The relationship between traumatic life events, high cortisol, and Alzheimer's disease

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ABSTRACT

Previous research has shown that the negative effects of stress may be a contributing factor to the development of Alzheimer's disease (AD). This pilot study investigated whether there is a relationship between the experience of stressful life events, levels of salivary cortisol, and the risk of developing AD in a sample of older adults from the Western Cape. Participants, all over the age of 55 years, included 11 possible or probable AD patients and 11 healthy controls. They completed demographic and life events questionnaires which provided life history information. Cognitive functioning was measured using a battery of neuropsychological tests. Furthermore, participants' salivary cortisol levels were measured to provide physiological markers of their amount of stress. Between-group comparisons suggest that there is a link between stressful life events, cortisol levels, and the risk of developing AD. Correlational and regression analyses identified age, low levels of education, and poor resilience as possible risk factors for the development of AD (p = 0.00048). In order to increase the possibility of obtaining more statistically significant and generalizable results, future research should aim to obtain larger sample sizes and those that are more representative of the broader South African population.

Keywords: Aging; stress; cognition; cortisol; dementia; Alzheimer's disease.

INTRODUCTION

In humans, the experience of stress is associated with adverse effects on both physical and mental health. The effects of excessive stress on cognition have, in particular, recently gathered strong attention from researchers. The fields of psychology and medicine have provided numerous findings supporting the notion that stress has a negative impact on human cognitive performance, and that this negative impact is aggravated in advanced old age (Stawski, Martin, Sliwinski, & Smyth, 2006).

Furthermore, research has shown that the negative effects of stress may be a contributing factor to the development of Alzheimer's disease (AD). Although much of the AD literature focuses broadly on the aetiology of and risk factors for the disease, the currently proposed research focuses exclusively on excessive stress as a risk factor for age-related cognitive decline and subsequent AD.

Stress and Cognition

It is problematic to provide a concise definition of stress, because within the scientific literature there are varying explanations of this term. Stress can be considered as a stimulus, a reaction to a stimulus, or the physiological effects of that reaction (Kemeny, 2003).

Within one particularly frequently cited framework, the neurobiological stress response occurs as a result of stressors, which are stressful life experiences that threaten a primary goal. Broadly speaking, stressors are categorized as either being physiological (i.e., presenting a threat to one's physical integrity) or psychological (i.e., presenting a threat to one's mental well-being) in nature (Dickerson & Kemeny, 2004; Stawski et al., 2006). Distinctions are also drawn between acute and chronic stressors, both of which may lead to a range of behavioural and physiological impairments. Chronic stressors are longer-lasting in duration, whilst the effect of acute stressors usually subsides shortly after the stressor itself has ceased to exist or is no longer present in the individual's life (Baum, Cohen, & Hall, 1993).

When humans are exposed to stressors of any kind, the body reacts by activating a sequence of events. First, the hypothalamic-pituitary-adrenal axis (HPA) is activated when the hypothalamus secretes corticotrophin releasing hormone (CRH). This secretion stimulates the anterior pituitary to produce adrenocorticotropin hormone (ACTH), which causes the adrenal

cortex to release glucocorticoids (GCs), known as cortisol in humans, into the bloodstream (Dickerson & Kemeny, 2004). GCs aid the body in preparation for survival during stressful situations; for instance, they provide support for heart rate, blood pressure and muscle tone. However, if exceptionally high or low amounts of GCs are released, cognitive and neural processes may be impaired (McDonald, 2002).

Findings from animal studies indicate that prolonged stress is associated with elevated glucocorticoid levels and consequent enduring effects on certain brain circuits and systems (McEwen & Sapolsky, 1995). The hippocampus is a brain region that serves a critical role in memory formation and is responsible for new learning and declarative memory, especially episodic memory processes. This is one of the regions primarily affected by the acute release of excess glucocorticoids and chronic exposure to those hormones (Backman, Jones, Berger, Laukka, & Small, 2005; Bremner, 2006; McDonald, 2002). Damage to the hippocampus results in negative feedback to the HPA axis, which leads to the release of even more glucocorticoids. This release is in turn associated with further damage to the hippocampus, and so the destructive cycle continues.

These cortisol elevations and consequent changes in hippocampal structure resulting from stress are linked with deficits in learning and memory function. Previous research, focusing mainly on rats, indicates that a mild increase in GC levels may enhance memory, but that extreme deficiencies or elevations disrupt memory (McEwen & Sapolsky, 1995). Similarly, Abercrombie, Kalin, Thurow, Rosenkranz, and Davidson (2003) reported findings of enhanced human memory following mild elevations in GCs, but impaired memory as a result of high levels of GCs.

Aging, Stress and Cognition

Previous research has also shown that there are age differences with regards to exposure and reactions to stress. For instance, Birditt, Fingerman, and Almeida (2005) found that physically and cognitively healthy older people reported fewer interpersonal tensions, and experienced fewer stressful events than younger controls. Additionally, when they did encounter stressors, they were less reactive in their responses to it than were younger people. In contrast, Krause (2005) reported that older people are more likely than young people to experience ongoing and

chronic stressors, particularly relating to financial and medical concerns. The experience of these stressors, he argued, leads to negative side-effects, including detrimental impacts on cognition.

Other studies, from both animal and human literature, have confirmed that stress is associated with the acceleration of age-related cognitive decline. For instance, Bodnoff et al. (1994) found that middle-aged rats were more susceptible to stress and corticosterone-induced impairments in spatial learning than were young adult rats. Their findings suggest that chronic exposure to glucocorticoids affects cognitive function and that this effect is age-related. Similarly, in humans, McDonald (2002) suggested that good versus poor cognitive aging may be the result of a combination of factors, one of which is exposure to chronic stressors and consequent elevated glucocorticoid levels. Confirming this prediction, Lupien et al. (1994) found that elderly participants with chronic glucocorticoid elevations showed significantly impaired declarative memory functioning. In community-based studies, Neupert, Almeida, Mroczek, and Spiro III (2006) found an association between daily stressors and everyday memory failures, even after controlling for the effects of neuroticism, life event stressors and physical health. They also discovered that life event stressors were positively correlated with everyday memory failures (see also Stawski et al., 2006). Furthermore, Caswell et al. (2003) studied older-adult caregivers of dementia patients and found a negative association between chronic stress and information processing, episodic memory, and general cognitive function in those individuals.

Furthermore, laboratory-based studies have shown that, in elderly persons, acute stressors also have negative effects on cognition. For instance, Lupien et al. (1997) found that acute psychosocial stress manipulations, such as public speaking tasks, reversibly impaired memory performance in elderly adults (see also Luine, Villegas, Martinez, & McEwen, 1994). Furthermore, Lupien et al. (1998) detected a direct and significant relationship between elevated cortisol levels, hippocampal shrinkage, and hippocampal-based memory deficits in older adults (Lupien et al., 1998).

In summary, chronological age is not a sufficient predictor of cognitive impairments, in that there are discrepancies in the occurrence of age-related cognitive decline amongst individuals of the same age. Stress is one of the moderating factors in this relationship, as is the occurrence of age-related disease, such as dementia of the Alzheimer's type.

Neuropsychology of Alzheimer's disease

Alzheimer's disease (AD) is a progressive, irreversible dementia in which the pathological process frequently begins in the hippocampal region. AD is the leading cause of dementia and is one of the ten foremost causes of death in developed countries (Fitzpatrick, Kuller, Ives, Lopez, Jagust, & Breitner, 2004). Gradual onset, continuing functional decline and personality changes epitomize the path followed by this disease (Braak & Braak, 1995).

With regard to neuropsychological functioning, AD is characterized by episodic memory deficits (particularly on free recall tasks) and learning impairment in the early stage, that gradually develop into a global cognitive impairment in late stages (Bemelmans et al., 2007; Mickes et al., 2007). This progression is consistent with the neuropathological characteristics of AD (as demonstrated by the histology of brain tissue, obtained from an autopsy). These include extreme formations of amyloid plaques and neurofibrillary tangles, which appear initially and primarily in the hippocampal areas, as well as eventual atrophy of the frontal, parietal and temporal lobes.

Criteria for the clinical diagnosis of AD generally include progressive memory impairment, and one (or more) of the following cognitive disturbances: aphasia (language problems), apraxia (decline in ability to perform motor activities despite complete motor function), agnosia (inability to identify objects despite operational sensory function), and disturbance in executive functioning (i.e., difficulties with planning, organizing, sequencing, problem-solving, and abstract reasoning), and perceptual difficulties. These memory impairments and other cognitive disturbances produce major difficulties in social or occupational functioning, and signify a considerable decline from a previous level of functioning. Neurological abnormalities associated with AD include increased muscle tone and a shuffling gait. Affective and behavioural symptoms such as depression, insomnia, incontinence, delusions, hallucinations, weight loss, sex problems, and substantial verbal, emotional and physical outbursts are also associated with AD (APA, 2000; McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984).

