.026
Difficulty falling asleep	-.051	**.745**	.050
Trembling, tingling etc.	-.063	-.036	**.671**
Worried about health	.146	.002	**.421**
Headaches/neckaches	.049	.118	**.312**
Maximum Guttmann's λ on rotated factors, using items bolded in factor loadings.	λ_2 = .764	λ_2 = .730	λ_2 = .487
Statistics for non-rotated factors	**1**	**2**	**3**
Eigenvalues	3.302	1.183	1.020
% of variance explained	36.683	13.143	11.330

Notes: major factor loadings over .3 appear in bold
Extraction Method: Principal Axis Factoring.
Rotation Method: Oblimin with Kaiser Normalization.

Appendix 4.B:

Exploratory Factor Analysis: Goldberg Depression Scale: Wave 1

A principal axis factor analysis was applied with oblique rotation (direct oblimin). Oblique rotation was chosen because any underlying factors were not expected to be independent within this well-defined, single construct. The Kaiser–Meyer–Olkin (KMO) measure reported the sampling adequacy with, KMO = .83 ('meritorious', according to Hutcheson & Sofroniou, 1999) and all KMO values for individual items were > .76 (from the diagonal of the anti-image correlation matrix, at Table 1), which is above the acceptable limit of .5 (Field, 2013). For reference, a correlation matrix is presented at Table 2. Eigenvalues were obtained for each factor in the data. Two factors had eigenvalues over Kaiser's criterion of 1 and in combination explained 47.99% of the variance. The scree plot showed an inflexion justifying only one factor. See Figure 1. Two factors were retained in order to interpret these differing results conservatively. Table 3 shows the factor loadings after rotation, together with internal consistency (using Maximum Guttmann's Lambda) along with Eigenvalues, and percentage of variance for each (non-rotated) factor. The consistency test on factor 2 indicated inadequate consistency. The items that cluster on the same factor suggest that: factor 1 was primarily about slowing down and lacking energy; factor 2 represented loss of confidence and interest, and feeling hopeless. Two items did not load onto either factor. They were Waking Early, and Lost Weight.

Table 1:
Anti-image Correlation Matrix

	Lacking energy	Lost interest	Lost confidence	Felt hopeless	Difficulty concentrating	Lost weight	Waking early	Slowed up	Feel worse in mornings
Lacking energy	.787[a]	-.123	-.048	.011	-.162	-.043	.027	-.463	-.101
Lost interest	-.123	.851[a]	-.304	-.144	-.185	-.011	-.019	-.038	-.026
Lost confidence	-.048	-.304	.809[a]	-.345	-.057	-.042	-.013	-.058	-.039
Felt hopeless	.011	-.144	-.345	.830[a]	-.127	-.035	.006	-.059	-.067
Difficulty concentrating	-.162	-.185	-.057	-.127	.885[a]	-.061	-.111	-.077	-.074
Lost weight	-.043	-.011	-.042	-.035	-.061	.926[a]	.000	-.019	-.021
Waking early	.027	-.019	-.013	.006	-.111	.000	.763[a]	-.108	.047
Felt slowed up	-.463	-.038	-.058	-.059	-.077	-.019	-.108	.781[a]	-.206
Feel worse in mornings	-.101	-.026	-.039	-.067	-.074	-.021	.047	-.206	.887[a]

a. Measures of Sampling Adequacy(MSA)

Table 2:
Correlation Matrix

	Lacking energy	Lost interest	Lost confidence	Felt hopeless	Difficulty concen-trating	Lost weight	Waking early	Slowed up	Feel worse in mornings
Lacking energy	1.000	.377	.327	.275	.402	.141	.096	.605	.345
Lost interest	.377	1.000	.509	.418	.411	.121	.104	.341	.242
Lost confidence	.327	.509	1.000	.516	.347	.137	.091	.328	.243
Felt hopeless	.275	.418	.516	1.000	.348	.127	.075	.298	.241
-Difficulty concentrating	.402	.411	.347	.348	1.000	.146	.166	.369	.266
Lost weight	.141	.121	.137	.127	.146	1.000	.031	.127	.097
Waking early	.096	.104	.091	.075	.166	.031	1.000	.158	.034
Felt slowed up	.605	.341	.328	.298	.369	.127	.158	1.000	.390
Feel worse in mornings	.345	.242	.243	.241	.266	.097	.034	.390	1.000

Notes:
Determinant = .140
All correlations are single tailed, $p < .001$

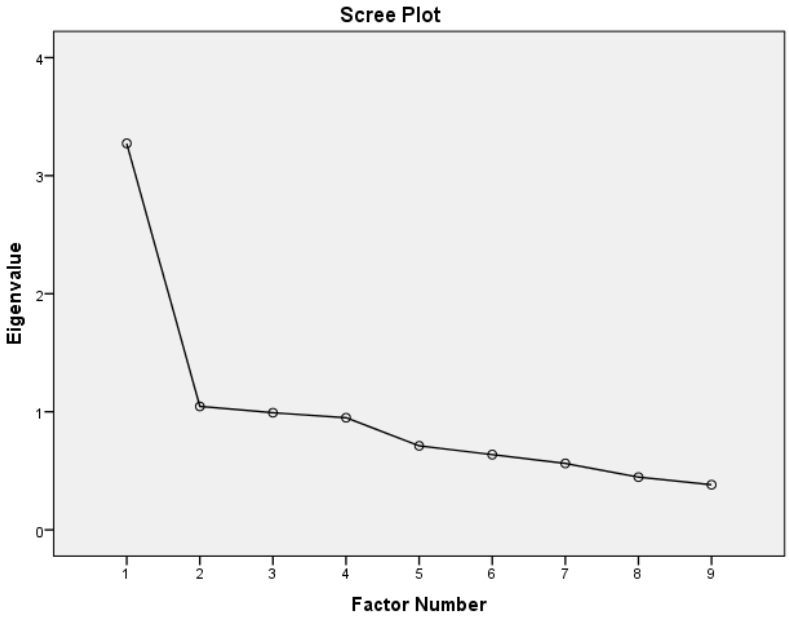


Figure 1. Scree plot from exploratory factor analysis of Goldberg Depression Scale for Wave 1 data of PATH, 60+ cohort (n = 2,409)

Table 3:
Summary of exploratory factor analysis of Goldberg Depression Scale for Wave 1 data of PATH, 60+ cohort (n = 2,409)

Items	Rotated Factor Loadings	
	1	2
Felt slowed up	**.855**	-.100
Lacking energy	**.787**	-.046
Feel worse in mornings	**.431**	.065
Difficulty concentrating	**.323**	**.321**
Waking early	.136	.051
Lost confidence	-.056	**.788**
Felt hopeless	-.029	**.682**
Lost interest	.111	**.598**
Lost weight	.107	.121
Maximum Guttmann's λ on rotated factors, using items bolded in factor loadings.	$\lambda_5 = .755$	$\lambda_4 = .733$
Statistics for non-rotated factors	**1**	**2**
Eigenvalues	3.273	1.046
% of variance explained	36.368	11.618

Notes: major factor loadings over .4 appear in bold
Extraction Method: Principal Axis Factoring.
Rotation Method: Oblimin with Kaiser Normalization

Appendix 6.A:

Settings For GEE

An example of syntax provided by these settings is available at the end of the following description of settings.

Settings in General Estimating Equations (GEE), were:

1. At the panel, "Repeated": Working Correlation Matrix: *Unstructured.*
2. At the panel: "Type of Model": *Scale Response / Linear*, or for binary outcomes (MCI & Dementia), Binary logistic.
3. At the panel, "Response": Dependent Variable, variously: PPb; SDMT; DSB; IR; MMSE; StW; MCI; and, Dementia. Each of these variables was prepared on SPSS "long" format, representing repeated measures over four or three waves, depending on the temporal treatment (see Section 6.2.4.4). For binary outcomes the reference category was set as "First (lowest value)" which refers to the zero values representing "no".
4. At the panel, "Predictors": Repeated measures (in SPSS long format), over four or three waves, depending on the temporal treatment (see Section 6.2.4.4), were entered as the main predictors as a covariate (CV) in each model. For temporal treatment calling on GAS as a lagged predictor (see Section 6.2.5), these lagged variables replaced the standard GAS variables by wave. Similarly, where an autoregressive model called for the dependent variable (DV) to be entered as a lagged predictor, this was entered in SPSS long format as a CV. Results (below) compare models with and without *time* entered as a CV. *Time* was not investigated in these models as a "Factor". To facilitate interpretation of

interactions including time, this categorical variable was transformed as 0, 1, 2, 3 to represent Waves 1, 2, 3, 4.

5. At the panel, “Model”: All effects considered were entered as “Main Effects”. Some interactions were also considered.
6. At the panel, “Estimations”: all settings were nominal, including the scale parameter method which was set as, “Maximum Likelihood Estimate”.
7. At the panel, “Statistics”: Analysis Type was Type I, which is described by SPSS as required when there are, “priori reasons for ordering predictors in the model”. The central predictor GAS was entered last, in order to establish its effect *after* all other CVs had been controlled. The exception was when a time-lagged DV was also entered as a CV. This was sequenced after the CV, *lagged-GAS*. Some of the other CVs were entered as closely as possible to the temporal and/or probable, causative precedence of the items in the CV list. For example, *sex* was entered before *age*. The strict order of other variables was not always determinable on such rational ground, but nor, therefore, did their sequence matter, provided the sequence order was kept consistent, which is was.
8. At the panel, “Save”: Residuals (raw and Pearson) were saved to the dataset for subsequent analysis of distribution.
9. At the other panels, settings were nominal.

The syntax for Model A of Appendix 6.C (models for PPb) is provided here as an exemplar of the coding produced by the GEE model setting described at Appendix 6.A:

```
DATASET ACTIVATE DataSet1.
* Generalized Estimating Equations.
GENLIN PPb_allWaves WITH Time
  /MODEL Time INTERCEPT=YES
```

DISTRIBUTION=NORMAL LINK=IDENTITY

/CRITERIA SCALE=MLE PCONVERGE=1E-006(ABSOLUTE) SINGULAR=1E-012 ANALYSISTYPE=1(WALD) CILEVEL=95

LIKELIHOOD=FULL

/REPEATED SUBJECT=pathid WITHINSUBJECT=Index1 SORT=YES CORRTYPE=UNSTRUCTURED ADJUSTCORR=YES

COVB=ROBUST MAXITERATIONS=100 PCONVERGE=1e-006(ABSOLUTE) UPDATECORR=1

/MISSING CLASSMISSING=EXCLUDE

/PRINT CPS DESCRIPTIVES MODELINFO FIT SUMMARY SOLUTION (EXPONENTIATED).

Appendix 6.B:

Adjustment for Time

Twisk (2013) discussed adjustment of multilevel models for *time*. Twisk noted a common misunderstanding in GEE analysis that adjustment for *time*, permits the interpretation of the regression coefficient of the covariate (CV) as limited to *within*-subject effects. On the contrary, when both the CV and the dependent variable (DV) are time-dependent, with or without adjustment for time, the coefficient remains as an effect of the combined influences of *within*- and *between*-subject associations. This combined effect is complex and difficult to interpret. Twisk further noted that adjustment for time could unnecessarily attenuate the association between predictor and outcome because it removes the variance between time points. On this basis, *time* can be an unintentional and unnecessary confounder in analysing associations between time-variant, CVs and DVs. Twisk recommended running models with and without adjustment for *time*, and interpreting the differences between the results. Accordingly, models to be examined here will be considered, with and without *time*-adjustment. Because final models were attenuated, random effects (isolated *between*-subject effects) were not required and so the combined influence of *within*- and *between*-subject was not identified as an issue in interpreting results.

A further recommendation by Twisk (2013) was that adjustments for *time* not be attempted by including *time* as a *factor* in the models, when there is more than a trivial content of missing data. *Time*, treated as a *factor*, in such circumstances, can produce misleading results. Missing data in PATH may be sufficient to be such an issue. Accordingly, the analyses reported here were restricted to entering *time* as a CV.

Appendix 6.C:

Detailed Models for Purdue Pegboard - Both Hands (PPb)

All standard temporal models were based on the full sample of participants who were cognitively healthy at baseline (n = 2,390). Alternative temporal treatments relied on outcome values at Wave 2 which had a reduced sample size due to attrition (n = 2,117). Therefore, standard and alternative temporal treatments are not comparable. CVs were at baseline values only, except for GAS which was a time-varying variable, as were all DVs.

Observations from Tables 1 to 4:

Table 1 demonstrated the standard temporal treatment (as explained at Chapter Six) for PPb as the DV.

Model A established that PPb declined over time.

Model B represented the *base model* for the main predictor GAS (as a time-varying variable, as explained at Chapter Six), in which an unadjusted but small association was shown, between GAS and PPb. As the *base model*, Model B also provided the model fit statistic (quasi -2 log likelihood) for comparison with other models.

Model C established that the inclusion of *time* improved the model fit (compared to B), and that GAS remained a significant predictor of PPb.

At Model D, the *time* interaction with GAS was introduced, and this slightly improved the model fit. As noted at Section 6.2.7, effects of lower order terms reported by interaction models are not main effects but conditional effects. The non-significance of the variable GAS, in this model (D), means only that at *time* = 0 (Wave 1), the GAS association with PPb was non-significant. The *time* interaction remained significant in this model, meaning the interaction of *time* and GAS was associated with PPb. The interaction was negative. Therefore, the relationship between *time* and GAS became weaker over duration of the study. The further, important comment here is that the fully adjusted models reported below

demonstrated that for the outcome variable, PPb, the *time* interaction with GAS was attenuated. Therefore, the observation from Table 6.1, Model D, that time*GAS demonstrated a significant interaction, is of relevance only within this restricted model and does not extend to an interpretation of the fully adjusted association between GAS and PPb.

At Model E, *time* and *time* interactions were temporarily dropped to investigate other effects. Model E introduced the core CVs, sex, age, and education – after which the model remained significant for association between GAS and PPb, although the model fit was not as good as for any previous model.

Model F demonstrated that adding *time* to Model E did not attenuate the model and *time* itself was significant, and the fit was better than for any previous model. Thus, the association between GAS and PPb was significant, and the model was a better fit, even when variance due to change in the DV over time, was *ex*cluded (See Section 6.2.4.2 regarding removal of variance between time points).

Model G demonstrated that adding the CVs, *time*, *consulted doctor Re memory* and *physical health*, attenuated the effect of GAS.

Intermediate models (not reported) investigating *depression*, found no effect on attenuation of the main effect of GAS.

Compared to Model G, the further addition in Model H of the *time* interaction (with GAS), improved the model fit but the effect of GAS remained attenuated.

Finally, for Model I, even upon removing *time* and the *time* interaction, (which were introduced in Models G & H), the model continued to attenuate the main effect of GAS. Model I was the simplest, model for which the association between GAS and DSB was attenuated, and, therefore, the *final model* for the associations between GAS and PPb.

To summarise Table 1, the base and final models were respectively models B and I. For Model I, the main effect of GAS was attenuated by the core CVs (*sex*, *age*, *education*, and

depression – although the last of these was not required), plus *consulted a doctor Re. memory*, and *physical health*. Adjustments for *time* (Models C, F, G) did not change the conclusions about which CVs would attenuate the effects of GAS.

Table 1:
Temporal Treatment 1: Standard Multilevel Models by GEE, for PPb, predicted by GAS

Model	CVs	B	SE	95% CI		*P* For Predictor	-2 Log Likelihood
				Lower	Upper		
A	Intercept	10.603	0.0354	10.533	10.672	0.000	25571.779
	Time	-0.548	0.0164	-0.581	-0.516	0.000	
B	Intercept	9.947	0.0325	9.883	10.010	0.000	27620.489
	GAS	-0.034	0.0106	-0.055	-0.013	**0.001**	
C	Intercept	10.601	0.0354	10.532	10.671	0.000	25498.690
	Time	-0.547	0.0164	-0.579	-0.515	0.000	
	GAS	-0.033	0.0102	-0.053	-0.013	**0.001**	
D	Intercept	10.601	0.0354	10.532	10.671	0.000	25475.796
	Time	-0.548	0.0164	-0.580	-0.516	0.000	
	GAS	-0.010	0.0126	-0.035	0.014	0.408	
	Time*GAS	-0.019	0.0074	-0.033	-0.005	0.010	
E	Intercept	9.700	0.0692	9.564	9.835	0.000	26560.962
	Sex	0.742	0.0643	0.616	0.868	0.000	
	Age	-0.044	0.0209	-0.085	-0.003	0.036	
	Education	0.071	0.0126	0.047	0.096	0.000	
	GAS	-0.041	0.0106	-0.062	-0.021	**0.000**	
F	Intercept	10.350	0.0703	10.213	10.488	0.000	24379.660
	Time	-0.551	0.0165	-0.583	-0.519	0.000	
	Sex	0.750	0.0641	0.624	0.876	0.000	
	Age	-0.044	0.0208	-0.084	-0.003	0.036	
	Education	0.085	0.0126	0.061	0.110	0.000	
	GAS	-0.040	0.0101	-0.060	-0.020	**0.000**	

Model	CVs	B	SE	95% CI		*P* For Predictor	-2 Log Likelihood
				Lower	Upper		
G	Intercept	9.037	0.1987	8.648	9.426	0.000	24044.964
	Time	-0.555	0.0164	-0.587	-0.523	0.000	
	Sex	0.782	0.0635	0.658	0.907	0.000	
	Age	-0.043	0.0206	-0.083	-0.003	0.037	
	Education	0.071	0.0125	0.047	0.096	0.000	
	Consulted Dr Re Mem	-0.042	0.0808	-0.200	0.116	0.604	
	Physical Health	0.027	0.0036	0.019	0.034	0.000	
	GAS	-0.017	0.0106	-0.037	0.004	0.113	
H	Intercept	9.000	0.199	8.610	9.390	0.000	24012.356
	Time	-0.557	0.016	-0.589	-0.525	0.000	
	Sex	0.780	0.063	0.656	0.905	0.000	
	Age	-0.043	0.021	-0.083	-0.002	0.038	
	Education	0.072	0.012	0.047	0.096	0.000	
	Consulted Dr Re Mem	-0.047	0.081	-0.205	0.112	0.564	
	Physical Health	0.027	0.004	0.020	0.034	0.000	
	GAS	0.012	0.013	-0.013	0.037	0.344	
	Time*GAS	-0.023	0.007	-0.038	-0.009	0.002	
I	Intercept	8.597	0.196	8.212	8.983	0.000	26322.192
	Sex	0.769	0.064	0.644	0.894	0.000	
	Age	-0.044	0.021	-0.084	-0.003	0.036	
	Education	0.060	0.013	0.035	0.084	0.000	
	Consulted Dr Re Mem	-0.058	0.081	-0.216	0.101	0.476	
	Physical Health	0.022	0.004	0.015	0.029	0.000	
	GAS	-0.020	0.011	-0.042	0.002	0.075	

The -2 Log Likelihood statistics are from the SPSS report, "Quasi Likelihood under Independence Model Criterion (QIC) using the full log quasi-likelihood function. This provides an estimate of goodness of fit based on the criteria that "smaller-is-better", but does not facilitate Chi Square estimates of probability. GAS and Lagged-GAS data were baseline-centred, for all models.

Tables 2 to 4 provided similar reports of results for each of the remaining temporal treatments, for the outcome variable, PPb.

At Table 2, the focus was on the association between PPb and prior GAS (lagged to the previous wave), as the primary predictor. Table 6.2 is much shorter than Table 6.1 because more basic models, than for the standard temporal treatment, demonstrated attenuation of the association between lagged-GAS and DSB. So the complex models were unnecessary. Model B was both the "base model" and the final model, demonstrating lagged-GAS was not associated with PPb even when unadjusted. At models C and D, adjustment for *time* and the *time* interaction, both demonstrated no association between lagged-GAS and DSB.

Table 2
Temporal Treatment 2: by GEE, PPb predicted by Lagged-GAS

Model	CVs	B	SE	95% CI		*P* For Predictor	-2 Log Likelihood
				Lower	Upper		
A	Intercept	10.378	0.039	10.301	10.454	0.000	19533.863
	Time	-0.763	0.025	-0.812	-0.714	0.000	
B	Intercept	9.783	0.036	9.713	9.853	0.000	19333.407
	Lagged-GAS	-0.016	0.014	-0.044	0.011	0.246	
C	Intercept	10.383	0.039	10.307	10.460	0.000	19349.512
	Time	-0.761	0.025	-0.810	-0.711	0.000	
	Lagged-GAS	-0.021	0.013	-0.046	0.004	0.096	
D	Intercept	10.386	0.0392	10.309	10.462	0.000	19333.407
	Time	-0.766	0.0255	-0.815	-0.716	0.000	
	Lagged-GAS	0.003	0.0153	-0.027	0.033	0.858	
	Time* Lagged-GAS	-0.030	0.0139	-0.057	-0.003	0.031	

The -2 Log Likelihood statistics are from the SPSS report, "Quasi Likelihood under Independence Model Criterion (QIC) using the full log quasi-likelihood function. This provides an estimate of goodness of fit based on the criteria that "smaller-is-better", but does not facilitate Chi Square estimates of probability.
GAS and Lagged-GAS data were baseline-centred, for all models.

Table 3 provided results for the auto-regressive temporal treatment, where the central predictor was lagged-GAS, and lagged-PPb was added as a CV. Note that the number of waves examined in time-lagged models is reduced. See Figures 6.1 to 6.4.

Model A demonstrated that PPb (at Waves 2 to 4) changed over time.

Model B, as the "base model", showed lagged-GAS was a significant predictor of PPb when adjusted for lagged-PPb.

At model C, adding *time* (to Model B) did not attenuate the association between lagged-GAS and PPb, suggesting variance between time points was not critical to the associations reported for Model B.

Model D, which included adjustment for *time* and the *time* interaction (with lagged-GAS), was attenuated for both the *time* interaction and the association between lagged-GAS and PPb. The non-significance of the time interaction indicates only that any association of GAS with PPb did not vary over time.

With or without *time*, at models E and F, adding the CVs, sex, age, and education, did not attenuate the model. However, at model F, the inclusion of *time* improved the model fit (compared to Model F).

Models, G & H, with added CVs for *depression*, *time* and the *time* interaction, were attenuated.

Model I was the final model for Table 6.3, demonstrating the minimum CVs required for attenuation were: sex, age, education, depression, and lagged-PPb.

Table 3
Temporal Treatment 3: Auto-Regressive by GEE, for PPb predicted by Lagged-GAS & Lagged-PPb

Model	CVs	B	SE	95% CI		*P* For Predictor	-2 Log Likelihood
				Lower	Upper		
A	Intercept	10.378	0.0390	10.301	10.454	0.000	19533.863

Model	CVs	B	SE	95% CI		*P* For Predictor	-2 Log Likelihood
				Lower	Upper		
	Time	-0.763	0.0249	-0.812	-0.714	0.000	
B	Intercept	1.802	0.1377	1.532	2.072	0.000	14544.773
	Lagged-PPb	0.774	0.0128	0.749	0.799	0.000	
	Lagged-GAS	-0.021	0.0090	-0.038	-0.003	**0.021**	
C	Intercept	2.743	0.1535	2.442	3.043	0.000	13773.596
	Time	-0.390	0.0287	-0.446	-0.334	0.000	
	Lagged-PPb	0.715	0.0138	0.688	0.742	0.000	
	Lagged-GAS	-0.024	0.0093	-0.042	-0.006	**0.010**	
D	Intercept	2.748	0.1533	2.447	3.048	0.000	13767.415
	Time	-0.394	0.0289	-0.450	-0.337	0.000	
	Lagged-PPb	0.714	0.0137	0.687	0.741	0.000	
	Lagged-GAS	-0.005	0.0137	-0.031	0.022	0.734	
	Time*Lagged-GAS	-0.023	0.0139	-0.050	0.005	0.104	
E	Intercept	2.981	0.1644	2.659	3.303	0.000	12947.011
	Time	-0.396	0.0298	-0.454	-0.338	0.000	
	Sex	0.164	0.0412	0.084	0.245	0.000	
	Age	-0.045	0.0128	-0.070	-0.020	0.000	
	Education	0.020	0.0077	0.005	0.035	0.008	
	Lagged-PPb	0.695	0.0149	0.666	0.724	0.000	
	Lagged-GAS	-0.027	0.0096	-0.046	-0.008	**0.005**	
F	Intercept	1.959	0.1474	1.670	2.248	0.000	13702.560
	Sex	0.110	0.0385	0.035	0.186	0.004	
	Age	-0.042	0.0120	-0.065	-0.018	0.000	
	Education	0.013	0.0071	-0.001	0.027	0.065	
	Lagged-PPb	0.763	0.0137	0.736	0.790	0.000	
	Lagged-GAS	-0.023	0.0093	-0.042	-0.005	**0.013**	
G	Intercept	3.050	0.1682	2.721	3.380	0.000	12931.391

Model	CVs	B	SE	95% CI		*P* For Predictor	-2 Log Likelihood
				Lower	Upper		
	Time	-0.398	0.0299	-0.457	-0.339	0.000	
	Sex	0.165	0.0413	0.084	0.246	0.000	
	Age	-0.045	0.0128	-0.070	-0.020	0.000	
	Education	0.020	0.0077	0.004	0.035	0.011	
	Lagged-PPb	0.693	0.0149	0.663	0.722	0.000	
	Depression	-0.029	0.0128	-0.054	-0.004	0.022	
	Lagged-GAS	-0.013	0.0111	-0.035	0.008	0.226	
H	Intercept	3.065	0.168	2.735	3.395	0.000	12920.660
	Time	-0.402	0.030	-0.462	-0.343	0.000	
	Sex	0.166	0.041	0.085	0.247	0.000	
	Age	-0.045	0.013	-0.070	-0.020	0.000	
	Education	0.020	0.008	0.005	0.035	0.011	
	Lagged-PPb	0.692	0.015	0.663	0.721	0.000	
	Depression	-0.032	0.013	-0.058	-0.007	0.014	
	Lagged-GAS	0.011	0.017	-0.022	0.043	0.520	
	Time*Lagged-GAS	-0.027	0.015	-0.056	0.002	0.069	
I	Intercept	2.007	0.1501	1.713	2.302	0.000	13692.274
	Sex	0.110	0.0386	0.035	0.186	0.004	
	Age	-0.042	0.0120	-0.065	-0.018	0.001	
	Education	0.013	0.0071	-0.001	0.026	0.078	
	Lagged-PPb	0.762	0.0138	0.735	0.789	0.000	
	Depression	-0.023	0.0121	-0.046	0.001	0.060	
	Lagged-GAS	-0.012	0.0108	-0.034	0.009	0.249	

The -2 Log Likelihood statistics are from the SPSS report, "Quasi Likelihood under Independence Model Criterion (QIC) using the full log quasi-likelihood function. This provides an estimate of goodness of fit based on the criteria that "smaller-is-better", but does not facilitate Chi Square estimates of probability.
GAS and Lagged-GAS data were baseline-centred, for all models.

Table 4 reported the temporal treatment for "change" in the measurement of the DV (PPb) between waves. The base model was Model B, which demonstrated a significant, unadjusted association between lagged-GAS and the change between waves in PPb.

However, the association was attenuated at model I, by the CVs: sex, age, education, and depression. *Time* and the *time* interaction had little effect, as can be seen by comparing models H and I, which were otherwise adjusted for the same CVs.

Table 4
Temporal Treatment 4: Cognitive-Change by GEE, for PPb-change (between waves), predicted by Lagged-GAS

Model	CVs	B	SE	95% CI		*P* For Predictor	-2 Log Likelihood
				Lower	Upper		
A	Intercept	-0.313	0.0306	-0.373	-0.253	0.000	16321.977
	Time	-0.251	0.0311	-0.312	-0.190	0.000	
B	Intercept	-0.538	0.016	-0.569	-0.506	0.000	16471.569
	Lagged-GAS	-0.018	0.008	-0.034	-0.001	**0.038**	
C	Intercept	-0.316	0.0306	-0.376	-0.256	0.000	16204.968
	Time	-0.253	0.0312	-0.314	-0.192	0.000	
	Lagged-GAS	-0.019	0.0085	-0.036	-0.003	**0.024**	
D	Intercept	-0.314	0.031	-0.374	-0.254	0.000	16202.902
	Time	-0.256	0.031	-0.317	-0.194	0.000	
	Lagged-GAS	-0.003	0.013	-0.029	0.024	0.845	
	Time*Lagged-GAS	-0.019	0.014	-0.047	0.009	0.176	
E	Intercept	-0.211	0.044	-0.298	-0.124	0.000	15320.589
	Time	-0.244	0.032	-0.308	-0.181	0.000	
	Sex	-0.062	0.034	-0.129	0.005	0.070	
	Age	-0.030	0.011	-0.052	-0.009	0.006	
	Education	-0.005	0.007	-0.018	0.008	0.468	
	Lagged-GAS	-0.017	0.009	-0.034	0.000	**0.045**	
F	Intercept	-0.423	0.036	-0.494	-0.352	0.000	15561.756
	Sex	-0.065	0.034	-0.131	0.002	0.056	
	Age	-0.031	0.011	-0.052	-0.009	0.005	
	Education	-0.006	0.006	-0.018	0.007	0.395	

Model	CVs	B	SE	95% CI		*P* For Predictor	-2 Log Likelihood
				Lower	Upper		
	Lagged-GAS	-0.016	0.009	-0.033	0.001	**0.063**	
G	Intercept	-0.194	0.050	-0.292	-0.097	0.000	15561.119
	Time	-0.245	0.032	-0.308	-0.181	0.000	
	Sex	-0.062	0.034	-0.129	0.005	0.068	
	Age	-0.030	0.011	-0.052	-0.009	0.006	
	Education	-0.005	0.007	-0.018	0.008	0.439	
	Depression	-0.011	0.011	-0.033	0.012	0.348	
	Lagged-GAS	-0.012	0.010	-0.032	0.007	0.223	
H	Intercept	-0.189	0.050	-0.287	-0.090	0.000	15315.899
	Time	-0.248	0.030	-0.312	-0.183	0.000	
	Sex	-0.062	0.034	-0.129	0.005	0.068	
	Age	-0.030	0.011	-0.052	-0.009	0.006	
	Education	-0.005	0.007	-0.018	0.008	0.436	
	Depression	-0.013	0.012	-0.036	0.010	0.265	
	Lagged-GAS	0.007	0.016	-0.025	0.038	0.675	
	Time*Lagged-GAS	-0.021	0.015	-0.050	0.009	0.171	
I	Intercept	-0.408	0.0409	-0.489	-0.328	0.000	15561.119
	Sex	-0.065	0.0339	-0.132	0.001	0.055	
	Age	-0.031	0.0109	-0.052	-0.009	0.005	
	Education	-0.006	0.0065	-0.019	0.007	0.372	
	Depression	-0.010	0.0113	-0.032	0.013	0.398	
	Lagged-GAS	-0.011	0.0100	-0.031	0.008	0.257	

The -2 Log Likelihood statistics are from the SPSS report, "Quasi Likelihood under Independence Model Criterion (QIC) using the full log quasi-likelihood function. This provides an estimate of goodness of fit based on the criteria that "smaller-is-better", but does not facilitate Chi Square estimates of probability.
GAS and Lagged-GAS data were baseline-centred, for all models.