There are many theories regarding the aetiology of Alzheimer's disease, although no consensus on this has yet been reached. Some researchers suggest the cause of Alzheimer's disease is the result of a single factor, such as a genetic predisposition (Farrer et al., 1997). Others propose that it arises due to a combination of factors. McDonald's (2002) summary of the

literature suggests that AD is the result of various co-factors, such as genes, neurotransmitter changes, vascular abnormalities, circadian rhythms, head trauma, seizures and stress hormones. Similarly, Patterson, Feightner, Garcia, and MacKnight (2007) conducted a systematic evidence review that identified systolic hypertension, stroke, sex hormones, depression, diet, physical and mental inactivity, occupation, education, and head trauma, as risk factors for dementia (including AD). Other studies have identified even more risk factors for AD, including smoking, oestrogen levels, and high serum cholesterol (Lezak, Howieson, & Loring, 2004). Although age is indisputably the greatest risk factor for AD, the experience of lifetime stress may also be responsible for the development of the disorder.

Stress and Alzheimer's disease

There may be some dispute regarding the notion that stress (as measured by high cortisol levels) is a risk factor for AD. Many researchers have, however, built on the link, established in other studies (e.g., McDonald, 2002), between elevated glucocorticoid levels and poor cognitive aging to focus on the association between those elevations and the development of AD. For instance, Csernansky et al. (2006) assessed, on an annual basis for up to 4 years, 33 subjects with very mild Alzheimer-type dementia and 21 subjects without dementia. Findings illustrated that a rise in plasma cortisol levels was related to increased disease progression in subjects with Alzheimer's disease. In concordance with these findings, Bemelmans et al. (2007) showed that plasma cortisol was negatively correlated with concerted retrieval efforts during memory tasks and with the progression of Alzheimer's disease. Moreover, Wilson et al. (2003) reported that, in elderly people who underwent a series of annual clinical evaluations, those who were prone to experience psychological distress were also more likely to develop AD than were age-equivalent, non-stressed individuals.

Summary

Analysis of the literature indicates that there is limited consensus regarding the aetiology of, and risk factors for, Alzheimer's disease. For the purposes of this research, the literature review focused predominantly on the risk factor of stress and its relationship to Alzheimer's disease. This is a topic that has received a great deal of attention from researchers who have found positive correlations between stress (as measured by cortisol levels) and impaired memory. It is

evident, though, that further research, specifically a combination of longitudinal and cross-sectional studies, needs to be conducted in order to develop a more conclusive and accurate understanding of the role that stress plays in the development of AD.

No South African research currently exists which examines the relationship between traumatic life events, high cortisol and Alzheimer's disease. Fewer than a hundred studies of the prevalence of dementia have been conducted worldwide, and only a few of those have been carried out in Africa (Ineichen, 2000). Nigeria is the only African country which has reported a considerable amount of research regarding the prevalence of dementia. For instance, a set of studies has compared the prevalence of AD amongst two elderly, community-dwelling populations in Ibadan in Nigeria and Indianapolis in the United States. Results indicate consistently low rates for dementia in Ibadan as compared to Indianapolis, especially for Alzheimer's disease (Hendrie et al., 2008).

Apart from the study described above, the prevalence of Alzheimer's disease in indigenous African populations is unknown. In fact, for many years there was even the question of whether it existed amongst those populations (Ferreira, 1999), although clinical anecdotal evidence suggests it does, and in similar rates to those in developed countries. It is only recently that systematic hospital surveys or community-based studies of AD in Africa have been initiated**.** There is a need for cross-cultural studies of prevalence rates of dementia (and of AD, in particular) in order to identify, for instance, whether there are unique, culture-based risk factors or inhibitors of the disease in African populations.

Specific aims and hypotheses

This research forms part of a much larger prospective longitudinal study that is in its beginning stages and that aims to describe the genetic, environmental, and psychosocial risk factors for Alzheimer's disease in a sample of older South African adults. The study also aims to determine whether older adults diagnosed with AD have higher salivary cortisol levels than healthy controls, and whether they have experienced multiple traumatic events which could contribute to a higher level of cortisol. This pilot study focused on a limited set of environmental and psychosocial risk factors for AD, with particular emphasis on exposure to traumatic life events. In addition, measures of salivary cortisol levels were taken from, and a neuropsychological test battery administered to, all participants.

The overarching hypothesis for this research is that individuals at greatest risk for age-related cognitive decline (and possible AD) will be those with the largest amounts of exposure to traumatic life events and concomitant high salivary cortisol levels. More specifically, individual hypotheses can be stated as follows:

1. Patients will have more experiences of trauma than controls
2. Patients will have higher cortisol levels than controls
3. Patients will have lower memory scores than controls
4. Patients will have both more experiences of trauma and higher cortisol levels and than controls
5. There are certain risk factor variables for the development of AD

METHODS

Research Design and Setting

This study is an example of relational research, wherein two or more variables were measured and related to one another. This type of study often takes place in the exploratory phase of a large research program (Rosenthal & Rosnow, 2008, p. 22), which is the case here. All study procedures were conducted in the Neurology Department at Groote Schuur Hospital, at the Rehoboth Age Exchange, or at the participant's residence.

Participants

AD patients (n = 11) were recruited from the Rehoboth Age Exchange (a non-governmental agency nursing home located near Cape Town) and from Groote Schuur Hospital's Memory Clinic. All of these patients had either been previously diagnosed as possible or probable AD in terms of NINCDS/ADRDA criteria (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984) or had been directly referred to the study by the GSH Memory Clinic. Control participants (n = 11) were healthy community-dwelling, self-caring volunteers. Health information was obtained from all the participants which indicated that participants did not differ substantially with regards to health status (see Table 1).

All participants in the study were over the age of 55 years. This age limit was set because 55 is the minimum approximate age of when dementia of the Alzheimer's type typically begins to develop (Ott et al., 1995). There were, however, statistically significant between-group differences in terms of age (patients were older than controls), $t(20) = -3.86$, $p = 0.00098$. There were also statistically significant between-group differences in terms of level of education (patients were less well-educated than controls), $t(20) = -4.32$, $p = 0.00033$.

Other inclusion criteria included literacy and a good command of either English or Afrikaans. Individuals in the advanced stages of dementia were excluded as they would most likely have been incapable of answering test questions and completing self-report questionnaires. Participants who fell below the cut-off score for depression were also excluded. Ethical approval for all study procedures was obtained from the Research Ethics Committee of the University of Cape Town, Faculty of Health Sciences (Approval #: 270/2007).

Table 1

Demographic Data for Controls and Patients

	Control *n* = 11	Patient *n* = 11
Age	66.27 (7.71)	78.45 (7.09)
Race (Coloured:White)	11:0	10:1
Handedness (L:R)	0:11	0:11
Sex (M:F)	2:9	2:9
Household income		
= > R10000	2	0
= > R5500	5	2
= > R2500	2	2
= > R1000	2	2
= > R500	0	5
= < R500	0	0
Education		
Level (years)	8.00 (1.81)	10.91 (1.14)
Quality (High:Low)	11:0	6:5
Health		
No health problems	8	1
Single health problems	1	2
Multiple health problems	10	8

Note. For Age and Education Level, means are presented with standard deviations in parentheses

Materials and Apparatus

As noted earlier, this study forms part of a larger project which employs numerous instruments to measure physiological and biochemical markers of stress, lifetime exposure to traumatic events, current stress levels, and cognitive, behavioural, affective, interpersonal, and adaptive functioning. Only a subset of those instruments was used in the current study, and only those are described here. These particular instruments were chosen because they have been used with some success in similar previous studies.

Sociodemographic and Affective, Behavioural, and Adaptive Functioning Questionnaires

The *Deterioration Cognitive Observee (DECO*; Ritchie & Fuhrer, 1996) was used as a pre-screening measure to determine the presence of dementia in participants. It is 19-item Likert-type scale that measures aspects of behaviour as well as cognition (activity level, semantic and visual memory, memory for places, events and procedures, visuospatial performance and new skill learning). As is custom, it was completed by an individual, nominated by the participant, who had had at least monthly contact with the participant over a period of 3 years. The English version of DECO is presented in Appendix A; as can be seen, low scores indicate that the participants' cognitive and behavioural performance has declined over the past year, whereas high scores indicate the absence of such decline. Psychometric studies of the DECO have shown that it has good face validity as well as high test-retest and inter-rater reliability and does not show bias with regards to education or social class (Ritchie & Fuhrer, 1996). The DECO has previously been used in a South African research studies (Heckman et al., 2004; Lenger, de Viliers, & Louw, 1996).

The *Geriatric Depression Scale (GDS;* Brink et al., 1982) was also used as a pre-screening measure to detect the presence of depression. Individuals suffering from depression, as indicated by this scale using a cut-off score of 6-7/15, would have been excluded from participation in the study. The GDS is a self-report 30-item scale that was developed as a basic screening measure for depression in older adults. For this study, participants were required to answer a shortened 15-item version of the scale (see Appendix B). For this 15-item scale a cut-off score of 6 – 7 was used in this study. A higher score indicates a greater number of symptoms of depression. Both the original and shortened versions of the GDS display high internal

consistency, test-retest reliability, and validity (Yesavage et al., 1983). The 15-item version has been found to be a suitable instrument for diagnosing depression in elderly populations (Craen, Heeren, & Gussekloo, 2003). This measure has previously been used in a South African study examining depression and social support in elderly people (Rodriguez, Brathwaite, & Dorsey, 2002).

Participants were required to complete a *demographic questionnaire*, specially created for this study, which asked for information on their age, sex, race, home language, education, and health (see Appendix C).

The *Bristol Activities of Daily Living Scale (BADLS;* Bucks, Ashworth, Wilcock, & Siegfried, 1996) provided a short assessment of the functional ability of participants, focusing on tasks such as handling finances, dressing, and eating. This 20-item scale was completed by the same informant who completed the DECO. The BADLS has high test-retest reliability and validity (Lezak et al., 2004). The maximum obtainable score for this scale is 60, which denotes the participant's total dependence on others. This measure has previously been administered to an elderly South African population in a study investigating the reliability and validity of a Xhosa version of a health-related quality of life measure (Jelsma, Mkoka, Amosun, & Nieuwveldt, 2004).

The *Connor-Davidson Resilience Scale (CD-RISC;* Connor & Davidson, 2003) is a 25-item self-rating assessment scale of resilience. Each item is rated on a 5-point scale (0-4), where higher ratings indicate greater resilience. Participants were required to think about how they felt over the last month when answering each statement. The developers note that the scale has been tested in both the general population and in clinical samples, where it has displayed reliable psychometric properties, including good internal consistency and test-retest reliability. They also note that the scale demonstrates validity when compared to other measures of stress and endurance. This instrument was used in South African research focusing on perceived social support in youth, and has been translated into Afrikaans (Bruwer, Emsley, Kidd, Lochner, & Seedat, 2008).

The *List of Threatening Life Events Questionnaire* (*LTE-Q*; Brugha & Cragg, 1990) consists of 11 statements; participants are required to indicate whether or not they have experienced any of the events described by those statements, and if so, whether the event occurred within the past 6 months (see Appendix D). The developers have shown that the LTE-Q

has high test-retest reliability and good agreement with informant information. A longer version of the LTE-Q has been used in South African research focusing on post-traumatic stress disorder and adolescents (Seedat, Nyamai, Njenga, Vythilingum, & Stein, 2004).

The *Perceived Stress Scale (PSS;* Cohen, Kamark, Mermelstein, 1983) is a 14-item scale that measures the degree to which particular events in one's life are considered stressful (see Appendix E). The developers have reported that the PSS shows adequate reliability and validity. This instrument has been used in South African research investigating depressive symptoms and perceived stress in South African adults (Hamad**,** Fernald**,** Karlan**,** & Zinman, 2008).

The *Neo-Five Factor Inventory (NEO-FFI;* McCrae & Costa, 1989) is a 60-item instrument measuring various aspects of personality. As the only personality dimension of interest in this study was neuroticism, only the six questions relating to that construct were included in the current set of questionnaires. Those questions asked the participant to rate, on a 5-point scale, his/her own tendencies toward anxiety, hostility, depression, self-consciousness, impulsiveness, and vulnerability to stress. A higher positive score indicates a greater tendency towards neuroticism. The NEO-FFI has well-established psychometric properties (Egan, Deary, & Austin, 2000), and has been used in South African research investigating personality traits of university students (Zhang, 2002).

Neuropsychological Test Battery

The Placing Test (TPT; Anderson, De Jager, & Iverson, 2006) was developed for use as a tool for the early detection of AD. It is a measure of implicit visual learning and memory that specifically assesses whether the participant can form associations between commonly-seen objects (for example, in this study, shoes or faces) and their location on the page of a stimulus booklet. Administration time is 5 minutes and the test is scored by the number of correct associations, with a maximum score of 10. The fact that this is a non-verbal test renders it more suitable for individuals whose first language is not English or who have a limited educational background. The TPT has never before been administered to a South African population in a published research study.

The *Trail Making Test-Revised* (*TMT***)** is an easily administered test of motor speed, visuomotor tracking, visual attention, and switching ability. (Lezak et al., 2004). The first part of the test (TMT-A) requires the participant to connect circled numbers in numerical order

ascending from 1 to 25. The second part of the test (TMT-B) requires the participant to connect numbers and letters in alternating order (i.e., 1-A-2-B-3-C, etc.). Time taken to complete the task serves as the score for that test. For this study, if the participant did not complete either TMT-A or TMT-B within 5 minutes, or if he/she was simply unable to meet the demands of the test, the researcher assigned a score of 300 seconds.

The TMT is sensitive to cognitive decline consistent with dementia (Kowalczyk, McDonald, Cranney, & McMahon, 2001), and is often used as measure of how much an older adult might struggle with complex daily activities, such as driving (Stutts, Stewart, & Martell, 1998). This test has fairly good psychometric properties (Lezak et al., 2004) and is frequently used in clinical settings in South Africa.

The *Executive Clock Drawing Task (CLOX;* Royall, Cordes, & Polk, 1998) assesses executive and visuospatial impairment in older adults. The first part of this task requires the patient to draw a clock with no help or cues from the examiner other than the instructions to "Draw me a clock that says 1:45pm. Set the hands and numbers on the face so that a child could read them." The second part of this task requires the patient to copy a clock drawn by the examiner. The CLOX has good internal consistency and high inter-rater reliability (Strauss, Sherman, & Spreen, 2006). This test has been used in studies focusing on the early detection of Alzheimer's disease (e.g., Toepper, Beblo, Thomas, & Driessen, 2008), and is used for this purpose at the GSH Memory Clinic.

The *Cambridge Cognitive Examination for Mental Disorders of the Elderly Examination-Revised* (*CAMCOG-R;* Huppert, Brayne, Gill, Paykel, & Beardsall, 1995) is a neuropsychological test battery that is part of the Cambridge Mental Disorders of the Elderly Examination-Revised (CAMDEX-R), and was devised to measure cognitive functioning for the early diagnosis and monitoring of dementia in the elderly (Leeds, Meara, Woods, & Hobson, 2001). The CAMCOG-R consists of 67 items divided into eight cognitive domains (Orientation, Language, Memory, Attention, Praxis, Calculation, Abstract Thinking, and Perception). The maximum possible score is 105, and it requires 25 minutes for administration. The CAMCOG-R test has been demonstrated to have high test retest and inter-rater reliability (O'Connor, Pollitt, Brook, & Reiss, 1989). This measure has been found to be sensitive to the detection of dementia (Hobson & Meara, 1999). Several CAMCOG-R items were altered for use in this study,

primarily because the original items contained elements not suitable for use with South African participants (for details on specific item changes, see Nortje, 2007).

Included in the CAMCOG-R are the 19 questions that comprise the *Mini-Mental State Examination* (*MMSE*; Folstein, Folstein & McHugh, 1975). The MMSE is the most commonly used and studied screening test for dementia. Despite controversies about its specificity and sensitivity, the MMSE has good test-retest and inter-rater reliability and high construct validity (Strauss, Sherman, & Spreen, 2006). This measure has been used in a South African study investigating early-onset Alzheimer's disease (Heckman et al., 2004), and is used regularly in South African clinical practice.

Physiological Measures

Salivettes were used to collect saliva samples. These devices are composed of cylindrical cotton sponges in a plastic holder fitted inside a centrifuge tube. Each patient was given two salivettes as well as a detailed instruction sheet explaining how to collect samples (see Appendix F). Salivettes are effective when obtaining cortisol measurements because they can be stored in a freezer without damaging the sample. They are also less invasive than blood samples, thus eliminating any potential collection stress for the patient (Ice, Katz-Stein, Himes, & Kane, 2004; Li et al., 2006).

Procedure

Participants were contacted either telephonically or via the institution or organization to which they were affiliated. Most spoke English as their first language and all were happy to be tested in English.

After the initial contact, patients were screened telephonically to determine if they met the study's inclusion criteria. Those who were eligible were required to give their verbal consent for participation in the study. In the case of AD patients, consent was also obtained from family members or legal guardians.

During the same telephone call, the researcher arranged day and time for the participant to attend a test session at Groote Schuur Hospital. The participant's caregiver/spouse/guardian/family member/informant was also asked to attend the session. Participants were reimbursed for travelling expenses.

The day before the test session, the researcher made a reminder telephone call to the participant. When the participant arrived at GSH, he or she was met by the researcher and escorted to the testing venue in the Neurology Department

The participant was required to sign an informed consent document (see Appendix G) before commencing testing procedures. The first part of the test session involved the participant and his/her informant completing the questionnaires described above.[1] If the participant was not able to complete the self-report questionnaires by him/herself, the researcher assisted by reading the questions and filling in the participant's responses. After completion of the questionnaires, the neuropsychological test battery was administered. The whole test session lasted between 1.25 and 2 hours.