Appendix 6.D:

Final Models

For all DVs, although there were small changes in the coefficients of GAS (or lagged-GAS) and CVs, when *time* was included or excluded, there was no difference in the choice of simplest, final model to represent attenuation for the given DV and temporal treatment. Therefore, the summary models from Table 1 onward, presented only these simpler, final versions of the models, excluding *time* and the *time* interactions.

At Table 1, the four temporal treatments, side-by-side, demonstrated there was no predictive associations between anxiety and PPb. Notable, is that for the unadjusted, time-lagged treatment there was no association.

For SDMT at Table 2, the four temporal treatments produced results similar to each other, with models attenuated by a short list of CVs. This list of CVs included baseline depression.

Tables 3 to 6 report results respectively for the outcome variables, DSB, IR, MMSE, and StW. DSB required only a short list of CVs to establish attenuation, as did the lagged-GAS treatment for StW. Base models for all other DVs and temporal treatments, were non-significant.

For MCI and dementia, Tables 7 & 8 demonstrated all temporal treatments produced similar results. There was no association between GAS and cognitive impairment, even for unadjusted models.

Table 1

*Temporal Treatments 1 to 4 for **PPb**, predicted by GAS or Lagged-GAS*

	Standard MLM				Lagged-GAS				Auto-Regressive				Cognitive Change			
		95% CI				95% CI				95% CI				95% CI		
CVs	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**
Intercept	0.188	8.189	8.927	0.000	9.783	9.713	9.853	0.000	2.007	1.713	2.302	0.000	-0.408	-0.489	-0.328	0.000
Sex	0.064	0.648	0.898	0.000					0.110	0.035	0.186	0.004	-0.065	-0.132	0.001	0.055
Age	0.021	-0.084	-0.003	0.037					-0.042	-0.065	-0.018	0.001	-0.031	-0.052	-0.009	0.005
Education	0.012	0.035	0.084	0.000					0.013	-0.001	0.026	0.078	-0.006	-0.019	0.007	0.372
Depression									-0.023	-0.046	0.001	0.060	-0.010	0.0113	-0.032	0.013
Physical Health	0.004	0.016	0.030	0.000												
Lagged-PPb									0.762	0.735	0.789	0.000				
GAS or Lagged-GAS	0.011	-0.042	0.001	0.060	-0.016	-0.044	0.011	0.246	-0.012	-0.034	0.009	0.249	-0.011	-0.031	0.008	0.257

GAS and Lagged-GAS data were baseline-centred, for all models.

Table 2

*Temporal Treatments 1 to 4 for **SDMT**, predicted by GAS or Lagged-GAS*

	Standard MLM				Lagged-GAS				Auto-Regressive				Cognitive Change			
		95% CI				95% CI				95% CI				95% CI		
CVs	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**
Intercept	49.421	48.658	50.185	0.000	48.928	48.113	49.743	0.000	4.213	0.4663	3.299	0.000	-1.048	-1.392	-0.704	0.000
Sex	1.316	0.640	1.991	0.000	1.299	0.573	2.025	0.000	0.425	0.1259	0.179	0.001	-0.749	-0.954	-0.544	0.000
Age	-0.361	-0.582	-0.141	0.001	-0.409	-0.642	-0.176	0.001	-0.089	0.0413	-0.169	0.032	0.284	0.047	0.521	0.019
Education	0.839	0.711	0.966	0.000	0.808	0.668	0.947	0.000	0.096	0.0239	0.049	0.000	-0.052	-0.133	0.028	0.201
Depression	-0.435	-0.633	-0.236	0.000	-0.375	-0.607	-0.143	0.002	-0.104	0.0462	-0.194	0.025	0.009	-0.033	0.052	0.661
Lagged-SDMT									0.883	0.866	0.900	0.000				
GAS or Lagged-GAS	-0.068	-0.151	0.015	0.109	-0.062	-0.172	0.048	0.272	-0.052	-0.129	0.025	0.188	-0.033	-0.111	0.045	0.405

GAS and Lagged-GAS data were baseline centred for all models.

Table 3

*Temporal Treatments 1 to 4 for **DSB**, predicted by GAS or Lagged-GAS*

	Standard MLM				Lagged-GAS				Auto-Regressive				Cognitive Change			
		95% CI				95% CI				95% CI				95% CI		
CVs	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**
Intercept	5.256	5.095	5.417	0.000	5.145	5.061	5.228	0.000	1.367	1.242	1.491	0.000	-1.048	-1.392	-0.704	0.000
Sex	-0.120	-0.271	0.032	0.121					-0.036	-0.107	0.035	0.317	-0.749	-0.954	-0.544	0.000
Age	-0.053	-0.103	-0.003	0.040					-0.030	-0.053	-0.007	0.011	0.284	0.047	0.521	0.019
Education	0.192	0.164	0.220	0.000					0.040	0.027	0.054	0.000	-0.052	-0.133	0.028	0.201
Depression													0.009	-0.033	0.052	0.661
Lagged DSB									0.754	0.735	0.772	0.000				
GAS or Lagged-GAS	-0.013	-0.034	0.009	0.248	-0.022	-0.048	0.005	0.111	-0.015	-0.032	0.002	0.085	-0.034	-0.161	0.013	0.096

GAS and Lagged-GAS data were baseline-centred, for all models.

Table 4

*Temporal Treatments 1 to 4 for **IR**, predicted by GAS or Lagged-GAS*

	Standard MLM				Lagged-GAS				Auto-Regressive				Cognitive Change			
		95% CI				95% CI				95% CI				95% CI		
CVs	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**
Intercept	6.657	6.573	6.741	0.000	6.335	6.260	6.411	0.000	1.301	1.169	1.434	0.000	-0.658	-0.693	-0.624	0.000
Lagged-IR									0.720	0.701	0.739	0.000				
GAS or Lagged-GAS	0.006	-0.043	0.054	0.821	-0.007	-0.034	0.021	0.645	-0.013	-0.030	0.004	0.139	-0.001	-0.019	0.016	0.880

GAS and Lagged-GAS data were baseline-centred, for all models.

Table 5

*Temporal Treatments 1 to 4 for **MMSE**, predicted by GAS or Lagged-GAS*

	Standard MLM				Lagged-GAS				Auto-Regressive				Cognitive Change			
		95% CI				95% CI				95% CI				95% CI		
CVs	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**
Intercept	30.660	30.435	30.886	0.000	29.122	29.080	29.165	0.000	11.367	8.488	14.246	0.000	-0.169	-0.193	-0.145	0.000
Lagged-MMSE									0.606	0.509	0.704	0.000				
GAS or Lagged-GAS	0.113	-0.017	0.244	0.088	-0.003	-0.020	0.013	0.684	0.005	-0.008	0.017	0.455	0.009	-0.002	0.021	0.108

GAS and Lagged-GAS data were baseline-centred, for all models.

Table 6

*Temporal Treatments 1 to 4 for **StW**, predicted by GAS or Lagged-GAS*

	Standard MLM				Lagged-GAS				Auto-Regressive				Cognitive Change			
		95% CI				95% CI				95% CI				95% CI		
CVs	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**	**B**	**Lower**	**Upper**	**p**
Intercept	52.65	52.44	52.85	0.000	52.85	52.43	53.27	0.000	3.950	2.683	5.216	0.000	0.275	0.231	0.320	0.000
Sex					0.05	-0.34	0.45	0.792								
Age					0.11	-0.02	0.25	0.093								
Education					0.80	0.72	0.88	0.000								
Lagged-StW									0.931	0.908	0.954	0.000				
GAS or Lagged-GAS	0.00	-0.04	0.03	0.820	-0.0	-0.07	0.01	0.097	-0.010	-0.031	0.011	0.353	-0.004	-0.024	0.016	0.698

GAS and Lagged-GAS data were baseline-centred, for all models.

Table 7

*Temporal Treatments 1 to 4 for **MCI**, predicted by GAS or Lagged-GAS*

	Standard MLM				Lagged-GAS				Auto-Regressive			
		95% CI				95% CI				95% CI		
CVs	B	Lower	Upper	p	B	Lower	Upper	p	B	Lower	Upper	p
Intercept	4.034	3.856	4.212	0.000	3.613	3.430	3.796	0.000	-3.720	-3.894	-3.546	0.000
Lagged-MCI									3.462	2.846	4.078	0.000
GAS or Lagged-GAS	-0.040	-0.113	0.032	0.278	-0.048	-0.119	0.023	0.183	0.061	-0.007	0.129	0.079

GAS and Lagged-GAS data were baseline-centred, for all models. The cognitive change panel is not provided because these data were not meaningful for MCI.

Table 8

*Temporal Treatments 1 to 4 for **Dementia**, predicted by GAS or Lagged-GAS*

	Standard MLM				Lagged-GAS				Auto-Regressive				Cognitive Change			
		95% CI				95% CI				95% CI				95% CI		
CVs	B	Lower	Upper	p	B	Lower	Upper	p	B	Lower	Upper	p	B	Lower	Upper	p
Intercept	-5.804	0.2117	-6.219	0.000	-5.427	0.2123	-5.843	0.000	-5.427	-5.843	-5.011	0.000	-5.086	-5.423	-4.748	0.000
Lagged-Dementia									0^							
GAS or Lagged-GAS	-0.138	0.0945	-0.323	0.144	-0.128	0.1202	-0.364	0.287	-0.128	-0.364	0.108	0.287	-0.050	-0.260	0.159	0.637

GAS and Lagged-GAS data were baseline-centred, for all models. ^ Set to zero because this parameter is redundant.

Appendix 6.E:

Fully adjusted Models, Standard Temporal Treatment

Table of Contents for this Appendix

Model A:
DV: PPb
Full Model: Excluding Time and all interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upper	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	6.028	1.6507	2.793	9.263	13.335	1.000	0.000	414.805	16.323	10540.978	4109.307	1.955	2.400
Sex	0.580	0.1943	0.200	0.961	8.923	1.000	**0.003**	1.787	1.221	2.615			
Age	-0.079	0.0601	-0.197	0.039	1.725	1.000	0.189	0.924	0.821	1.040			
Education	0.055	0.0383	-0.020	0.130	2.061	1.000	0.151	1.056	0.980	1.139			
Depression	0.064	0.0544	-0.043	0.170	1.362	1.000	0.243	1.066	0.958	1.186			
Dr Re Mem.	0.040	0.2104	-0.372	0.453	0.037	1.000	0.848	1.041	0.689	1.573			
Anxiolytics	0.604	0.3586	-0.099	1.306	2.834	1.000	0.092	1.829	0.906	3.693			
Physical Health	0.023	0.0113	0.001	0.046	4.310	1.000	**0.038**	1.024	1.001	1.047			
Soc Supp Gen Neg	-0.065	0.0450	-0.153	0.023	2.080	1.000	0.149	0.937	0.858	1.024			
Soc Supp Gen Pos	-0.002	0.0515	-0.103	0.099	0.002	1.000	0.967	0.998	0.902	1.104			
Soc Supp Partner Neg	-0.020	0.0451	-0.108	0.068	0.200	1.000	0.654	0.980	0.897	1.071			
Soc Supp Partner Pos	0.040	0.0465	-0.051	0.131	0.745	1.000	0.388	1.041	0.950	1.140			
Mastery	0.029	0.0295	-0.029	0.086	0.942	1.000	0.332	1.029	0.971	1.090			
Freq Phys Act Mild	0.231	0.1422	-0.048	0.510	2.639	1.000	0.104	1.260	0.953	1.665			
Freq Phys Act Mod	-0.003	0.1165	-0.231	0.225	0.001	1.000	0.980	0.997	0.794	1.253			
Freq Phys Act Vig	-0.007	0.0815	-0.167	0.152	0.008	1.000	0.928	0.993	0.846	1.164			
Alcohol	-0.063	0.0771	-0.214	0.088	0.671	1.000	0.413	0.939	0.807	1.092			
Life Events	-0.021	0.0749	-0.167	0.126	0.076	1.000	0.783	0.980	0.846	1.135			
Smoker	0.439	0.3096	-0.168	1.046	2.007	1.000	0.157	1.551	0.845	2.845			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upper	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	0.015	0.0295	-0.042	0.073	0.276	1.000	0.599	1.016	0.959	1.076			
(Scale)	3.731												

Note: SD of DV = standard deviation of the dependent variable

Model B:
DV: PPb
Full Model: Including Time and Time interactions; Excluding other interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	6.046	1.6753	2.762	9.329	13.024	1	0.000	422.368	15.838	11264.015	3751.590	1.955	11.086
Time	-0.159	0.1304	-0.414	0.097	1.483	1	0.223	0.853	0.661	1.102			
Sex	0.593	0.1964	0.208	0.978	9.119	1	0.003	1.809	1.231	2.659			
Age	-0.067	0.0599	-0.185	0.050	1.262	1	0.261	0.935	0.831	1.051			
Education	0.063	0.0395	-0.014	0.141	2.554	1	0.110	1.065	0.986	1.151			
Depression	0.072	0.0544	-0.035	0.178	1.730	1	0.188	1.074	0.966	1.195			
Dr Re Mem.	0.028	0.2077	-0.379	0.435	0.018	1	0.894	1.028	0.684	1.545			
Anxiolytics	0.584	0.3620	-0.125	1.294	2.603	1	0.107	1.793	0.882	3.646			
Physical Health	0.027	0.0115	0.005	0.049	5.561	1	0.018	1.027	1.005	1.051			
Soc Supp Gen Neg	-0.052	0.0457	-0.142	0.038	1.296	1	0.255	0.949	0.868	1.038			
Soc Supp Gen Pos	-0.001	0.0534	-0.106	0.103	0.001	1	0.981	0.999	0.899	1.109			
Soc Supp Partner Neg	-0.027	0.0450	-0.115	0.061	0.359	1	0.549	0.973	0.891	1.063			
Soc Supp Partner Pos	0.040	0.0454	-0.049	0.129	0.768	1	0.381	1.041	0.952	1.137			
Mastery	0.037	0.0293	-0.021	0.094	1.581	1	0.209	1.037	0.980	1.099			
Freq Phys Act Mild	0.228	0.1441	-0.055	0.510	2.502	1	0.114	1.256	0.947	1.666			
Freq Phys Act Mod	0.014	0.1152	-0.212	0.239	0.014	1	0.906	1.014	0.809	1.270			
Freq Phys Act Vig	-0.002	0.0838	-0.166	0.163	0.000	1	0.985	0.998	0.847	1.177			
Alcohol	-0.039	0.0765	-0.189	0.111	0.256	1	0.613	0.962	0.828	1.118			
Life Events	-0.025	0.0758	-0.174	0.123	0.111	1	0.739	0.975	0.840	1.131			
Smoker	0.422	0.3178	-0.201	1.045	1.763	1	0.184	1.525	0.818	2.843			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	0.001	0.0372	-0.072	0.074	0.000	1	0.989	1.001	0.930	1.076			
Time*Time	-0.136	0.0425	-0.219	-0.052	10.191	1	0.001	0.873	0.803	0.949			
Time*GAS	0.044	0.0523	-0.058	0.146	0.712	1	0.399	1.045	0.943	1.158			
Time*Time*GAS	-0.018	0.0175	-0.053	0.016	1.083	1	0.298	0.982	0.949	1.016			
(Scale)	3.399												