After completing the tests, the researcher provided the participant and/or his or her caregiver/informant/relative with two sets of salivettes and the appropriate instructions. For those participants with memory problems, the instructions and salivettes were given to the caregiver/informant who then assisted the participant in obtaining the saliva sample. Participants were required to collect their saliva sample at 09:00, two mornings in a row. Once both saliva samples had been taken, the researcher collected the salivettes from the patient. The salivettes were then stored in a freezer at -20° C at GSH before being taken for analysis at the hospital's Chemical Pathology Laboratory.

Data Analysis

All the data was sorted, checked for missing data, and cleaned. Descriptive and statistical analyses were performed using Microsoft Office Excel, Statistica 8, or SPSS 16.0. Descriptive statistical analysis was performed on the socio-demographic data. Measures of central tendency (mean, median and mode) were calculated for the variables. Any missing data was replaced by the measure that most closely approximated the central score. Boxplots were constructed for all the continuous independent variables in order to detect outliers that may have influenced the measures of central tendency. Following this, inferential statistics such as regression and correlation were used. Descriptive statistics and correlation matrices were performed for initial analysis of the data. Between-group comparisons were performed for cortisol, trauma, & memory score, using *t*-tests where possible, or non-parametric analyses such as Mann-Whitney

[1]If the informant was not present, the questionnaires were completed telephonically or electronically.

U-test. Between-group comparisons were also performed for domains of functioning and neuropsychological performance. As the research is based on previous theoretical findings, a hierarchical multiple regression analysis was used. The results of this were analysed and the significant predictor variables identified. The significant predictor variables were those with significant *F*-values and those that explained most strongly for the variance in the model as shown by their high R^2 values. These predictors formed the final regression model and diagnostic tests were run on the final model. Finally, analysis of the residuals was performed to detect the presence of outliers.

RESULTS

Lifetime Trauma and Current Cortisol Levels

Table 2 shows data from the LTE-Q, on which participants reported their experiences of trauma over their lifetime. These self-reports seem to suggest that patients had experienced more traumatic life events than had controls. A chi-square analysis showed that this difference was not statistically significant, however, $\chi^2(2, N = 22) = 4.71$, $p = .095$.

Table 2
Lifetime Experiences of Trauma for Controls and Patients

Occurrence of trauma	Controls *n* = 11	Patients *n* =11
No trauma	63.64%	18.18%
Single trauma	9.09%	18.18%
Multiple trauma	27.27%	63.64%

Although patients had higher average levels of cortisol ($M = .84$, $SD = .33$) than did the controls ($M = .65$, $SD = .28$), there was no statistically significant between-group difference in this regard, $t(20) = -1.46$, $p = 0.160$. This lack of statistical significance is likely due to the small sample size, given that the achieved power in this case was only 0.29. The value of the biserial correlation coefficient for the association between self-reported trauma history (dichotomized

into no trauma/single trauma versus multiple trauma) and current cortisol levels was not statistically significant, r_b = -0.12.

Current Affective, Behavioural, and Adaptive Functioning

Table 3

Between-Group Comparisons of Domains of Current Affective, Behavioural, and Adaptive Functioning for Controls and Patients

	Control n = 11	Patient n = 11	Test Statistic	*df*	*p*	Cohen's *d*
BADLS	.82 (2.09)	11.36 (8.38)	5.00	20	0.00003***	1.73
DECO	36.91 (1.70)	21.00 (7.04)	4.00	20	0.00005***	-3.11
CD-RISC	83.91 (11.82)	66.45 (13.07)	17.50	20	0.03998*	-1.40
GDS	1.36 (1.75)	3.45 (2.38)	29.00	20	0.33165	----
PSS	18.91 (10.77)	20.55 (8.81)	52.00	20	0.606318	0.17
NEO-FFI	-3.55 (5.37)	-1.27 (4.05)	45.00	20	0.00318**	1.01

Note. Means are presented with standard deviations in parentheses. Test statistic for Mann-Whitney U-test. *p < .05; **p < .01; ***p < .001

Table 3 shows the results of between-group comparisons for the measures of affective, behavioural, and adaptive functioning used in this study. Data for the dependent variables were not normally distributed; therefore a Mann-Whitney U-test was used to assess the between-group differences. Results showed significant differences between patients and controls in several different domains of functioning. On the DECO, the mean score for patients was significantly lower than that for controls (lower scores on this instrument indicate a worse level of general cognitive functioning, as reported by the informants). On the BADLS, the mean score for patients was significantly higher than that for controls (high scores on this instrument indicate a lower level of ability to complete activities of daily living). For the CD-RISC, the mean score for controls was significantly higher than that for patients (higher scores represent a greater level of resilience). Mean scores on the GDS measure were slightly higher for patients than controls

(higher scores indicate more symptoms of depression); however, the difference was not statistically significant, and scores for both groups fell below the cut-off score (7/15). On the PSS, mean scores for patients were higher than for controls (higher scores indicate greater perceived stress), but the difference was not statistically significant. For the NEO-FFI, the mean score for patients was significantly lower than that for controls (a higher positive score indicates a greater tendency towards neuroticism), showing that controls reported greater levels of neuroticism than patients.

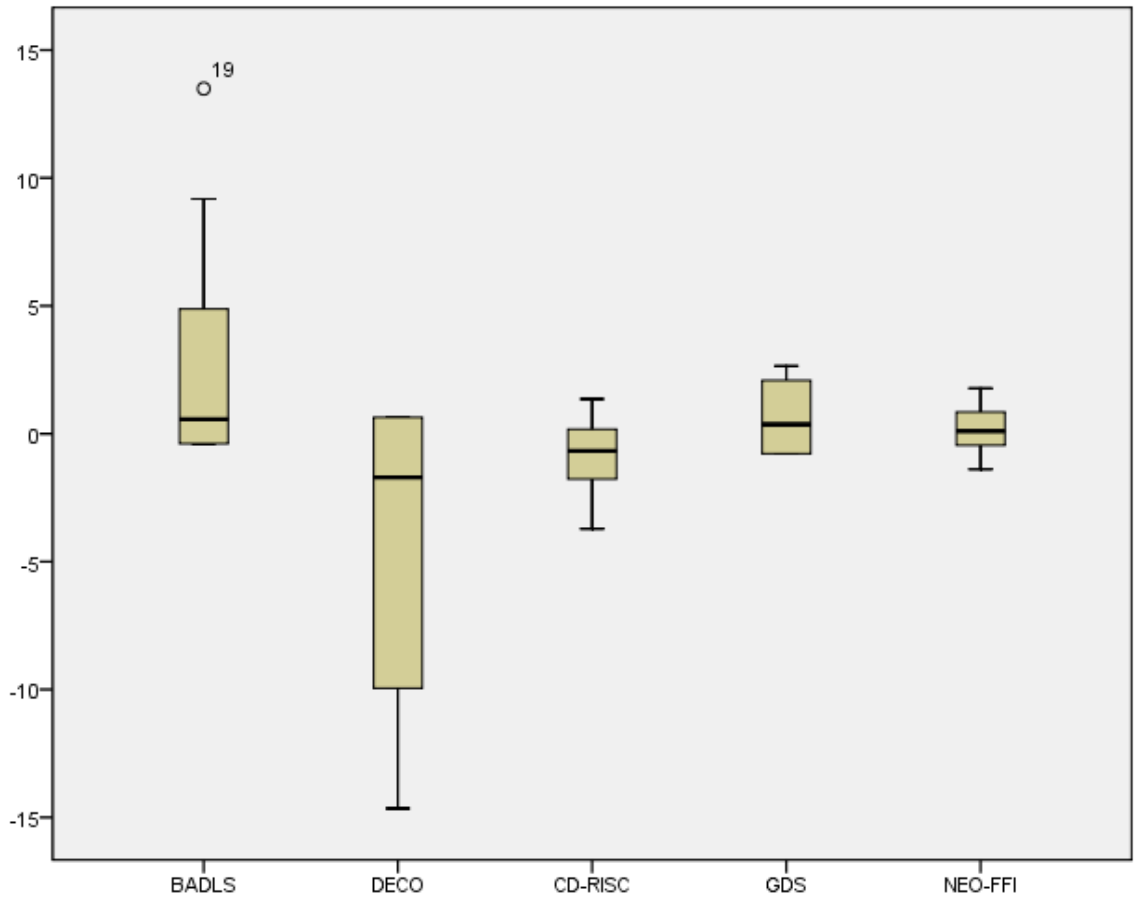

Figure 1. Boxplots for distributions of z-scores on the measures of functioning used in the current study.

Figure 1 shows that the data for domains of functioning are well distributed. Two of the most obvious differences are seen for the BADLS and DECO measure, where scores are well above, and well below, the mean respectively.

Neuropsychological Test Performance

Table 4 shows the results of between-group comparisons for the measures of neuropsychological functioning used in the current study. Data for the dependent variables were not all normally distributed, and in some cases Levene's test for homogeneity of variance was statistically significant; therefore, I used a non-parametric test, the Kolmogorov-Smirnov test for two independent samples, to assess between-group differences.[2]

The results shown in the table indicate that patients performed statistically significantly more poorly than did controls on the MMSE, TMT (Part A and Part B), and both CLOX drawing tasks. In terms of the CAMCOG subscales, islands of preservation were noted only for the Abstract Thinking subscale. Statistically significant results, and therefore areas of impairment were found for the other subscales, the most predominant of these being the Learning, Memory, and Perception subscales.

Table 4
Between-Group Comparisons of Neuropsychological Test Scores for Controls and Patients

	Controls (n =11)	Patients (n = 11)	Test Statistic	*df*	*p*	Cohen's *d*
MMSE	26.91 (1.76)	18.55 (6.09)	2.132	20	0.001***	-1.87
TPT	13.00 (6.16)	6.09 (1.92)	1.706	20	0.006**	-1.51
TMT - A	44.72 (13.03)	125.36 (50.29)	2.132	20	0.001***	2.20
TMT - B	106.73 (46.05)	296.73 (128.91)	1.919	20	0.001***	1.96
CLOX 1	12.36 (2.03)	8.55 (2.73)	1.706	20	0.006**	-1.58
CLOX 2	14.36 (0.81)	10.55 (1.97)	2.132	20	0.001**	-2.53
CAMCOG						

[2]This test was used rather than the Mann-Whitney U test because it compares two distribution functions.

Learning	14.18 (1.54)	4.36 (2.46)	2.345	20	0.001***	-4.79
Memory	20.91 (2.39)	7.00 (3.63)	2.345	20	0.001***	
Orientation	9.45 (6.84)	6.09 (2.77)	1.706	20	0.006**	-0.64
Language	26.18 (1.47)	20.18(6.84)	1.492	20	0.023*	-1.21
Att/Calc	8.09 (0.83)	4.55 (2.84)	1.706	20	0.006**	-1.69
Praxis	10.18 (1.17)	7.45 (2.16)	1.492	20	0.023*	-1.57
Abstract Thinking	6.45 (1.29)	3.09 (2.66)	1.279	20	0.76	-1.99
Perception	8.09 (1.22)	4.73 (2.05)	1.919	20	0.001**	-4.79

Note. Means are presented with standard deviations in parentheses. The test statistic is for the Kolmogorov-Smirnov test. MMSE = Mini-Mental Status Examination; TPT = The Placing Test; TMT – A = Trail Making Test (Part A); TMT – B = Trail Making Test (Part B); CLOX 1 = Executive Clock Drawing Task (Part 1); CLOX 2 = Executive Clock Drawing Task (Part 2); CAMCOG = Cambridge Cognitive Examination for Mental Disorders of the Elderly Examination-Revised; Att/Calc = Attention/Calculation. *p < .05; **p < .01; ***p < .001

Table 5
CAMCOG Subscale: Between-Group Comparison of Memory Scores for Controls and Patients

	Controls Valid *n* = 11	Patients Valid *n* = 11			
	M (SD)	M (SD)	Test Statistic	*p*	Cohen's d
Memory	20.91 (2.39)	7 (3.63)	2.345	*p* = 0.000***	-4.53

Note. Means are presented with standard deviations in parentheses. *p < .05; **p < .01; *** p < .001

Because one of my hypotheses centres specifically on memory functioning, that domain of neuropsychological functioning is explored in more detail here. Figure 2 shows a graphic comparison of patient and control performance on the major tests of learning and memory in the current battery. As can be seen, the patient group performed consistently worse than the control group on all three measures of memory.

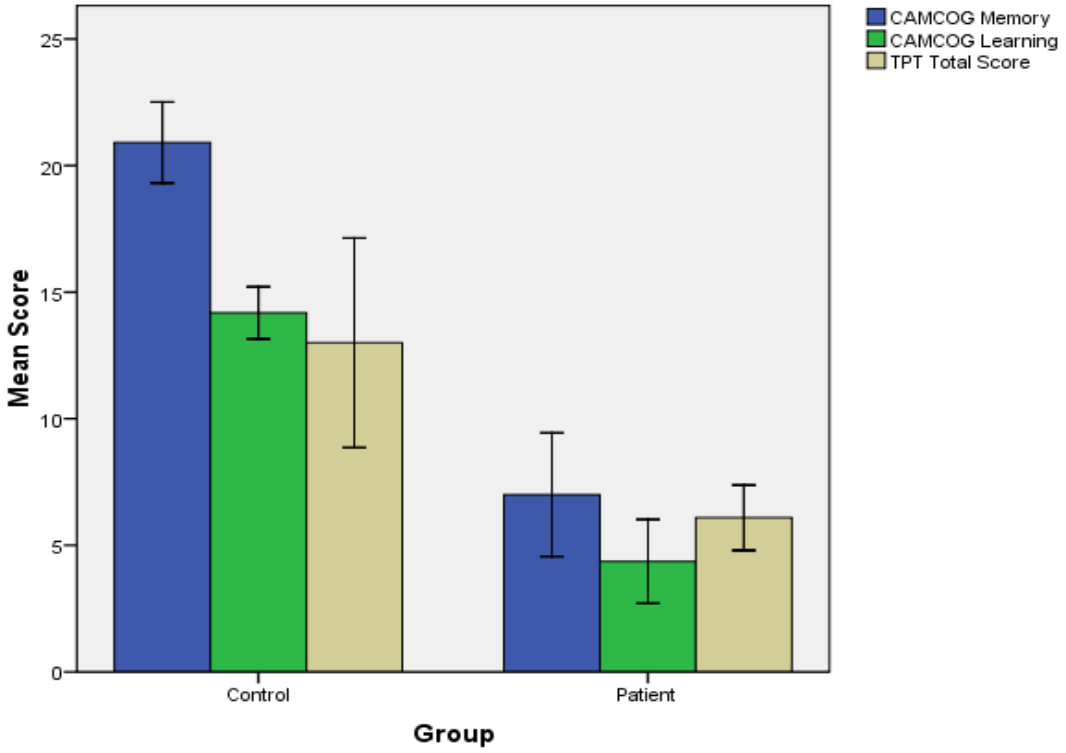

Figure 2. Mean scores for patients and controls on the major neuropsychological tests of learning and memory. Error bars represent 95% confidence intervals.

Figure 3 is a graphic summary of the state of the hypotheses to this point in the analysis. As can be seen, patients had higher cortisol levels (1st column), more lifetime experiences of trauma (2nd column), and poorer memory performance (3rd column) than did controls.

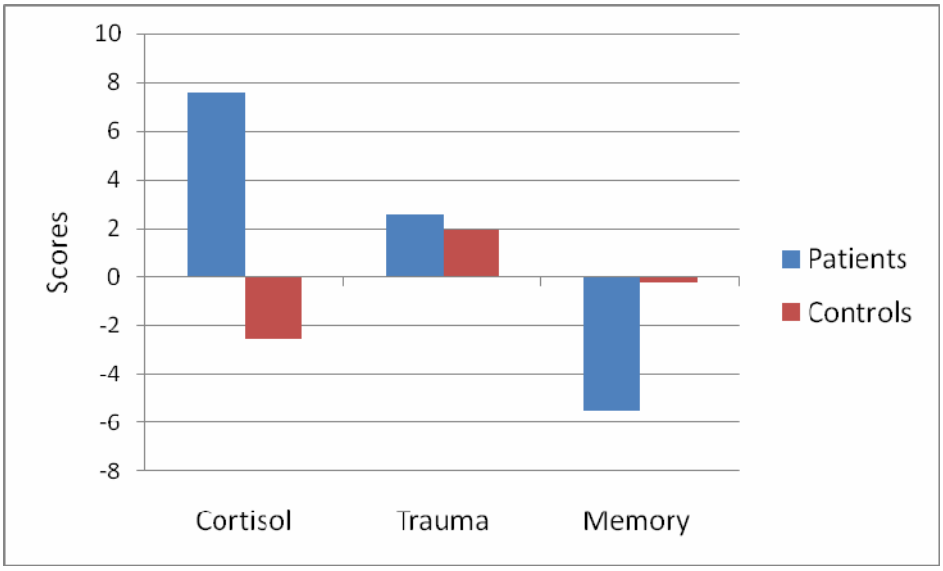

Figure 3. Between-group comparisons of cortisol, trauma, & memory score for controls and patients

Regression Model

As noted earlier, because the research is at least partly based on previous theoretical findings, I used a hierarchical multiple regression analysis in an attempt to model, in the current sample, the relationship between identified risk factors for AD and behavioural, cognitive, and neuropsychological indicators of AD. The predictor variables were entered into the model using hierarchical (blockwise entry). For this method, known predictors (established from former research), are entered into the model in order of their importance in predicting the outcome (Field, 2005). Thus, the predictor variables were (in order of entry into the model) age, level of education, lifetime trauma (as measured by the LTE-Q), current everyday stress levels (as measured by the PSS), and resiliency (as measured by the CD-RISC). The criterion variable was a composite called Functioning, and was created by averaging the sample's standard scores on the DECO, the BADLS, the TPT, and the CAMCOG Learning subscale. The latter two neuropsychological outcome variables formed part of the composite because they were judged (based on previous literature; see, e.g., Kowalczyk, McDonald, Cranney, & McMahon, 2001; Hobson & Meara, 1999) to be the best representatives of domains of neuropsychological functioning typically impaired in AD.