Note: SD of DV = standard deviation of the dependent variable

Model C:
DV: PPb:
Full Model: Including Interactions with GAS; Excluding Time and Time interactions

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	6.477	1.6991	3.146	9.807	14.530	1	0.000	649.766	23.254	18155.652	4108.956	1.955	2.333
Sex	0.573	0.1968	0.187	0.959	8.469	1	0.004	1.773	1.206	2.608			
Age	-0.080	0.0600	-0.198	0.037	1.793	1	0.181	0.923	0.820	1.038			
Education	0.059	0.0378	-0.015	0.133	2.445	1	0.118	1.061	0.985	1.143			
Depression	0.066	0.0545	-0.041	0.172	1.448	1	0.229	1.068	0.960	1.188			
Dr Re Mem.	0.059	0.2134	-0.359	0.477	0.077	1	0.781	1.061	0.698	1.612			
Anxiolytics	0.572	0.3596	-0.133	1.277	2.532	1	0.112	1.772	0.876	3.585			
Physical Health	0.018	0.0116	-0.005	0.041	2.471	1	0.116	1.018	0.996	1.042			
Soc Supp Gen Neg	-0.065	0.0450	-0.153	0.023	2.106	1	0.147	0.937	0.858	1.023			
Soc Supp Gen Pos	-0.002	0.0511	-0.102	0.098	0.002	1	0.965	0.998	0.903	1.103			
Soc Supp Partner Neg	-0.023	0.0453	-0.112	0.066	0.258	1	0.611	0.977	0.894	1.068			
Soc Supp Partner Pos	0.037	0.0462	-0.054	0.128	0.639	1	0.424	1.038	0.948	1.136			
Mastery	0.027	0.0295	-0.031	0.085	0.857	1	0.355	1.028	0.970	1.089			
Freq Phys Act Mild	0.239	0.1422	-0.040	0.517	2.816	1	0.093	1.269	0.961	1.677			
Freq Phys Act Mod	-0.003	0.1172	-0.233	0.227	0.001	1	0.981	0.997	0.793	1.255			
Freq Phys Act Vig	-0.012	0.0814	-0.172	0.147	0.022	1	0.881	0.988	0.842	1.159			
Alcohol	-0.067	0.0775	-0.219	0.085	0.746	1	0.388	0.935	0.804	1.089			
Life Events	-0.021	0.0751	-0.168	0.126	0.079	1	0.778	0.979	0.845	1.134			
Smoker	0.442	0.3117	-0.169	1.053	2.008	1	0.156	1.555	0.844	2.866			
GAS	-0.168	0.1283	-0.420	0.083	1.720	1	0.190	0.845	0.657	1.087			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Sex*GAS	-0.011	0.0559	-0.121	0.098	0.042	1	0.837	0.989	0.886	1.103			
Physical Health*GAS	0.004	0.0026	-0.001	0.009	2.259	1	0.133	1.004	0.999	1.009			
(Scale)	3.734												

Note: SD of DV = standard deviation of the dependent variable

Model D:
DV: SDMT
Full Model: Excluding Time and all interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	38.296	7.7810	23.046	53.547	24.224	1	0.000	4.284E+16	1.020E+10	1.799E+23	81735.716	8.968	7.297
Sex	0.941	0.9561	-0.933	2.815	0.969	1	0.325	2.563	0.394	16.696			
Age	-0.892	0.2982	-1.476	-0.307	8.944	1	**0.003**	0.410	0.229	0.735			
Education	0.577	0.1630	0.258	0.896	12.533	1	**0.000**	1.781	1.294	2.451			
Depression	0.002	0.2565	-0.500	0.505	0.000	1	0.993	1.002	0.606	1.657			
Dr Re Mem.	-1.041	0.9216	-2.847	0.765	1.276	1	0.259	0.353	0.058	2.150			
Anxiolytics	1.774	1.9422	-2.033	5.581	0.834	1	0.361	5.894	0.131	265.231			
Physical Health	0.088	0.0514	-0.013	0.189	2.916	1	0.088	1.092	0.987	1.208			
Soc Supp Gen Neg	-0.476	0.2376	-0.942	-0.011	4.021	1	0.045	0.621	0.390	0.989			
Soc Supp Gen Pos	0.329	0.2512	-0.163	0.821	1.716	1	0.190	1.390	0.849	2.273			
Soc Supp Partner Neg	-0.036	0.2247	-0.476	0.405	0.025	1	0.874	0.965	0.621	1.499			
Soc Supp Partner Pos	-0.066	0.2150	-0.487	0.355	0.094	1	0.759	0.936	0.614	1.427			
Mastery	0.049	0.1254	-0.196	0.295	0.155	1	0.694	1.051	0.822	1.343			
Freq Phys Act Mild	0.329	0.5633	-0.775	1.433	0.341	1	0.559	1.390	0.461	4.192			
Freq Phys Act Mod	0.611	0.5906	-0.547	1.768	1.069	1	0.301	1.842	0.579	5.861			
Freq Phys Act Vig	0.017	0.4485	-0.862	0.896	0.001	1	0.970	1.017	0.422	2.450			
Alcohol	0.585	0.4670	-0.330	1.500	1.570	1	0.210	1.795	0.719	4.483			
Life Events	-0.294	0.4238	-1.125	0.536	0.482	1	0.488	0.745	0.325	1.710			
Smoker	0.829	1.3058	-1.730	3.389	0.403	1	0.525	2.292	0.177	29.628			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	0.099	0.0941	-0.085	0.283	1.106	1	0.293	1.104	0.918	1.328			
(Scale)	74.556												

Note: SD of DV = standard deviation of the dependent variable

Model E:
DV: SDMT:
Standard Temporal Treatment, Including Time and Time interactions; Excluding other interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	38.557	7.8423	23.186	53.928	24.173	1	0.000	5.560E+16	1.174E+10	2.633E+23	77129.697	8.968	12.217
Time	-1.169	0.3781	-1.910	-0.428	9.564	1	**0.002**	0.311	0.148	0.652			
Sex	0.989	0.9554	-0.883	2.862	1.072	1	0.300	2.689	0.413	17.491			
Age	-0.812	0.2970	-1.394	-0.229	7.467	1	0.006	0.444	0.248	0.795			
Education	0.575	0.1629	0.256	0.895	12.469	1	0.000	1.778	1.292	2.446			
Depression	0.006	0.2501	-0.485	0.496	0.001	1	0.982	1.006	0.616	1.642			
Dr Re Mem.	-0.954	0.9562	-2.828	0.920	0.996	1	0.318	0.385	0.059	2.509			
Anxiolytics	1.883	1.9443	-1.928	5.694	0.938	1	0.333	6.572	0.145	296.955			
Physical Health	0.112	0.0515	0.012	0.213	4.773	1	0.029	1.119	1.012	1.238			
Soc Supp Gen Neg	-0.462	0.2368	-0.926	0.002	3.801	1	0.051	0.630	0.396	1.002			
Soc Supp Gen Pos	0.318	0.2498	-0.172	0.807	1.617	1	0.204	1.374	0.842	2.242			
Soc Supp Partner Neg	-0.067	0.2264	-0.510	0.377	0.087	1	0.768	0.935	0.600	1.458			
Soc Supp Partner Pos	-0.049	0.2161	-0.472	0.375	0.051	1	0.821	0.952	0.624	1.454			
Mastery	0.066	0.1276	-0.184	0.316	0.270	1	0.603	1.069	0.832	1.372			
Freq Phys Act Mild	0.298	0.5589	-0.798	1.393	0.284	1	0.594	1.347	0.450	4.028			
Freq Phys Act Mod	0.544	0.5887	-0.609	1.698	0.855	1	0.355	1.723	0.544	5.463			
Freq Phys Act Vig	0.014	0.4528	-0.873	0.902	0.001	1	0.975	1.014	0.418	2.464			
Alcohol	0.662	0.4701	-0.259	1.584	1.985	1	0.159	1.939	0.772	4.874			
Life Events	-0.259	0.4207	-1.084	0.565	0.379	1	0.538	0.772	0.338	1.760			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Smoker	0.684	1.3611	-1.984	3.352	0.253	1	0.615	1.982	0.138	28.560			
GAS	0.216	0.1301	-0.039	0.472	2.766	1	0.096	1.242	0.962	1.602			
Time*Time	-0.256	0.1276	-0.506	-0.006	4.022	1	**0.045**	0.774	0.603	0.994			
Time*GAS	-0.225	0.1405	-0.501	0.050	2.571	1	0.109	0.798	0.606	1.051			
Time*Time*GAS	0.056	0.0497	-0.042	0.153	1.264	1	0.261	1.057	0.959	1.166			
(Scale)	70.599												

Note: SD of DV = standard deviation of the dependent variable

Model F:
DV: SDMT:
Standard Temporal Treatment. Including Interactions with GAS; Excluding: Time and Time interactions

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	38.165	7.7723	22.931	53.398	24.111	1	0.000	3.756E+16	9.097E+09	1.551E+23	81816.668	8.968	7.039
Sex	0.946	0.9570	-0.930	2.822	0.977	1	0.323	2.576	0.395	16.805			
Age	-0.859	0.3045	-1.456	-0.262	7.953	1	0.005	0.424	0.233	0.770			
Education	0.578	0.1634	0.257	0.898	12.493	1	0.000	1.782	1.293	2.454			
Depression	0.009	0.2579	-0.497	0.514	0.001	1	0.974	1.009	0.608	1.672			
Dr Re Mem.	-1.054	0.9265	-2.870	0.762	1.294	1	0.255	0.349	0.057	2.143			
Anxiolytics	1.830	1.9500	-1.992	5.652	0.881	1	0.348	6.233	0.136	284.782			
Physical Health	0.088	0.0517	-0.013	0.190	2.910	1	0.088	1.092	0.987	1.209			
Soc Supp Gen Neg	-0.477	0.2377	-0.942	-0.011	4.019	1	0.045	0.621	0.390	0.989			
Soc Supp Gen Pos	0.320	0.2508	-0.171	0.812	1.631	1	0.202	1.377	0.843	2.252			
Soc Supp Partner Neg	-0.035	0.2253	-0.477	0.407	0.024	1	0.877	0.966	0.621	1.502			
Soc Supp Partner Pos	-0.064	0.2156	-0.487	0.358	0.089	1	0.766	0.938	0.615	1.431			
Mastery	0.048	0.1258	-0.198	0.295	0.147	1	0.701	1.049	0.820	1.343			
Freq Phys Act Mild	0.305	0.5678	-0.808	1.417	0.288	1	0.592	1.356	0.446	4.126			
Freq Phys Act Mod	0.629	0.5927	-0.533	1.791	1.126	1	0.289	1.876	0.587	5.993			
Freq Phys Act Vig	0.004	0.4518	-0.881	0.890	0.000	1	0.992	1.004	0.414	2.435			
Alcohol	0.598	0.4683	-0.319	1.516	1.633	1	0.201	1.819	0.727	4.555			
Life Events	-0.306	0.4241	-1.137	0.525	0.520	1	0.471	0.737	0.321	1.691			
Smoker	0.834	1.3068	-1.727	3.396	0.408	1	0.523	2.303	0.178	29.836			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	0.201	0.1541	-0.101	0.503	1.701	1	0.192	1.223	0.904	1.654			
Age*GAS	-0.045	0.0514	-0.145	0.056	0.751	1	0.386	0.956	0.865	1.058			
Education*GAS	-0.003	0.0431	-0.087	0.082	0.004	1	0.949	0.997	0.916	1.085			
(Scale)	74.763												

Note: SD of DV = standard deviation of the dependent variable

Model G:
DV: DSB:
Full Model: Excluding Time and all interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	5.518	1.6370	2.309	8.726	11.362	1	**0.001**	249.114	10.069	6163.140	5411.185	2.256	5.743
Sex	-0.162	0.2388	-0.630	0.307	0.458	1	0.499	0.851	0.533	1.359			
Age	-0.110	0.0675	-0.243	0.022	2.674	1	0.102	0.896	0.785	1.022			
Education	0.145	0.0384	0.069	0.220	14.162	1	**0.000**	1.156	1.072	1.246			
Depression	0.019	0.0634	-0.105	0.144	0.094	1	0.759	1.020	0.900	1.155			
Dr Re Mem.	0.513	0.2063	0.109	0.917	6.190	1	**0.013**	1.671	1.115	2.503			
Anxiolytics	-0.958	0.4673	-1.873	-0.042	4.199	1	**0.040**	0.384	0.154	0.959			
Physical Health	0.014	0.0127	-0.011	0.038	1.172	1	0.279	1.014	0.989	1.039			
Soc Supp Gen Neg	-0.091	0.0544	-0.198	0.015	2.809	1	0.094	0.913	0.820	1.016			
Soc Supp Gen Pos	-0.005	0.0625	-0.128	0.118	0.006	1	0.937	0.995	0.880	1.125			
Soc Supp Partner Neg	-0.016	0.0505	-0.115	0.083	0.095	1	0.758	0.985	0.892	1.087			
Soc Supp Partner Pos	-0.028	0.0526	-0.131	0.075	0.288	1	0.591	0.972	0.877	1.078			
Mastery	-0.016	0.0365	-0.088	0.055	0.202	1	0.653	0.984	0.916	1.057			
Freq Phys Act Mild	-0.080	0.1351	-0.345	0.185	0.353	1	0.553	0.923	0.708	1.203			
Freq Phys Act Mod	0.080	0.1213	-0.158	0.317	0.431	1	0.511	1.083	0.854	1.374			
Freq Phys Act Vig	0.023	0.1022	-0.177	0.223	0.050	1	0.824	1.023	0.837	1.250			
Alcohol	0.170	0.1037	-0.033	0.373	2.690	1	0.101	1.185	0.967	1.453			
Life Events	0.102	0.0845	-0.063	0.268	1.461	1	0.227	1.108	0.939	1.307			
Smoker	0.066	0.3855	-0.690	0.821	0.029	1	0.864	1.068	0.502	2.274			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	-0.006	0.0298	-0.064	0.052	0.041	1	0.840	0.994	0.938	1.054			
(Scale)	4.797												