Appendix H shows the results of the full hierarchical regression model. Table 6 shows the final regression model, including age, education level, and resilience as the predictors. These predictor variables were retained for this model as they demonstrated statistically significant *F*-values and explained most strongly the variance at various stages of the hierarchical model (as shown by their high R^2 values). As can be seen, the final model was statistically significant, $F(3, 18) = 9.761$, $p = 0.00048$, $R^2 = .62$. However, none of the predictor variables were statistically significant and analysis of the beta coefficients indicated that they all seemed to account for similar amounts of variance in the model.

A full set of diagnostic tests were run on the final model. Table H2 and Figures H1 and H2 graphically illustrate aspects of these diagnostic tests (see Appendix H). Briefly, analysis of the partial correlations suggested that none of the predictors contributed a large amount of unique variance. However, the tolerance levels were high, suggesting no problems with multicollinearity in the data, and the R^2 values low, suggesting that there is a relatively small amount of shared variance between the variables. Analysis of the residuals showed that the data were normally distributed, linear, and that there did not seem to be any serious outliers that required attention.

In summary, the final regression model was, from a statistical significance perspective, a good fit for the observed data, suggesting that the model as a whole is a good predictor of behavioural, cognitive, and neuropsychological functioning in this sample. However, the individual predictors themselves were not found to be significant. This means that when combined, these predictors produce a good model of overall functioning, but that they cannot be completely separated from one another when accounting for the variance in the model.

Table 6
Regression Model: Predictors of Functioning in the Current Sample

	B	*SE B*	ß
Constant			-2.40
Age	-.31	0.17	-0.05
Education Level	.31	0.17	0.18
Resilience	.37	0.17	0.04

Note. $R^2 = .62$; $p = 0.00048$

DISCUSSION

This study aimed to investigate the relationship between traumatic life events, high cortisol, and Alzheimer's disease in a sample of South African older adults. My overarching hypothesis, based on a wealth of previous international literature, was that individuals at greatest risk for age-related cognitive decline (and possible AD) would be those with the largest amounts of exposure to traumatic life events and concomitant high salivary cortisol levels. This broad hypothesis was explored by investigating four more specific hypotheses. Each of these is discussed in turn below.

The first specific hypothesis was that patients would have more experiences of trauma than controls. Patients were found to have had experienced more traumatic life events than controls. Although these results were not statistically significant, they did indicate an obvious difference between the groups. These results concur with previous research by Bemelmans et al. (2007) who reported that elderly people who were prone to experience psychological distress were more likely to develop AD than were non-stressed individuals. Scores relating to levels of perceived stress indicated a statistically significant result between patients and controls. Patients perceived their lives as more stressful than controls perceived their own lives to be. This may be attributed to the fact that the majority of patients had experienced more traumatic life events than had the controls. The higher levels of perceived stress in the patient group are supplemented by the higher cortisol levels shown for this group.

The second specific hypothesis was that patients would have higher cortisol levels than controls. The difference between cortisol levels for patients and controls was not statistically significant; however, the results did indicate that patients had higher levels of cortisol than controls. Although this was a relatively small difference, a trend is shown for patients to have higher cortisol levels.

The third hypothesis was that patients would have lower memory scores than controls. Between-group comparisons indicated that patients had significantly lower memory scores than controls. This is consistent with AD literature as memory is one of the major cognitive domains affected by the progression of the disease (Bemelmans et al., 2007; Mickes et al., 2007).

The fourth hypothesis was that patients would have both more experiences of trauma and higher cortisol levels than controls. The combination of the results discussed above, in concordance with the hypotheses, show that patients had both higher cortisol levels and more experiences of traumatic life events than the controls. The preliminary results from this study, discussed so far, indicate that there is a trend towards supporting these hypotheses as well as my overarching hypothesis.

Correlational analyses also provided data that served to confirm the hypotheses. Correlations were performed to assess possible relationships between trauma, cortisol, and memory. A Pearson Product-Moment correlation showed that a weak, negative correlation was found between memory and cortisol (r = -.15). These results suggest that higher cortisol levels are associated with memory impairment, although only a weak relationship was indicated. This association concurs with previous research that reports the negative association between cortisol and concerted memory retrieval efforts (Bemelmans et al., 2007). Furthermore, the results from this study correspond with former literature that found a relationship between chronically high levels of cortisol and impaired memory functioning (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003).

One of the features of AD is a general decline in areas of functioning. The results showed differences between the two groups when compared for level of functioning. Statistically significant results were found between patients and controls across all the measures of functioning, barring depression. Informant-reported results indicated poorer levels of activities of daily functioning and cognitive functioning, for patients than for controls.

Interestingly, levels of neuroticism were significantly higher for controls than for patients. This contradicts previous research which suggests that patients experience higher levels of neuroticism than controls (Neupert, Almeida, Mroczek, & Spiro III, 2006). A possible explanation for this may be that all of the patients came from strong support structures, composed of family, friends, and nursing staff. It appeared that the patients were comfortable in their surroundings and there was not much about which they could worry. They also did not seem overly concerned about their financial status, as most of them were cared for and supported by family members. In contrast though, some of the controls were single, lived alone and belong to lower SES strata. They may not have had a good support structure and might have been required to handle financial problems on their own. These factors may explain the higher levels of neuroticism for controls than for patients.

The presence of symptoms of depression was not statistically significant between the two groups. This is what one would hope to find in this field of research as the presence of depression may confound the results due to its association with memory impairment (Basso & Bornstein, 1999). As the groups did not differ in terms of depression, and as the levels of depression were well below the cut-off score, it is safe to say that none of the neuropsychological functioning was influenced by the presence of depression.

Measures of neuropsychological functioning indicated that patients performed statistically significantly more poorly than did controls on measures of visual learning and memory, motor speed and visual attention, executive and visuospatial impairment, and general cognition. The subscales of the general cognition measure identified only one island of preservation, namely Abstract Thinking. This means that this subscale was the only subscale on which patients and controls did not differentiate significantly. Therefore, patients' ability to complete abstract thinking tasks successfully (e.g., identifying general relationships between objects) was not impaired by the presence of AD. Significant results, and therefore areas of impairment, were found for the other subscales, the most predominant of these being the Learning, Memory, and Perception subscales. One would expect that the learning and memory domains of cognition would be significantly impaired as this is a common feature of AD. Perception is not generally regarded as a commonly impaired cognitive function as a result of AD.

My last hypothesis investigated risk factor variables for the development of AD. Results from the hierarchical regression indicate that Age, Education Level, and Resilience were indicated as significant predictors of functioning. Based on previous literature, it is not surprising that these three variables were found to be significant predictors of functioning. Age is commonly understood as one of the main predictors of physical and cognitive decline and is indisputably associated with the development and progression of AD. Prior findings have also highlighted a low level of education as a possible risk factor for the development of AD. Education as a risk factor for AD was identified by Kukull et al. (2002) in their study on dementia and Alzheimer's disease incidence. Their study reported that education level (>15 years vs. <12 years) was negatively associated with a risk of AD and positively associated with the baseline cognitive test score. Similarly, Ott et al. (1995) found a significantly higher prevalence of AD for participants with lower levels of education. Another explanation for why education is a risk factor for AD is that people who have lower levels of education are less likely to stimulate themselves cognitively as they age. Cognitive inactivity has been linked to an increased risk for developing AD (Wilson, Mendes de Leon, Barnes, et al., 2002).

Resilience has also been associated with AD in that some research has suggested that high levels of resilience may serve as a protective factor against the disease. Harris (2006) suggests that resilience should be a goal for all elderly people, with or without dementia, because it can assist successful aging and may be protective against age-related illnesses. As mentioned earlier, stress brings about both physiological and psychological reactions which, if excessive, can cause damage to the mind and body. Having restorative processes in place which replenish one's physiological reserves may help to protect one against future stress (Cacioppo, Hawkley, & Berntson, 2003). In contrast, a lack of resilience and therefore restorative processes may cause one to be at a higher risk for experiencing stress and the possible consequent development of cognitive disorders.

Once these three predictors were put into a regression model of their own, although the model was significant, the predictors themselves were not significant. Each variable was also shown to account for almost exactly the same amount variance in the model. This suggests that the variables were not actually separate from each other and that they overlapped in some way. When considering the context of these variables it seems reasonable to suggest that it is not possible to separate these variables from one another in such a model.

There are some possible explanations for why these three variables may be interrelated. This sample consisted of predominantly elderly people who are less likely to have completed education beyond Grade 9, due to Apartheid, education systems, social class, and social norms of that time period. This provides a possible reason as to why age and education may be interrelated. Age may also be interrelated with resilience, because as people get older they may either become more resilient or less resilient. Some research suggests that older people are more resilient as they have had a lifetime of learning and experiencing things and are better able and more experienced to deal with things in old age. These researchers couched their findings within lifespan theoretical frameworks, which suggest that as people grow older, they develop more cognitive maturity and are thus better able to deal with problems (Birditt, Fingerman, & Almeida, 2005).