Note: SD of DV = standard deviation of the dependent variable

Model H:
DV: DSB:
Full Model: Including Time and Time interactions; Excluding other interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	5.488	1.6346	2.284	8.692	11.273	1	0.001	241.794	9.820	5953.829	5396.585	2.256	5.733
Time	0.027	0.1379	-0.244	0.297	0.037	1	0.847	1.027	0.784	1.346			
Sex	-0.155	0.2376	-0.621	0.310	0.427	1	0.513	0.856	0.537	1.364			
Age	-0.110	0.0673	-0.242	0.022	2.688	1	0.101	0.896	0.785	1.022			
Education	0.143	0.0383	0.068	0.218	13.986	1	0.000	1.154	1.070	1.244			
Depression	0.015	0.0629	-0.108	0.138	0.055	1	0.814	1.015	0.897	1.148			
Dr Re Mem.	0.507	0.2068	0.102	0.913	6.022	1	0.014	1.661	1.108	2.491			
Anxiolytics	-0.966	0.4683	-1.883	-0.048	4.252	1	0.039	0.381	0.152	0.953			
Physical Health	0.014	0.0127	-0.011	0.039	1.208	1	0.272	1.014	0.989	1.040			
Soc Supp Gen Neg	-0.089	0.0541	-0.195	0.017	2.727	1	0.099	0.915	0.823	1.017			
Soc Supp Gen Pos	-0.006	0.0621	-0.128	0.115	0.010	1	0.919	0.994	0.880	1.122			
Soc Supp Partner Neg	-0.017	0.0504	-0.115	0.082	0.111	1	0.739	0.983	0.891	1.085			
Soc Supp Partner Pos	-0.025	0.0525	-0.128	0.077	0.234	1	0.629	0.975	0.880	1.081			
Mastery	-0.018	0.0364	-0.089	0.053	0.246	1	0.620	0.982	0.915	1.055			
Freq Phys Act Mild	-0.081	0.1346	-0.345	0.183	0.361	1	0.548	0.922	0.708	1.201			
Freq Phys Act Mod	0.080	0.1212	-0.158	0.317	0.432	1	0.511	1.083	0.854	1.373			
Freq Phys Act Vig	0.020	0.1018	-0.180	0.219	0.037	1	0.847	1.020	0.835	1.245			
Alcohol	0.173	0.1034	-0.030	0.376	2.795	1	0.095	1.189	0.971	1.456			
Life Events	0.101	0.0843	-0.064	0.266	1.438	1	0.230	1.106	0.938	1.305			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Smoker	0.054	0.3835	-0.698	0.806	0.020	1	0.888	1.055	0.498	2.238			
GAS	0.036	0.0396	-0.041	0.114	0.838	1	0.360	1.037	0.959	1.121			
Time*Time	0.007	0.0454	-0.082	0.096	0.022	1	0.883	1.007	0.921	1.100			
Time*GAS	-0.058	0.0615	-0.178	0.063	0.886	1	0.347	0.944	0.837	1.065			
Time*Time*GAS	0.011	0.0207	-0.030	0.051	0.272	1	0.602	1.011	0.971	1.053			
(Scale)	4.797												

Note: SD of DV = standard deviation of the dependent variable

Model I:
DV: DSB:
Full Model: Including Interactions with GAS; Excluding Time and Time interactions

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	5.529	1.6277	2.339	8.719	11.538	1	0.001	251.862	10.367	6118.885	5326.3766	2.256	7.064
Sex	-0.123	0.2387	-0.591	0.345	0.264	1	0.607	0.885	0.554	1.412			
Age	-0.106	0.0671	-0.237	0.026	2.489	1	0.115	0.900	0.789	1.026			
Education	0.152	0.0381	0.077	0.227	15.929	1	0.000	1.164	1.081	1.255			
Depression	0.013	0.0633	-0.111	0.137	0.044	1	0.834	1.013	0.895	1.147			
Dr Re Mem.	0.541	0.2148	0.121	0.962	6.357	1	0.012	1.718	1.128	2.618			
Anxiolytics	-1.805	0.4466	-2.680	-0.929	16.330	1	0.000	0.165	0.069	0.395			
Physical Health	0.013	0.0129	-0.012	0.038	1.050	1	0.306	1.013	0.988	1.039			
Soc Supp Gen Neg	-0.090	0.0542	-0.196	0.016	2.769	1	0.096	0.914	0.822	1.016			
Soc Supp Gen Pos	-0.019	0.0623	-0.141	0.103	0.091	1	0.763	0.981	0.869	1.109			
Soc Supp Partner Neg	-0.014	0.0504	-0.113	0.085	0.078	1	0.780	0.986	0.893	1.088			
Soc Supp Partner Pos	-0.019	0.0523	-0.122	0.083	0.135	1	0.713	0.981	0.885	1.087			
Mastery	-0.016	0.0364	-0.088	0.055	0.197	1	0.657	0.984	0.916	1.057			
Freq Phys Act Mild	-0.069	0.1311	-0.326	0.188	0.279	1	0.597	0.933	0.722	1.206			
Freq Phys Act Mod	0.072	0.1206	-0.165	0.308	0.353	1	0.552	1.074	0.848	1.361			
Freq Phys Act Vig	0.017	0.1019	-0.183	0.217	0.028	1	0.866	1.017	0.833	1.242			
Alcohol	0.160	0.1020	-0.040	0.359	2.450	1	0.118	1.173	0.961	1.433			
Life Events	0.090	0.0831	-0.073	0.253	1.174	1	0.279	1.094	0.930	1.288			
Smoker	0.102	0.3757	-0.634	0.839	0.074	1	0.785	1.108	0.530	2.314			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	-0.014	0.0331	-0.079	0.051	0.172	1	0.678	0.986	0.924	1.053			
Education*GAS	-0.012	0.0108	-0.033	0.010	1.141	1	0.285	0.989	0.968	1.010			
Anxiolytics*GAS	0.324	0.1020	0.124	0.523	10.073	1	**0.002**	1.382	1.132	1.688			
Dr Re Memory*GAS	-0.018	0.0506	-0.118	0.081	0.133	1	0.715	0.982	0.889	1.084			
(Scale)	4.730												

Note: SD of DV = standard deviation of the dependent variable

Model J:
DV: IR
Full Model: Excluding: Time and all interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	1.697	1.6751	-1.586	4.980	1.026	1	0.311	5.458	0.205	145.488	11568.415	3.287	4.781
Sex	0.948	0.2757	0.408	1.489	11.835	1	**0.001**	2.581	1.504	4.431			
Age	-0.127	0.0706	-0.265	0.011	3.243	1	0.072	0.881	0.767	1.011			
Education	0.142	0.0385	0.067	0.218	13.612	1	**0.000**	1.153	1.069	1.243			
Depression	0.048	0.0755	-0.100	0.196	0.407	1	0.523	1.049	0.905	1.217			
Dr Re Mem.	-0.119	0.1603	-0.433	0.195	0.551	1	0.458	0.888	0.648	1.216			
Anxiolytics	1.260^	0.4303	0.416	2.103	8.568	1	**0.003**	3.524	1.516	8.192			
Physical Health	0.020	0.0122	-0.004	0.044	2.626	1	0.105	1.020	0.996	1.045			
Soc Supp Gen Neg	0.026	0.0478	-0.067	0.120	0.305	1	0.581	1.027	0.935	1.128			
Soc Supp Gen Pos	0.097	0.0609	-0.022	0.217	2.558	1	0.110	1.102	0.978	1.242			
Soc Supp Partner Neg	-0.029	0.0489	-0.125	0.067	0.360	1	0.549	0.971	0.882	1.069			
Soc Supp Partner Pos	-0.066	0.0486	-0.161	0.029	1.857	1	0.173	0.936	0.851	1.029			
Mastery	0.023	0.0338	-0.044	0.089	0.442	1	0.506	1.023	0.957	1.093			
Freq Phys Act Mild	-0.137	0.1361	-0.404	0.129	1.018	1	0.313	0.872	0.668	1.138			
Freq Phys Act Mod	0.230	0.1668	-0.097	0.557	1.898	1	0.168	1.258	0.907	1.745			
Freq Phys Act Vig	-0.026	0.0977	-0.217	0.165	0.071	1	0.790	0.974	0.805	1.180			
Alcohol	0.240	0.1323	-0.020	0.499	3.285	1	0.070	1.271	0.981	1.647			
Life Events	0.068	0.0810	-0.091	0.226	0.694	1	0.405	1.070	0.913	1.254			
Smoker	-0.227	0.3569	-0.926	0.473	0.404	1	0.525	0.797	0.396	1.604			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	0.096	0.1222	-0.143	0.336	0.621	1	0.430	1.101	0.867	1.399			
(Scale)	10.290												

^ Coefficients for anxiolytics were reverse coded for these analyses. So, for example, if reverse coding had been removed, anxiolytics predicted a negative effect on IR scores. SD of DV = standard deviation of the dependent variable.

Model K:
DV: IR
Full Model: Including: Time and Time interactions; Excluding: other interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	1.764	1.6670	-1.503	5.031	1.120	1	0.290	5.835	0.222	153.129	11557.843	3.287	9.675
Time	0.252	0.1768	-0.094	0.599	2.036	1	0.154	1.287	0.910	1.820			
Sex	0.954	0.2749	0.415	1.492	12.037	1	0.001	2.595	1.514	4.448			
Age	-0.118	0.0714	-0.258	0.022	2.713	1	0.100	0.889	0.773	1.023			
Education	0.143	0.0387	0.068	0.219	13.729	1	0.000	1.154	1.070	1.245			
Depression	0.046	0.0747	-0.101	0.192	0.374	1	0.541	1.047	0.904	1.212			
Dr Re Mem.	.217	0.2823	-0.336	0.771	0.593	1	0.441	1.243	0.715	2.161			
Anxiolytics	-1.288	0.4354	-2.141	-.434	8.748	1	0.003	.276	.118	.648			
Physical Health	0.024	0.0122	8.724E-05	0.048	3.870	1	0.049	1.024	1.000	1.049			
Soc Supp Gen Neg	0.036	0.0478	-0.058	0.129	0.557	1	0.455	1.036	0.944	1.138			
Soc Supp Gen Pos	0.109	0.0595	-0.008	0.225	3.334	1	0.068	1.115	0.992	1.253			
Soc Supp Partner Neg	-0.034	0.0492	-0.131	0.062	0.487	1	0.485	0.966	0.877	1.064			
Soc Supp Partner Pos	-0.076	0.0495	-0.173	0.021	2.350	1	0.125	0.927	0.841	1.021			
Mastery	0.030	0.0335	-0.036	0.096	0.808	1	0.369	1.031	0.965	1.100			
Freq Phys Act Mild	-0.124	0.1377	-0.394	0.146	0.812	1	0.367	0.883	0.674	1.157			
Freq Phys Act Mod	0.250	0.1611	-0.065	0.566	2.415	1	0.120	1.285	0.937	1.761			
Freq Phys Act Vig	-0.035	0.0954	-0.222	0.152	0.138	1	0.711	0.965	0.801	1.164			
Alcohol	0.262	0.1308	0.006	0.519	4.024	1	0.045	1.300	1.006	1.680			
Life Events	0.054	0.0825	-0.107	0.216	0.434	1	0.510	1.056	0.898	1.241			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Smoker	-0.281	0.3498	-0.967	0.404	0.646	1	0.422	0.755	0.380	1.499			
GAS	0.083	0.0808	-0.075	0.241	1.054	1	0.305	1.086	0.927	1.273			
Time*Time	-0.292	0.0620	-0.413	-0.170	22.162	1	0.000	0.747	0.662	0.843			
Time*GAS	0.176	0.2603	-0.334	0.686	0.457	1	0.499	1.192	0.716	1.986			
Time*Time*GAS	-0.071	0.0944	-0.256	0.114	0.561	1	0.454	0.932	0.774	1.121			
(Scale)	9.761												

^ Coefficients for anxiolytics were reverse coded for these analyses. So, for example, if reverse coding had been removed, anxiolytics predicted a negative effect on IR scores. SD of DV = standard deviation of the dependent variable.

Model L:
DV: IR
Full Model: Including: Interactions with GAS; Excluding: Time and Time interactions

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	1.581	1.8653	-2.075	5.237	0.719	1	0.397	4.861	0.126	188.155	11554.160	3.287	4.877
Sex	0.835	0.2236	0.397	1.273	13.956	1	0.000	2.305	1.487	3.573			
Age	-0.124	0.0703	-0.262	0.013	3.133	1	0.077	0.883	0.769	1.013			
Education	0.135	0.0359	0.065	0.205	14.127	1	0.000	1.144	1.067	1.228			
Depression	0.046	0.0777	-0.106	0.198	0.347	1	0.556	1.047	0.899	1.219			
Dr Re Mem.	-0.057	0.1762	-0.402	0.288	0.104	1	0.747	0.945	0.669	1.334			
Anxiolytics	1.314^	0.4538	0.425	2.204	8.389	1	0.004	3.722	1.530	9.058			
Physical Health	0.020	0.0124	-0.005	0.044	2.514	1	0.113	1.020	0.995	1.045			
Soc Supp Gen Neg	0.023	0.0488	-0.073	0.118	0.213	1	0.644	1.023	0.929	1.125			
Soc Supp Gen Pos	0.097	0.0596	-0.020	0.213	2.631	1	0.105	1.101	0.980	1.238			
Soc Supp Partner Neg	-0.020	0.0476	-0.114	0.073	0.180	1	0.672	0.980	0.893	1.076			
Soc Supp Partner Pos	-0.062	0.0490	-0.158	0.034	1.623	1	0.203	0.940	0.854	1.034			
Mastery	0.031	0.0331	-0.034	0.096	0.885	1	0.347	1.032	0.967	1.101			
Freq Phys Act Mild	-0.122	0.1424	-0.401	0.157	0.734	1	0.391	0.885	0.669	1.170			
Freq Phys Act Mod	0.205	0.1864	-0.160	0.571	1.213	1	0.271	1.228	0.852	1.769			
Freq Phys Act Vig	-0.023	0.1021	-0.223	0.177	0.049	1	0.825	0.978	0.800	1.194			
Alcohol	0.212	0.1151	-0.014	0.438	3.395	1	0.065	1.236	0.987	1.549			
Life Events	0.071	0.0818	-0.089	0.231	0.752	1	0.386	1.074	0.915	1.260			
Smoker	-0.302	0.3570	-1.001	0.398	0.714	1	0.398	0.740	0.367	1.489			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	0.149	0.2567	-0.354	0.652	0.338	1	0.561	1.161	0.702	1.920			
Sex*GAS	0.225	0.2842	-0.332	0.782	0.628	1	0.428	1.253	0.718	2.186			
Education*GAS	0.025	0.0336	-0.041	0.091	0.545	1	0.460	1.025	0.960	1.095			
Anxiolytics*GAS	-0.074	0.1319	-0.332	0.185	0.314	1	0.575	0.929	0.717	1.203			
(Scale)	10.280												

^ Coefficients for anxiolytics were reverse coded for these analyses. So, for example, if reverse coding had been removed, anxiolytics predicted a negative effect on IR scores. SD of DV = standard deviation of the dependent variable.

Model M:
DV: MMSE
Full Model: Excluding: Time and all interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	-3.201	60.6175	-122.009	115.607	0.003	1	0.958	0.041	1.028E-53	1.612E+50	618445.741	11.358	-322.338
Sex	3.642	8.4322	-12.885	20.169	0.187	1	0.666	38.177	2.537E-06	574566027.782			
Age	2.459	1.6690	-0.812	5.730	2.171	1	0.141	11.694	0.444	308.057			
Education	0.772	1.2206	-1.620	3.164	0.400	1	0.527	2.164	0.198	23.670			
Depression	-5.774	2.1819	-10.050	-1.497	7.002	1	0.008	0.003	4.317E-05	0.224			
Dr Re Mem.	0.082	8.3794	-16.342	16.505	0.000	1	0.992	1.085	7.996E-08	14724737.145			
Anxiolytics	20.356	19.4938	-17.851	58.563	1.090	1	0.296	6.926E+08	1.767E-08	2.714E+25			
Physical Health	-0.244	0.3591	-0.948	0.460	0.461	1	0.497	0.784	0.388	1.584			
Soc Supp Gen Neg	-0.465	1.3005	-3.014	2.084	0.128	1	0.721	0.628	0.049	8.036			
Soc Supp Gen Pos	-2.210	1.6433	-5.431	1.011	1.809	1	0.179	0.110	0.004	2.747			
Soc Supp Partner Neg	-0.656	1.2153	-3.038	1.726	0.292	1	0.589	0.519	0.048	5.616			
Soc Supp Partner Pos	0.752	1.6589	-2.500	4.003	0.205	1	0.650	2.121	0.082	54.769			
Mastery	-0.148	1.1549	-2.411	2.116	0.016	1	0.898	0.863	0.090	8.296			
Freq Phys Act Mild	1.340	3.2652	-5.060	7.739	0.168	1	0.682	3.818	0.006	2296.841			
Freq Phys Act Mod	6.810	3.6973	-0.436	14.057	3.393	1	0.065	907.234	0.647	1273078.477			
Freq Phys Act Vig	-1.767	2.8586	-7.370	3.836	0.382	1	0.536	0.171	0.001	46.323			
Alcohol	8.128	4.1549	-0.015	16.271	3.827	1	0.050	3387.977	0.985	11657536.233			
Life Events	0.093	2.5100	-4.826	5.013	0.001	1	0.970	1.098	0.008	150.354			
Smoker	-4.569	11.1139	-26.352	17.214	0.169	1	0.681	0.010	3.593E-12	29914262.995			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	0.313	0.5163	-0.699	1.325	0.367	1	0.545	1.367	0.497	3.760			
(Scale)	544.829												

SD of DV = standard deviation of the dependent variable.

Model N:
DV: MMSE
Full Model: Including: Time and Time interactions; Excluding: other interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	-5.643	59.7562	-122.763	111.477	0.009	1	0.925	0.004	4.840E-54	2.594E+48	488348.086	11.358	-234.378
Time	0.685	1.0351	-1.344	2.714	0.438	1	0.508	1.984	0.261	15.087			
Sex	3.982	8.3842	-12.450	20.415	0.226	1	0.635	53.642	3.916E-06	734734744.697			
Age	2.436	1.6009	-0.702	5.574	2.315	1	0.128	11.427	0.496	263.434			
Education	0.779	1.1895	-1.553	3.110	0.429	1	0.513	2.179	0.212	22.425			
Depression	-5.333	1.8954	-9.048	-1.618	7.916	1	0.005	0.005	0.000	0.198			
Dr Re Mem.	1.283	8.1991	-14.787	17.353	0.024	1	0.876	3.608	3.786E-07	34389564.010			
Anxiolytics	20.715	18.6862	-15.909	57.339	1.229	1	0.268	9.917E+08	1.232E-07	7.982E+24			
Physical Health	-0.184	0.3474	-0.864	0.497	0.279	1	0.597	0.832	0.421	1.644			
Soc Supp Gen Neg	-0.082	1.2509	-2.534	2.369	0.004	1	0.948	0.921	0.079	10.692			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Soc Supp Gen Pos	-1.996	1.6530	-5.236	1.244	1.458	1	0.227	0.136	0.005	3.468			
Soc Supp Partner Neg	-0.571	1.1601	-2.845	1.703	0.242	1	0.622	0.565	0.058	5.488			
Soc Supp Partner Pos	0.706	1.6361	-2.501	3.912	0.186	1	0.666	2.025	0.082	50.017			
Mastery	-0.117	1.1690	-2.408	2.175	0.010	1	0.921	0.890	0.090	8.799			
Freq Phys Act Mild	1.324	3.2205	-4.988	7.636	0.169	1	0.681	3.758	0.007	2071.395			
Freq Phys Act Mod	7.121	3.7136	-0.158	14.399	3.676	1	0.055	1237.073	0.854	1792451.013			
Freq Phys Act Vig	-2.085	2.9736	-7.913	3.743	0.492	1	0.483	0.124	0.000	42.226			
Alcohol	8.778	3.9670	1.003	16.554	4.897	1	0.027	6492.918	2.727	15456844.906			
Life Events	-0.230	2.4885	-5.107	4.647	0.009	1	0.926	0.795	0.006	104.320			
Smoker	-5.372	10.8397	-26.617	15.874	0.246	1	0.620	0.005	2.756E-12	7831191.564			
GAS	0.437	0.8551	-1.239	2.113	0.261	1	0.609	1.548	0.290	8.272			
Time*Time	0.280	0.3548	-0.415	0.976	0.623	1	0.430	1.323	0.660	2.653			
Time*GAS	-0.558	0.8955	-2.314	1.197	0.389	1	0.533	0.572	0.099	3.310			
Time*Time*GAS	0.192	0.2472	-0.292	0.677	0.604	1	0.437	1.212	0.747	1.967			
(Scale)	431.358												

SD of DV = standard deviation of the dependent variable.

Model O:
DV: MMSE:
Full Model: Including: Interactions with GAS; Excluding: Time and Time interactions

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	2.081	60.3807	-116.263	120.425	0.001	1	0.973	8.012	3.218E-51	1.995E+52	557837.915	11.358	-281.461
Sex	1.715	7.8499	-13.671	17.100	0.048	1	0.827	5.555	1.156E-06	26700818.515			
Age	2.020	1.5537	-1.025	5.065	1.690	1	0.194	7.538	0.359	158.419			
Education	0.922	1.2223	-1.474	3.317	0.568	1	0.451	2.513	0.229	27.582			
Depression	-4.890	2.1560	-9.116	-0.664	5.144	1	0.023	0.008	0.000	0.515			
Dr Re Mem.	-0.305	8.1321	-16.243	15.634	0.001	1	0.970	0.737	8.823E-08	6162396.614			
Anxiolytics	17.360	16.9642	-15.890	50.609	1.047	1	0.306	3.461E+07	1.257E-07	9.531E+21			
Physical Health	-0.275	0.3534	-0.967	0.418	0.604	1	0.437	0.760	0.380	1.519E+00			
Soc Supp Gen Neg	-0.272	1.2627	-2.746	2.203	0.046	1	0.830	0.762	0.064	9.055			
Soc Supp Gen Pos	-1.858	1.5034	-4.804	1.089	1.527	1	0.217	0.156	0.008	2.971			
Soc Supp Partner Neg	-0.747	1.1710	-3.042	1.548	0.407	1	0.523	0.474	0.048	4.700			
Soc Supp Partner Pos	0.684	1.6637	-2.576	3.945	0.169	1	0.681	1.983	0.076	51.682			
Mastery	-0.183	1.1611	-2.459	2.093	0.025	1	0.875	0.833	0.086	8.106			
Freq Phys Act Mild	2.254	3.0534	-3.730	8.239	0.545	1	0.460	9.528	0.024	3785.026			
Freq Phys Act Mod	7.277	3.5370	0.345	14.210	4.233	1	0.040	1447.072	1.412	1483032.418			
Freq Phys Act Vig	-1.952	2.8341	-7.507	3.603	0.474	1	0.491	0.142	0.001	36.703			
Alcohol	7.533	4.1809	-0.662	15.727	3.246	1	0.072	1868.363	0.516	6764535.143			
Life Events	-0.496	2.5058	-5.407	4.415	0.039	1	0.843	0.609	0.004	82.704			
Smoker	-3.895	11.2788	-26.001	18.211	0.119	1	0.730	0.020	5.103E-12	81088970.002			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	-0.038	1.7403	-3.449	3.373	0.000	1	0.982	0.962	0.032	29.158			
Depression*GAS	-0.250	0.2715	-0.782	0.282	0.849	1	0.357	0.779	0.457	1.326			
Alcohol*GAS	0.280	0.5128	-0.725	1.285	0.298	1	0.585	1.323	0.484	3.614			
(Scale)	492.096												

SD of DV = standard deviation of the dependent variable.

Model P:
DV: StW:
Full Model: Excluding: Time and all interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	49.296	4.7815	39.924	58.668	106.289	1	0.000	2.564E+21	2.182E+17	3.013E+25	21348.541	4.879	17.116
Sex	0.409	0.6145	-0.795	1.614	0.444	1	0.505	1.506	0.452	5.021			
Age	0.017	0.1627	-0.302	0.335	0.010	1	0.919	1.017	0.739	1.398			
Education	0.717	0.1005	0.520	0.914	50.910	1	0.000	2.049	1.682	2.495			
Depression	0.210	0.1470	-0.078	0.498	2.037	1	0.153	1.234	0.925	1.646			
Dr Re Mem.	-0.108	0.5486	-1.183	0.967	0.039	1	0.844	0.898	0.306	2.631			
Anxiolytics	-0.288	0.8837	-2.020	1.444	0.106	1	0.744	0.750	0.133	4.237			
Physical Health	0.087	0.0313	0.026	0.149	7.781	1	0.005	1.091	1.026	1.160			
Soc Supp Gen Neg	-0.005	0.1285	-0.257	0.246	0.002	1	0.967	0.995	0.773	1.280			
Soc Supp Gen Pos	-0.094	0.1578	-0.403	0.215	0.356	1	0.551	0.910	0.668	1.240			
Soc Supp Partner Neg	-0.192	0.1412	-0.469	0.085	1.845	1	0.174	0.825	0.626	1.089			
Soc Supp Partner Pos	-0.002	0.1413	-0.279	0.275	0.000	1	0.987	0.998	0.756	1.316			
Mastery	0.022	0.0836	-0.141	0.186	0.072	1	0.789	1.023	0.868	1.205			
Freq Phys Act Mild	-0.599	0.3613	-1.307	0.109	2.751	1	0.097	0.549	0.271	1.115			
Freq Phys Act Mod	0.261	0.3116	-0.350	0.872	0.701	1	0.402	1.298	0.705	2.391			
Freq Phys Act Vig	0.193	0.2410	-0.279	0.665	0.643	1	0.423	1.213	0.757	1.945			
Alcohol	0.598	0.2259	0.155	1.040	7.000	1	0.008	1.818	1.168	2.830			
Life Events	0.067	0.2106	-0.346	0.480	0.101	1	0.750	1.069	0.708	1.616			
Smoker	-0.534	1.0196	-2.532	1.465	0.274	1	0.601	0.586	0.079	4.326			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	-0.001	0.0408	-0.081	0.079	0.001	1	0.982	0.999	0.922	1.082			
(Scale)	19.730												

SD of DV = standard deviation of the dependent variable.

Model Q:
DV: StW:
Full Model: Including: Time and Time interactions; Excluding: other interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	49.285	4.7637	39.948	58.622	107.038	1	0.000	2.537E+21	2.236E+17	2.879E+25	21173.494	4.879	17.499
Time	0.701	0.1591	0.389	1.013	19.421	1	0.000	2.016	1.476	2.753			
Sex	0.381	0.6121	-0.818	1.581	0.388	1	0.533	1.464	0.441	4.860			
Age	0.009	0.1624	-0.309	0.327	0.003	1	0.955	1.009	0.734	1.387			
Education	0.715	0.1006	0.518	0.912	50.527	1	0.000	2.044	1.678	2.490			
Depression	0.190	0.1474	-0.099	0.479	1.665	1	0.197	1.209	0.906	1.614			
Dr Re Mem.	-0.110	0.5478	-1.184	0.964	0.040	1	0.841	0.896	0.306	2.622			
Anxiolytics	-0.260	0.8727	-1.970	1.451	0.089	1	0.766	0.771	0.139	4.267			
Physical Health	0.085	0.0312	0.024	0.146	7.449	1	0.006	1.089	1.024	1.157			
Soc Supp Gen Neg	-0.011	0.1283	-0.263	0.240	0.008	1	0.931	0.989	0.769	1.272			
Soc Supp Gen Pos	-0.098	0.1575	-0.407	0.211	0.389	1	0.533	0.906	0.666	1.234			
Soc Supp Partner Neg	-0.197	0.1405	-0.472	0.078	1.970	1	0.160	0.821	0.623	1.081			
Soc Supp Partner Pos	-0.007	0.1408	-0.283	0.269	0.003	1	0.959	0.993	0.753	1.308			
Mastery	0.021	0.0835	-0.143	0.185	0.063	1	0.802	1.021	0.867	1.203			
Freq Phys Act Mild	-0.608	0.3592	-1.312	0.096	2.864	1	0.091	0.544	0.269	1.101			
Freq Phys Act Mod	0.265	0.3116	-0.345	0.876	0.725	1	0.395	1.304	0.708	2.401			
Freq Phys Act Vig	0.192	0.2402	-0.278	0.663	0.641	1	0.423	1.212	0.757	1.941			
Alcohol	0.588	0.2258	0.145	1.030	6.778	1	0.009	1.800	1.156	2.802			
Life Events	0.067	0.2100	-0.344	0.479	0.103	1	0.748	1.070	0.709	1.614			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Smoker	-0.531	1.0116	-2.513	1.452	0.275	1	0.600	0.588	0.081	4.271			
GAS	0.061	0.0539	-0.044	0.167	1.291	1	0.256	1.063	0.957	1.182			
Time*Time	-0.166	0.0530	-0.270	-0.062	9.811	1	0.002	0.847	0.764	0.940			
Time*GAS	-0.085	0.0684	-0.219	0.049	1.530	1	0.216	0.919	0.804	1.051			
Time*Time*GAS	0.021	0.0235	-0.025	0.067	0.791	1	0.374	1.021	0.975	1.069			
(Scale)	19.638												

SD of DV = standard deviation of the dependent variable.