In contrast with that set of findings, other research suggests that elderly people are less resilient as they feel less capable of looking after themselves and may experience more medical and financial problems than in their younger years. Results from this study show that the patients are less resilient than the controls. This may be because the patients are aware of their disease, which may cause anxiety and distress for the patient and cause them feel that they are not as well-equipped to deal with things as when they were healthy and younger. Low levels of resilience may also be related to low educational achievements, as previous research suggests that having a higher education level may better equip one to deal with life stressors. For example, Callahan et al. (1996) found that educational achievements were protective against the development of AD.

The results of this research, which confirm the original hypotheses, suggest that individuals at greatest risk for age-related cognitive decline (and possible AD) are those with the largest amounts of exposure to traumatic life events and concomitant high salivary cortisol levels. The results also suggest that old age, low education level, and poor resilience may be plausible risk factors for the development of Alzheimer's disease.

Limitations and Recommendations for Future Research

The largest limitation of this study was that the sample size was too small to obtain multiple statistically significant results. The analysis of data also involved multiple comparisons, which may have increased the risk of Type 1 errors. Furthermore, the patient and control groups were

not age-matched which increased the difficulty in obtaining statistically significant between-group differences that were not confounded by age. Another limitation would be the statistical significance and generalizability of the results as the population group included predominantly Coloured people, one White person and no Black African people. In order to increase the possibility of obtaining more statistically significant and generalizable results, future research should strive to obtain larger sample sizes as well as samples that are more representative of the broader South African population.

In conclusion, therefore, this pilot study has indicated that the larger project within which this study was nested is feasible and worth pursuing. The procedure and methods are adequate and provide a good foundation upon which to build the larger project. The results, although not all statistically significant, are encouraging, as they still indicate a trend towards supporting the hypotheses. This trend suggests that use of a larger sample size is likely to yield statistically significant results. Lastly, as the first study on trauma, cortisol, and Alzheimer's disease to be conducted in South Africa, the results indicate that this population group does not seem to differ dramatically from international populations. However, the larger study focusing on risk factors for AD will include Black African participants, who have not yet been studied within this field of research. The outcomes of that study should provide necessary and innovative information regarding the presence and characteristics of, and risk factors for, AD within this population group. Overall, then, our future endeavours in this field will provide novel and urgently required information regarding AD in South Africa.

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APPENDIX A

Deterioration Cognitive Observee (DECO)

We would like you to tell us how your relative was a year ago. The following questions ask about a number of everyday situations. We would like you to tell us whether in these situations he/she is doing about the same, not as well or much worse, than a year ago. Place a tick in the relevant column to show your response.

	Better or about the same	Not as well	Much worse
1. Does he/she remember as well as before which day of the week and which month it is?			
2. When he/she goes out of the house, does he/she know her way as well as before?			
3. Have there been changes in his/her ability to remember his/her own address or telephone number			
4. In the house, does he/she remember as well as before where things are usually kept?			
5. And when an object isn't in its usual place, is he/she capable of finding it again?			
6. In comparison with a year ago, how well is he/she able to use household appliances (washing machine, etc….)?			
7. Has his/her ability to dress or undress changed at all?			
8. How well does he/she manage his/her money, for example, doing the shopping?			
9. Apart from difficulties due to physical problems, has there been a reduction in his/her activity level?			
10. How well can he/she follow a story on television, in a book or told by someone?			

11. And writing letters for business or to friends; does he/she do this as well as a year ago?			
12. How well does he/she recall a conversation you had with him/her a few days ago? Has this changed over the past year?			
13. And if you remind him/her of this conversation, does he/she still have difficulty remembering it in comparison to a year ago?			
14. Does he/she forget what he/she wanted to say in the middle of a conversation? Has this changed over the past year?			
15. In a conversation, does he/she sometimes have difficulty finding the right word?			
16. In comparison with a year ago, how well does he/she recognize the faces of people he/she knows well?			
17. And how well does he/she remember the names of these people?			
18. In comparison with a year ago, how well does he/she remember other details concerning people he/she knows well; where they live, what they do?			
19. Over the past year, have there been changes in his/her ability to remember what has happened recently?			

APPENDIX B

Geriatric Depression Scale

Choose the best answer for <u>how you have felt over the past week</u>:

1. Are you basically satisfied with your life?	YES / NO
2. Have you dropped many of your activities and interests?	YES / NO
3. Do you feel that your life is empty?	YES / NO
4. Do you often get bored?	YES / NO
5. Are you in good spirits most of the time?	YES / NO
6. Are you afraid that something bad is going to happen to you?	YES / NO
7. Do you feel happy most of the time?	YES / NO
8. Do you often feel helpless?	YES / NO
9. Do you prefer to stay at home, rather than going out and doing new things?	YES / NO
10. Do you feel you have more problems with memory than most?	YES / NO
11. Do you think it is wonderful to be alive now?	YES / NO
12. Do you feel pretty worthless the way you are now?	YES / NO
13. Do you feel full of energy?	YES / NO
14. Do you feel that your situation is hopeless?	YES / NO
15. Do you think that most people are better off than you are?	YES / NO

APPENDIX C

Demographic Questionnaire

1. **Age: _____**
2. **Date of Birth (d/m/y): _____**
3. **Sex (circle one):** Male Female
4. **Race (circle one):** White Black Coloured
   Indian Other: specify: _____
5. **Handedness (circle one):** Left Right Ambidextrous
6. **Home Language**:

_____

7. **Do you speak any other languages**? Please specify:

_____

8. **Who was/were your primary caregiver(s) during your childhood?** (E.g., parents, mother, father, grandmother, grandfather, uncle, aunt, etc.)

_____

9. **Are you a caregiver?** (Who do you care for?) -

_____

10. **What is the total monthly income of the household in which you live? If you are a student please take care to put your immediate caregivers monthly income not your own (circle one):**

R0 – R499 R500 – R999 R1000 - R2499
R2500 – R5499 R5500 – R9999 R10 000+

11. **What term best describes the kind of neighbourhood in which you grew up?**
    SUBURBAN
    URBAN
    TOWNSHIP
    INTERMEDIATE

12. What is the name of the neighbourhood in which you grew up?

_____

SECTION A. EDUCATION

13. Education (highest degree or grade completed):

_____

14. What are the names of the schools you attended during your schooling career?

Junior school

_____

High School

_____

15. If you attended multiple schools in high school, how many months/years roughly did you spend at each and which schools were they?

_____

16. Was most of your school education completed in a rural or urban setting (circle one)?

RURAL URBAN

17. In which language was most of your school education completed?

_____

18. Did you have to repeat any grades? YES NO

If yes, please specify which grade(s):

_____

19. Did you receive a matric certificate? _____

20. If so, at which school did you complete your matric? _____

21. Did you matriculate from a public high school or a private high school (circle one)?

PUBLIC PRIVATE

22. Roughly how many students were there per teacher in high school (that which you matriculated from)?

---

23. Did you, or are you presently, attending any tertiary education?

YES NO

If yes, what are you studying?

_____

Where are you studying?

_____

Please only answer the following questions if you currently are NOT receiving any level of education

24. Did you receive any further education post-matric? YES NO

If yes, please specify at which institution/college etc. this was received:

_____

25. How many years of education did you receive post-matric? _____

26. What field of study was this in? _____

27. *EDUCATION (HIGHEST DEGREE OR GRADE COMPLETED AS OF 2008):*

_____

SECTION B. HEALTH

(Please circle the appropriate answer for each of the questions below)

28. Would you say your birth was: NORMAL ABNORMAL

DON'T KNOW

29. Have you ever experienced a head injury? (e.g., being hit on the head with an object and losing consciousness as a result)

YES NO

If yes, please specify:

_____

30. Have you ever been involved in a motor vehicle accident?

YES NO

If yes, how old were you at the time?

_____

31. Have you ever had surgery? YES NO

If yes:

What type of surgery?

_____

How old were you at the time of surgery?

_____

32. Do you now, or have you ever, experienced any of the following medical conditions:

32.1. Allergies YES NO

If yes, please specify:

_____

32.2. Asthma YES NO

32.3. Tuberculosis YES NO

32.4. Hypertension (high blood pressure) YES NO

32.5. Epilepsy (i.e., seizures or fits) YES NO

32.6. Neurological problems YES NO

If yes, please specify:

_____

32.7. Depression YES NO

32.8. Treated for/ diagnosed with any memory problems or disorders

YES NO

If yes, please specify:

_____

32.9. Learning difficulties (dyslexia, ADD/ADHD) YES NO

If yes, please specify:

_____

32.10. Problems with your vision YES NO

If yes, please specify:

_____

32.11. Problems with your hearing YES NO

If yes, please specify:

_____

33. Do you have any family history of any of the above medical conditions?

YES NO

If yes, please specify:

_____

_____

34. Are you currently taking any prescription medication(s)?

YES NO

If yes, what medication(s)?