Model R:
DV: StW
Full Model: Including: Interactions with GAS; Excluding: Time and Time interactions

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	50.198	4.8972	40.600	59.796	105.070	1	0.000	6.319E+21	4.287E+17	9.315E+25	21287.140	4.879	17.142
Sex	0.434	0.6185	-0.778	1.646	0.492	1	0.483	1.543	0.459	5.187			
Age	0.022	0.1616	-0.295	0.339	0.018	1	0.892	1.022	0.745	1.403			
Education	0.721	0.1011	0.523	0.919	50.866	1	0.000	2.056	1.687	2.506			
Depression	0.208	0.1478	-0.082	0.497	1.972	1	0.160	1.231	0.921	1.644			
Dr Re Mem.	-0.057	0.5511	-1.137	1.023	0.011	1	0.918	0.945	0.321	2.782			
Anxiolytics	-0.483	0.8975	-2.242	1.276	0.289	1	0.591	0.617	0.106	3.584			
Physical Health	0.077	0.0340	0.010	0.144	5.094	1	0.024	1.080	1.010	1.154			
Soc Supp Gen Neg	-0.006	0.1289	-0.259	0.247	0.002	1	0.964	0.994	0.772	1.280			
Soc Supp Gen Pos	-0.097	0.1572	-0.405	0.211	0.380	1	0.538	0.908	0.667	1.235			
Soc Supp Partner Neg	-0.186	0.1410	-0.462	0.091	1.734	1	0.188	0.831	0.630	1.095			
Soc Supp Partner Pos	0.002	0.1418	-0.276	0.280	0.000	1	0.989	1.002	0.759	1.323			
Mastery	0.020	0.0830	-0.143	0.183	0.058	1	0.810	1.020	0.867	1.200			
Freq Phys Act Mild	-0.614	0.3627	-1.325	0.096	2.870	1	0.090	0.541	0.266	1.101			
Freq Phys Act Mod	0.254	0.3101	-0.354	0.862	0.669	1	0.413	1.289	0.702	2.367			
Freq Phys Act Vig	0.180	0.2396	-0.290	0.650	0.563	1	0.453	1.197	0.748	1.915			
Alcohol	0.652	0.2291	0.203	1.101	8.092	1	0.004	1.919	1.225	3.007			
Life Events	0.078	0.2110	-0.336	0.491	0.136	1	0.713	1.081	0.715	1.634			
Smoker	-0.589	1.0188	-2.585	1.408	0.334	1	0.563	0.555	0.075	4.089			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
GAS	-0.140	0.2943	-0.717	0.437	0.226	1	0.635	0.870	0.488	1.548			
Education*GAS	0.009	0.0164	-0.024	0.041	0.279	1	0.598	1.009	0.977	1.042			
Physical Health*GAS	0.008	0.0050	-0.002	0.017	2.303	1	0.129	1.008	0.998	1.017			
Alcohol*GAS	-0.074	0.0425	-0.157	0.010	3.008	1	0.083	0.929	0.855	1.010			
(Scale)	19.724												

SD of DV = standard deviation of the dependent variable.

Model S:
DV: MCI
Full Model: Excluding: Time and all interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper	
Intercept	-5.972	3.7525	-13.327	1.382	2.533	1	0.111	0.003	1.630E-06	3.985	^
Sex	0.171	0.3981	-0.610	0.951	0.184	1	0.668	1.186	0.544	2.588	
Age	0.054	0.1078	-0.157	0.265	0.252	1	0.616	1.056	0.855	1.304	
Education	-0.167	0.0962	-0.356	0.021	3.029	1	0.082	0.846	0.700	1.021	
Depression	0.133	0.1258	-0.114	0.379	1.114	1	0.291	1.142	0.892	1.461	
Dr Re Mem.	-1.007	0.5046	-1.996	-0.018	3.984	1	0.046	0.365	0.136	0.982	
Anxiolytics	-1.009	0.6445	-2.272	0.255	2.448	1	0.118	0.365	0.103	1.290	
Physical Health	0.062	0.0334	-0.004	0.127	3.428	1	0.064	1.064	0.996	1.136	
Soc Supp Gen Neg	-0.072	0.0886	-0.246	0.101	0.665	1	0.415	0.930	0.782	1.107	
Soc Supp Gen Pos	0.183	0.1403	-0.092	0.458	1.693	1	0.193	1.200	0.912	1.580	
Soc Supp Partner Neg	0.109	0.1242	-0.134	0.353	0.772	1	0.380	1.115	0.874	1.423	
Soc Supp Partner Pos	0.196	0.1225	-0.044	0.437	2.571	1	0.109	1.217	0.957	1.547	
Mastery	-0.046	0.0824	-0.208	0.115	0.313	1	0.576	0.955	0.812	1.122	
Freq Phys Act Mild	-0.217	0.2829	-0.772	0.337	0.590	1	0.442	0.805	0.462	1.401	
Freq Phys Act Mod	0.290	0.2749	-0.249	0.829	1.115	1	0.291	1.337	0.780	2.291	
Freq Phys Act Vig	-0.167	0.1771	-0.514	0.181	0.884	1	0.347	0.847	0.598	1.198	
Alcohol	-0.005	0.1936	-0.385	0.374	0.001	1	0.978	0.995	0.681	1.454	
Life Events	0.052	0.2104	-0.360	0.464	0.061	1	0.805	1.053	0.697	1.591	
Smoker	-1.360	0.6329	-2.600	-0.119	4.617	1	0.032	0.257	0.074	0.887	
GAS	0.043	0.0924	-0.138	0.224	0.216	1	0.642	1.044	0.871	1.251	

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper	
(Scale)	1										

^ Invalid result for variance explained.

Model T:
DV: MCI
Full Model: Including: Time and Time interactions; Excluding: other interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper	
Intercept	-7.427	4.4206	-16.091	1.237	2.823	1	0.093	0.001	1.027E-07	3.446	^
Time	0.609	0.5953	-0.558	1.776	1.046	1	0.306	1.838	0.572	5.904	
Sex	0.305	0.4434	-0.564	1.174	0.473	1	0.492	1.357	0.569	3.235	
Age	0.028	0.1274	-0.221	0.278	0.050	1	0.824	1.029	0.801	1.321	
Education	-0.189	0.1024	-0.390	0.012	3.407	1	0.065	0.828	0.677	1.012	
Depression	0.121	0.1389	-0.151	0.394	0.764	1	0.382	1.129	0.860	1.482	
Dr Re Mem.	-1.128	0.6225	-2.348	0.092	3.283	1	0.070	0.324	0.096	1.097	
Anxiolytics	-1.157	0.8295	-2.783	0.469	1.945	1	0.163	0.314	0.062	1.598	
Physical Health	0.056	0.0395	-0.022	0.133	2.000	1	0.157	1.057	0.979	1.142	
Soc Supp Gen Neg	-0.117	0.0969	-0.307	0.073	1.449	1	0.229	0.890	0.736	1.076	
Soc Supp Gen Pos	0.225	0.1682	-0.104	0.555	1.798	1	0.180	1.253	0.901	1.742	
Soc Supp Partner Neg	0.141	0.1355	-0.125	0.406	1.077	1	0.299	1.151	0.883	1.501	
Soc Supp Partner Pos	0.242	0.1363	-0.025	0.509	3.147	1	0.076	1.274	0.975	1.664	
Mastery	-0.071	0.0836	-0.235	0.093	0.713	1	0.398	0.932	0.791	1.098	
Freq Phys Act Mild	-0.244	0.3538	-0.937	0.450	0.475	1	0.491	0.784	0.392	1.568	
Freq Phys Act Mod	0.230	0.3168	-0.391	0.851	0.526	1	0.468	1.258	0.676	2.341	
Freq Phys Act Vig	-0.153	0.1882	-0.522	0.216	0.659	1	0.417	0.858	0.594	1.241	
Alcohol	-0.074	0.2143	-0.494	0.346	0.119	1	0.730	0.929	0.610	1.414	
Life Events	0.072	0.2264	-0.372	0.515	0.100	1	0.752	1.074	0.689	1.674	
Smoker	-1.589	0.7047	-2.970	-0.208	5.085	1	0.024	0.204	0.051	0.812	

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper	
GAS	0.019	0.1678	-0.310	0.348	0.013	1	0.909	1.019	0.734	1.416	
Time*Time	0.221	0.1988	-0.169	0.610	1.231	1	0.267	1.247	0.844	1.841	
Time*GAS	0.240	0.1932	-0.139	0.618	1.540	1	0.215	1.271	0.870	1.856	
Time*Time*GAS	-0.079	0.0720	-0.220	0.063	1.190	1	0.275	0.924	0.803	1.065	
(Scale)	1										

^ Invalid result for variance explained

Model U:
DV: MCI
Full Model: Including: Interactions with GAS; Excluding: Time and Time interactions

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper	
Intercept	-6.578	4.0741	-14.563	1.407	2.607	1	0.106	0.001	4.734E-07	4.082	^
Sex	0.182	0.3939	-0.590	0.954	0.213	1	0.644	1.199	0.554	2.596	
Age	0.056	0.1017	-0.143	0.255	0.304	1	0.581	1.058	0.867	1.291	
Education	-0.172	0.0947	-0.358	0.013	3.309	1	0.069	0.842	0.699	1.013	
Depression	0.111	0.1259	-0.136	0.358	0.778	1	0.378	1.117	0.873	1.430	
Dr Re Mem.	-0.893	0.5456	-1.962	0.176	2.680	1	0.102	0.409	0.141	1.193	
Anxiolytics	-1.137	0.6566	-2.424	0.150	2.999	1	0.083	0.321	0.089	1.162	
Physical Health	0.063	0.0351	-0.005	0.132	3.270	1	0.071	1.066	0.995	1.141	
Soc Supp Gen Neg	-0.060	0.0877	-0.232	0.112	0.467	1	0.495	0.942	0.793	1.119	
Soc Supp Gen Pos	0.186	0.1431	-0.094	0.467	1.691	1	0.193	1.205	0.910	1.595	
Soc Supp Partner Neg	0.110	0.1213	-0.128	0.347	0.820	1	0.365	1.116	0.880	1.416	
Soc Supp Partner Pos	0.195	0.1224	-0.044	0.435	2.550	1	0.110	1.216	0.957	1.545	
Mastery	-0.047	0.0847	-0.213	0.120	0.302	1	0.583	0.955	0.808	1.127	
Freq Phys Act Mild	-0.241	0.2998	-0.828	0.347	0.645	1	0.422	0.786	0.437	1.414	
Freq Phys Act Mod	0.309	0.2813	-0.242	0.860	1.207	1	0.272	1.362	0.785	2.364	
Freq Phys Act Vig	-0.157	0.1814	-0.512	0.199	0.747	1	0.388	0.855	0.599	1.220	
Alcohol	-0.033	0.1840	-0.394	0.328	0.032	1	0.858	0.968	0.675	1.388	
Life Events	0.082	0.2097	-0.329	0.493	0.152	1	0.696	1.085	0.720	1.637	
Smoker	-1.014	0.8862	-2.751	0.722	1.310	1	0.252	0.363	0.064	2.060	
GAS	0.573	0.3693	-0.151	1.297	2.409	1	0.121	1.774	0.860	3.658	

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper	
Dr Re Memory*GAS	-0.092	0.1375	-0.362	0.177	0.452	1	0.502	0.912	0.696	1.194	
Smoker*GAS	-0.274	0.2038	-0.674	0.125	1.810	1	0.179	0.760	0.510	1.133	
(Scale)	1										

^ Invalid result for variance explained

Model V:
DV: Dementia
Maximum Model: Excluding: Time and all interactions with GAS

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper	
Intercept	-6.562	0.5070	-7.556	-5.569	167.526	1	0.000	0.001	0.001	0.004	^
Sex	-0.240	0.4338	-1.091	0.610	0.307	1	0.580	0.786	0.336	1.840	
Age	0.308	0.1272	0.059	0.558	5.880	1	0.015	1.361	1.061	1.746	
Education	0.017	0.0830	-0.146	0.180	0.041	1	0.839	1.017	0.864	1.197	
Depression	0.030	0.1180	-0.201	0.262	0.067	1	0.796	1.031	0.818	1.299	
GAS	-0.146	0.1284	-0.398	0.106	1.292	1	0.256	0.864	0.672	1.112	
(Scale)	1										

Note: For Model V, the maximum model was limited to the CVs presented. Models attempted with additional CVs would not converge or would not run. This was possibly attributable to an excess of small cell sizes or empty cells, particularly in the early waves of data when there was small or zero conversion to dementia. For the fully adjusted model, the SPSS warning was that maximum likelihood estimates do not exist.
^ Invalid result for variance explained

Appendix 6.F:

Fully adjusted, Interaction Models for DSB, Alternative Temporal Treatments

DSB Interactions; **Model A: Lagged-GAS**

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	4.861	1.6724	1.583	8.138	8.447	1	0.004	129.100	4.869	3423.353	3579.379	2.235	7.939
Sex	-0.251	0.2542	-0.749	0.247	0.974	1	0.324	0.778	0.473	1.281			
Age	-0.166	0.0737	-0.311	-0.022	5.094	1	0.024	0.847	0.733	0.978			
Education	0.176	0.0411	0.095	0.256	18.345	1	0.000	1.192	1.100	1.292			
Depression	0.055	0.0734	-0.089	0.199	0.569	1	0.450	1.057	0.915	1.221			
Dr Re Mem.	0.578	0.2436	0.100	1.055	5.627	1	0.018	1.782	1.106	2.873			
Anxiolytics	-1.996	0.3581	-2.698	-1.294	31.066	1	0.000	0.136	0.067	0.274			
Physical Health	0.021	0.0149	-0.009	0.050	1.927	1	0.165	1.021	0.992	1.051			
Soc Supp Gen Neg	-0.098	0.0589	-0.213	0.017	2.772	1	0.096	0.907	0.808	1.018			
Soc Supp Gen Pos	-0.022	0.0645	-0.148	0.105	0.112	1	0.738	0.979	0.862	1.111			
Soc Supp Partner Neg	0.020	0.0546	-0.087	0.127	0.129	1	0.719	1.020	0.916	1.135			
Soc Supp Partner Pos	-0.002	0.0537	-0.107	0.103	0.001	1	0.971	0.998	0.898	1.109			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	4.861	1.6724	1.583	8.138	8.447	1	0.004	129.100	4.869	3423.353	3579.379	2.235	7.939
Mastery	-0.013	0.0380	-0.088	0.061	0.125	1	0.724	0.987	0.916	1.063			
Freq Phys Act Mild	0.038	0.1481	-0.252	0.328	0.066	1	0.797	1.039	0.777	1.389			
Freq Phys Act Mod	-0.001	0.1264	-0.249	0.247	0.000	1	0.995	0.999	0.780	1.280			
Freq Phys Act Vig	0.068	0.1105	-0.149	0.284	0.379	1	0.538	1.070	0.862	1.329			
Alcohol	0.152	0.1135	-0.070	0.375	1.806	1	0.179	1.165	0.932	1.455			
Life Events	0.055	0.0955	-0.132	0.242	0.335	1	0.563	1.057	0.876	1.274			
Smoker	0.037	0.4075	-0.761	0.836	0.008	1	0.927	1.038	0.467	2.307			
Lagged-GAS	-0.046	0.0404	-0.125	0.033	1.311	1	0.252	0.955	0.882	1.033			
Anxiolytics*Lagged-GAS	0.241	0.0829	0.079	0.404	8.475	1	0.004	1.273	1.082	1.498			
(Scale)	4.601												

DSB Interactions; Model B: Autoregressive

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	1.366	0.7384	-0.081	2.813	3.421	1	0.064	3.919	0.922	16.662	2437.141	2.237	35.646
Sex	-0.042	0.1006	-0.239	0.155	0.173	1	0.678	0.959	0.787	1.168			
Age	-0.047	0.0291	-0.104	0.010	2.613	1	0.106	0.954	0.901	1.010			
Education	0.048	0.0166	0.016	0.081	8.503	1	0.004	1.050	1.016	1.084			
Depression	0.023	0.0291	-0.033	0.080	0.653	1	0.419	1.024	0.967	1.084			
Dr Re Mem.	0.058	0.0936	-0.126	0.242	0.384	1	0.536	1.060	0.882	1.273			
Anxiolytics	-0.602	0.1513	-0.899	-0.305	15.825	1	0.000	0.548	0.407	0.737			
Physical Health	0.006	0.0064	-0.007	0.018	0.848	1	0.357	1.006	0.993	1.019			
Soc Supp Gen Neg	0.007	0.0225	-0.037	0.051	0.098	1	0.755	1.007	0.964	1.052			
Soc Supp Gen Pos	-0.033	0.0253	-0.083	0.016	1.727	1	0.189	0.967	0.921	1.016			
Soc Supp Partner Neg	-0.008	0.0215	-0.050	0.034	0.125	1	0.723	0.992	0.952	1.035			
Soc Supp Partner Pos	0.020	0.0192	-0.017	0.058	1.104	1	0.293	1.020	0.983	1.059			
Mastery	-0.006	0.0139	-0.033	0.022	0.158	1	0.691	0.994	0.968	1.022			
Freq Phys Act Mild	0.053	0.0644	-0.073	0.180	0.689	1	0.407	1.055	0.930	1.197			
Freq Phys Act Mod	-0.025	0.0535	-0.130	0.080	0.223	1	0.637	0.975	0.878	1.083			
Freq Phys Act Vig	0.018	0.0463	-0.073	0.109	0.153	1	0.695	1.018	0.930	1.115			
Alcohol	-0.018	0.0422	-0.101	0.065	0.180	1	0.671	0.982	0.904	1.067			
Life Events	0.009	0.0364	-0.062	0.080	0.060	1	0.807	1.009	0.940	1.083			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Smoker	-0.060	0.1769	-0.406	0.287	0.114	1	0.735	0.942	0.666	1.332			
Lagged-DSB	0.760	0.0222	0.716	0.803	1168.872	1	0.000	2.138	2.047	2.233			
Lagged-GAS	-0.056	0.0262	-0.107	-0.004	4.512	1	0.034	0.946	0.899	0.996			
Anxiolytics*Lagged-GAS	0.115	0.0581	0.001	0.229	3.940	1	0.047	1.122	1.001	1.257			
(Scale)	3.220												

DSB Interactions; Model C: Cognitive Change

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Intercept	-0.161	0.7327	-1.597	1.275	0.048	1	0.826	0.851	0.202	3.579	2977.907	1.968	-1.783
Sex	0.015	0.0935	-0.168	0.198	0.025	1	0.875	1.015	0.845	1.219			
Age	0.000	0.0281	-0.055	0.055	0.000	1	0.991	1.000	0.946	1.056			
Education	0.011	0.0160	-0.020	0.043	0.497	1	0.481	1.011	0.980	1.044			
Depression	0.007	0.0262	-0.045	0.058	0.063	1	0.802	1.007	0.956	1.060			
Dr Re Mem.	-0.062	0.0900	-0.238	0.114	0.477	1	0.490	0.940	0.788	1.121			
Anxiolytics	0.042	0.2238	-0.397	0.480	0.034	1	0.853	1.042	0.672	1.616			
Physical Health	0.003	0.0062	-0.009	0.016	0.304	1	0.581	1.003	0.991	1.016			
Soc Supp Gen Neg	0.030	0.0209	-0.011	0.071	2.055	1	0.152	1.030	0.989	1.073			
Soc Supp Gen Pos	-0.014	0.0256	-0.064	0.036	0.305	1	0.581	0.986	0.938	1.037			
Soc Supp Partner Neg	-0.021	0.0214	-0.063	0.021	0.979	1	0.322	0.979	0.939	1.021			
Soc Supp Partner Pos	0.027	0.0188	-0.010	0.064	2.079	1	0.149	1.028	0.990	1.066			
Mastery	0.000	0.0132	-0.026	0.025	0.001	1	0.975	1.000	0.974	1.026			
Freq Phys Act Mild	0.070	0.0613	-0.050	0.190	1.315	1	0.251	1.073	0.951	1.210			
Freq Phys Act Mod	-0.045	0.0551	-0.152	0.063	0.654	1	0.419	0.956	0.859	1.065			
Freq Phys Act Vig	0.026	0.0452	-0.062	0.115	0.335	1	0.563	1.027	0.939	1.122			
Alcohol	-0.055	0.0388	-0.131	0.021	2.024	1	0.155	0.946	0.877	1.021			
Life Events	0.021	0.0350	-0.048	0.089	0.343	1	0.558	1.021	0.953	1.093			

CV	B	SE	95% CI for B		Hypothesis Test			Exp(B)	95% Wald CI for Exp(B)		-2LL	SD of DV	% Variance Explained by Model
			Lower	Upped	Wald Chi-Squared	df	Sig.		Lower	Upper			
Smoker	-0.113	0.1535	-0.414	0.188	0.545	1	0.460	0.893	0.661	1.206			
Lagged-GAS	-0.026	0.0261	-0.077	0.025	1.017	1	0.313	0.974	0.926	1.025			
Anxiolytics*Lagged-GAS	-0.049	0.0654	-0.177	0.080	0.552	1	0.457	0.953	0.838	1.083			
(Scale)	3.943												

Appendix 6.G:

Table of Statistical Power from PATH Dataset

This table and description are reproduced here (with author permission), from a 2018 Grant Proposal (application ID APP1159838; CIA Anstey, K.J.). The table describes PATH power ratios (for future projects) in the context of expected attrition levels.

Table 3. Statistical power for gender specific analyses

Analysis / outcome	Wave 7 (n=400)	Wave 6 (n=575)	Data linkage (n=1000)
Precision of estimates: continuous outcomes	±0.1 SD	±0.085 SD	±0.065 SD
Precision of estimates: proportions of 50%	±5%	±4%	±3%
proportion of 20%	±4%	±3.5%	±2.5%
proportions of 5%	±2%	±2%	±1.5%
Difference in means Equal size groups	0.3 SD	0.25 SD	0.18 SD
Group size ratio of 4:1	0.35 SD	0.3 SD	0.25 SD
Group size ratio of 19:1	0.65 SD	0.55 SD	0.4 SD
Difference in proportions Equal size groups	8-14%	6.5-12%	5-9%
Group size ratio of 4:1	11-17%	9-15%	6.5-11%
Group size ratio of 19:1	25-30%	20-25%	15-20%
Correlation among continuous measures	0.14	0.1	0.09
Hazard ratios: for failure rates of 0.5-0.25	0.3-0.57	0.35-0.63	0.45-0.7

Attrition and Power analysis. Our power analysis (Table 3) demonstrates that our sample size is sufficient to detect a wide range of associations. Power calculations are conservatively based on anticipated sample sizes at follow-ups, gender specific analyses, (48% female), and 93% consent for data linkage. For outcomes involving data linkage, at least 1000 participants for each gender will be available from baseline. At least 400 participants per gender at Wave 7 and at least 575 at Wave 6 will be available.

Appendix 7.A:

Methods for Linear Multilevel Modelling

Data were in SPSS "long" format. A sample of source code follow the description of SPSS options selected.

The following options were selected within the SPPSS LMM dialogue boxes:

1. First Panel:
    a. Subjects: participant identifier
    b. "Repeated": Wave
    c. Repeated Covariance Type: Diagonal (default setting)
2. Second Panel:
    a. Dependent Variable: SDMT, DSB, or StW.
    b. Factors: None
    c. Covariates: See Section 7.2.2 and Table 6.13. All CVs were used unless they were both binary and for subgrouping.
    d. Residual Weight: None
    e. Fixed:
        i. all CVs entered into model as main effects only
        ii. Intercept Included
        iii. Sum of squares: Type III
    f. Random:
        i. Covariance Type: Unstructured
        ii. Model: None unless a significant result was found for fixed effects, in which case GAS would have been entered.
        iii. Intercept Included
        iv. Subject Groupings: Participant identifier added to "combinations"

g. Estimation: Nominal (default)

h. Statistics: All options, except case processing summary and Descriptive statistics; Confidence interval: 95%.

i. EM Means: none

j. Save: Residuals

k. Bootstrap: No.

Example of LLM syntax follows. This is for the fully adjusted model for the *anxiolytics*=yes subgroup.

```
MIXED DSB_allWaves WITH Sex Age Education goldberg_dep mem_doc Rand_phc
SS_w1_gen_neg SS_w1_gen_pos
  SS_w1_ptnr_neg SS_w1_ptnr_pos masteryb phy_act1 phy_act2 phy_act3 audit_class
lifevent smoke_now
  GAS_centred_allWaves
 /CRITERIA=CIN(95) MXITER(100) MXSTEP(10) SCORING(1)
SINGULAR(0.000000000001) HCONVERGE(0,
  ABSOLUTE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0.000001,
ABSOLUTE)
 /FIXED=Sex Age Education goldberg_dep mem_doc Rand_phc SS_w1_gen_neg
SS_w1_gen_pos SS_w1_ptnr_neg
  SS_w1_ptnr_pos masteryb phy_act1 phy_act2 phy_act3 audit_class lifevent
smoke_now
  GAS_centred_allWaves | SSTYPE(3)
 /METHOD=REML
```

```
/PRINT=SOLUTION
/RANDOM=INTERCEPT | SUBJECT(pathid) COVTYPE(UN) SOLUTION
/REPEATED=Index1 | SUBJECT(pathid) COVTYPE(DIAG).
```

Appendix 7.B:

Subgroup Results

Table 1
*Subgroups for Associations of GAS with **SDMT**.*

Subgroups by		Coefficient (95% CI) n
Age (A)	Low	.298 (-.003 to .600) n = 723
	High	.077 (-.171 to.325) n= 1,694
Education (E)	Low	.279 (-.070 to .628) n = 1,061
	High	.031 (-.205 to .267) n = 1,234
Persistently High GAS (PHG)	No	.125 (-.116 to .366) n = 2,080
	Yes	.192 (-.174 to.558) n = 337
Chronic GAS (CG)	No	.089 (-.121 to .298) n = 2,328
	Yes	.262 (-.197 to .721) n = 89
A.PHG^	Low age Not PHG	.317 (-.061 to .696) n = 634
	Low age yes, PHG	.261 (-.243 to .764) n = 89
	High age Not PHG	.018 (-.289 to .325) n = 1,446
	High age Yes PHG	.125 (-.116 to .366) n = 248
A.CG^	Low age Not PHG	.317 (-.061 to .696) n = 589
	Low age PHG	Model did not converge; n = 89
	High age Not PHG	.018 (-.289 to .325) n = 1,446
	High age PHG	.262 (-.197 to .721) n = 248
E.PHG^	Low E Not PHG	.357 (-.082 to .796) n = 899
	Low E yes, PHG	.087 (-.511 to .685) n = 162
	High E Not PHG	-.026 (-.308 to .256) n= 1,075
	High E Yes PHG	.207 (-.265 to .678) n = 159

Subgroups by		Coefficient (95% CI) n
E.CG^	Low E Not CG	.263 (-.114 to .640) n= 1,015
	Low E yes, CG	.650 (-.492 to 1.792) n = 46
	High E Not CG	-.029 (-.278 to .220) n = 1.199
	High E Yes CG	Not positive definite n = 35

^ Sub-subgroups are nominated by reference to the subgroup abbreviations and a full-stop between these abbreviations. E.G., E.PHG is the sub-subgroup formed from the subgroup *Persistently High GAS*, within the subgroup *Education.*

At Table 7.1, the DV was SDMT, and the CVs remaining in significant association within the fully adjusted model (Chapter Six), were: age and education. These were dichotomised about their means to facilitate subgrouping and compounding with each of persistently-high GAS and chronic GAS (as defined at Methods). The compound model for lower age and chronic GAS did not converge. The compound model for higher education and chronic GAS was reported as “The final Hessian matrix is not positive definite . . .”. This outcome may have been a consequence of the small cell size (n = 35). Apart from these two exceptional results, all subgroups examined reported non-significant results.

Table 7.2
*Subgroups for Associations of GAS with **DSB**.*

Subgroups by		Coefficient (95% CI) n
Education (E)	Low	.014 (-.079 to .107) n = 1,061
	High	-.004 (-.075 to .067) n = 1,234
Anxiolytics (An)	No	-.013 (-.072 to .045) n = 2,289
	Yes	**.215 (.001 to .429)** n = 126
Dr Re Memory (Dr)	No	Hessian matrix not positive definite, *n* = 2,351
	Yes	Hessian matrix not positive definite**,** *n* = 66
Persistently High GAS (PHG)	No	.033 (-.036 to .102) n = 2,080
	Yes	-.048 (-.159 to .063) n = 337
Chronic GAS (CG)	No	.016 (-.044 to .077) n = 2,328
	Yes	-.071 (-.267 to .126) n = 89
E.PHG^	Low E Not PHG	.026 (-.090 to .142) n = 899
	Low E PHG	.022 (-.150 to .194) n = 81
	High E NOT PHG	.031 (-.055 to .117) n = 1,075
	High E PHG	-.086 (-.299 to .058) n = 159
E.CG^	Low E Not CG	.027 (-.072 to .126) n = 1,015
	Low E CG	Not positive definite; n = 46
	High E Not CG	.011 (-.065 to .087) n = 1,199
	High E CG	Not positive definite; n = 35

Subgroups by		Coefficient (95% CI) n
An.PHG^	No An Not PHG	.025 (-.046 to .096) n=2,008
	An Not PHG	Hessian matrix not positive definite; n = 71
	No AN PHG	-.087 (-.203 to .029) n = 281
	An PHG	Hessian matrix not positive definite; n = 55
An.CG^	No An Not CG	.004 (-.058 to .066) n = 2,226
	An Not CG	.146 (-.098 to .390) n = 101
	No AN CG	Not positive definite; n = 63
	An CG	Not positive definite; n = 25

^ Sub-subgroups are nominated by reference to the subgroup abbreviations and a full-stop between these abbreviations. E.G., E.PHG is the sub-subgroup formed from the subgroup *Persistently High GAS*, within the subgroup *Education.*

At Table 7.2, the DV was DSB, and the CVs remaining in significant association within the fully adjusted model (Chapter Six), were: education, and anxiolytics (consumed at baseline). Again, education was dichotomised about its mean to facilitate compound subgrouping with each of persistently high GAS and chronic GAS. The compound models for: lower education and chronic GAS; higher education and chronic GAS; anxiolytics but not persistently high GAS; anxiolytics and persistently high GAS, were all invalid, due either to a "not positive definite" report or because the model did not converge. In each case the cell size was small. Other compound subgroups were non-significant.

The subgrouping on *anxiolytics* was repeated for the alternative temporal treatments *time-lagged* and *autoregressive*. Results were non-significant.

More extensive investigation of the *anxiolytics* subgroups for the *standard* temporal treatment, appears at Section 7.3.2.

The "yes" subgroup for *Dr Re Memory*, was reported for a subgroup of 66 participants and there was a moderately large increase in expected DSB score, with significance of p = .022.

Table 7.3
*Results for Subgroups for Association of GAS with **StW***

Subgroups by		**StW**
Education (E)	Low	-.090 (-.245 to .064) n=1,061
	High	.024 (-.049 to .100) n = 1,234
Physical Health (PH)	Low	-.112 (-.234 to .010) n = 826
	High	.060 (-.026 to .146) n = 1588
Harmful consumption of Alcohol (HA)	No	.441 (-.165 to 1.047) n= 2,269
	Yes	.007 (-.068 to .082) n= 143
Persistently High GAS (PHG)	No	-.018 (-.100 to .064) n = 2,080
	Yes	.002 (-.137 to .141) n = 1,348
Chronic GAS (CG)	No	.003 (-.071 to .078) n = 2,328
	Yes	-.131 (-.355 to .093) n = 89

At Table 7.3, the DV was StW. The subgrouping CVs from Table 6.1 were *education*, *physical health*, and a harmful level of consumption of *alcohol* at baseline. There was no significant result. Compound subgroups were not investigated.

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