_____

APPENDIX D

List of Threatening Life Events Questionnaire

	Did this occur in past 6 months? (circle correct answer)	Impact (circle correct answer)	Did this occur more than 6 months ago? (circle correct answer)	Impact (circle correct answer)
You yourself suffered a serious illness, injury or an assault.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
A serious illness, injury or assault happened to a close relative.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
Your parent, child or spouse died.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
A close family friend or another relative (aunt, cousin, Grandparent) died.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
You had a separation due to marital difficulties.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
You broke off a steady relationship.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
You had a serious problem with a close friend, neighbor or relative.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
You were fired from your job.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
You had a major financial crisis.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
You had problems with the police and a court appearance.	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**
Something you valued was lost or stolen	**Yes / No**	**None/Some/ Significant**	**Yes / No**	**None/Some/ Significant**

APPENDIX E

Perceived Stress Scale

Items and Instructions

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate *how often* you felt or thought a certain way. Although some of the questions are similar, there are differences between them and you should treat each one as a separate question. The best approach is to answer each question fairly quickly. That is, don't try to count up the number of times you felt a particular way, but rather indicate the alternative that seems like a reasonable estimate.

For each question choose from the following alternatives:

1. In the last month, how often have you been upset because of something that happened unexpectedly?

   0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

2. In the last month, how often have you felt that you were unable to control the important things in your life?

   0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

3. In the last month, how often have you felt nervous and "stressed"?

   0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

4. In the last month, how often have you dealt successfully with irritating life hassles?

   0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

5. In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

6. In the last month, how often have you felt confident about your ability to handle your personal problems?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

7. In the last month, how often have you felt that things were going your way?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

8. In the last month, how often have you found that you could not cope with all the things that you had to do?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

9. In the last month, how often have you been able to control irritations in your life?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

10. In the last month, how often have you felt that you were on top of things?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

11. In the last month, how often have you been angered because of things that happened that were outside of your control?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

12. In the last month, how often have you found yourself thinking about things that you have to accomplish?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

13. In the last month, how often have you been able to control the way you spend your time?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

14. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

0. Never 1. Almost never 2. Sometimes 3. Fairly often 4. Very often

APPENDIX F

Instructions for saliva samples

Saliva Samples

Thank you again for agreeing to participate in this study. The following are the instructions for submitting 2 saliva samples, 2 consecutive days at 9:00AM.

24 hours before collecting a sample, the participant must not:

1. Drink any alcohol/smoke cigarettes
2. Have any dairy products, e.g., cheese, yoghurt, milk
3. Have any fizzy drinks,
   oranges, lemons, pine-apples (no citrus)
   sweets
   chocolates
4. Ingest or inhale any steroids, e.g., prednisone, prednisolone, methylprednisolone

When taking the sample at 9:00AM:

1. Make sure you have had breakfast by 7:00AM.
2. Wash out your mouth with water 10 minutes before taking the sample.
3. Remove the saliva "sponge" collection device from container and chew on it for a minute.
4. Place the sponge back in the container and make sure it is tightly closed/sealed.
5. Place in freezer

After you have taken the sample:

1. Once both samples are collected please call Katharine James for collection: 082-593-4684 or 021-531-8295

APPENDIX G

Informed consent form

Informed Consent to participate in research and

authorization for the collection and use

of the results of cognitive tests and other personal information.

UCT Faculty of Health Sciences Research Ethics Committee Approval reference:

You are being asked to take part in a research study. This form provides you with information about the study and seeks your authorization for the collection and use of your cognitive test results, your salivary cortisol levels, your blood cortisol levels, as well as other personal information necessary for the study. The Principal Investigator will also describe this study to you and answer any questions you may have. Your participation is entirely voluntary. Before you decide whether or not to take part, please read the information below and ask questions about anything you do not understand. By participating in this study you will not jeopardize any future treatment of your condition.

1. **Name of Participant ("Study Subject")**

_____

2. **Title of Research Study**

The relationship between life events, resilience, high cortisol, and Alzheimer's disease

3. **Principal Investigators and Telephone Number(s)**

Kevin G. F. Thomas, Ph.D.
Senior Lecturer
Department of Psychology
University of Cape Town
021-650-4608

Marc Combrinck, M.D.
Department of Neurology
Groote Schuur Hospital
021-404-3198

Katharine James

Postgraduate Student

Department of Psychology

University of Cape Town

082-593-4684

4. **Source of Funding or Other Material Support**

National Research Foundation

5. **What will be done if you take part in this research study?**

First, you will be screened by a study representative. The screening procedure takes place because it is important to know your medical history and other personal information. If you are eligible for participation in the study, a meeting will be arranged between you and the researcher. You and an informant (your spouse/partner/close relative) will be asked to come to Groote Schuur Hospital at 9am on a day that is mutually convenient.

A researcher will meet you at Ward E7 and show you to the testing room. The researcher will then ask you and your informant to complete some paper-and-pencil questionnaires that ask about your background, previous experiences of traumatic life events, levels of stress, ways in which you cope with stress, and your everyday activities. After completing the questionnaires, the researcher will test your memory and other mental functions using paper-and-pencil instruments.

The entire session should not take longer than two (2) hours. If you require breaks in between questionnaires or test instruments, please let the researcher know.

After completing the tests, the researcher will give you three sets of cotton bud swabs. They will look very similar to cotton buds, except that the tip will have a triangular piece of cotton on it. You should take these cotton bud swabs home with you. The day after you have met the researcher, you must swab your saliva at 9am. You should do this for three consecutive days, at 9am every day. You will be given detailed instructions about how to swab your saliva. If you think that you might forget to swab your saliva at 9am, the researcher will ask for your permission to phone you at 8:55 am on each of the collection days to remind you.

After three days, the researcher will phone you and arrange to pick up the swabs from you. Please do not take the swabs out of the freezer until the researcher comes to your house. It is important that the swabs do not defrost.

Remember, you are free to withdraw from the study at any stage without needing to provide a reason. Your future treatment will not in any way be adversely affected if you decide to do so.

Please contact the Principal Investigators listed above to let one of us know if you no longer wish to take part in this study.

The researcher will not be able to give you your individual scores, but if you wish to know the overall results of the entire study, you may contact one of the Principal Investigators.

6. **If you choose to participate in this study, how long will you be expected to participate in the research?**

The testing session will take 2 hours, and you will be asked to swab your saliva for three days. The total duration is therefore four days.

7. **How many people are expected to participate in the research?**

100 participants

8. **What are the possible discomforts and risks?**

There are no physical, psychological, or social risks involved in this study. You might experience mild discomfort when you have blood drawn, and you might get tired and/or possibly frustrated during the neuropsychological tests. If you do feel tired and need to take a break, please feel free to tell us.

9. **What are the possible benefits to you?**

There is a potential benefit for the participants involved, as their participation will entitle them to receive a free health scan. The researcher will, with your permission, make available the results of the memory and cognitive test scores to your doctor.

10. **What are the possible benefits to others?**

We are interested in the relationship between stress levels, cortisol, cognitive/memory functions, and aging, particularly Alzheimer's disease. This knowledge may allow for new risk factors for dementias such as Alzheimer's disease to be identified, and may lead to better management of these conditions in the long term. Additionally, it may result in better treatment options.

11. **If you choose to take part in this research study, will it cost you anything?**

No.

12. **Will you receive compensation for taking part in this research study?**

You will be reimbursed R150.00 for your travelling expenses.

13. **Can you withdraw from this research study?**

You may withdraw from this study at any stage, and do not need to provide a reason for doing so. Your future treatment will not be adversely affected by your decision.

If you have any questions regarding your rights as a research subject, you may phone the Psychology Department offices at 021-650-4530.

14. **If you withdraw, can information about you still be used?**

Yes, with your permission, your information may still be used within the study.

15. **Once information is collected, how will it be kept secret (confidential) in order to protect your privacy?**

Information collected will be stored in locked filing cabinets or in computers with security passwords. All information will be stored by code number, rather than by name. Only the researchers involved in this study will have access to this information. The University of Cape Town has the right to verify the authenticity of the information collected.

16. **What information about you may be collected, used and shared with others?**

This information gathered from you will include a medical history, some personal information, your cognitive tests results and cortisol levels. The information will be kept and stored by research code. This project forms part of a larger five-year project and your information may be included in this study.

17. **How will the researcher(s) benefit from your being in the study?**

This research forms part of Ms. James' Honours degree in Psychology. It is also part of a larger study that commences this year.

18. **Signatures**

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternatives to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

_____ _____

Signature of Person Obtaining Consent & Authorization Date

Consenting Adults. You have been informed about this study's purpose, procedures, possible benefits, and risks; the alternatives to being in the study; and how your protected health information will be collected, used and shared with others. You have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been

told that you can ask other questions at any time.

Adult Consenting for Self. By signing this form, you voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your protected health information as described in the sections above. By signing this form, you are not waiving any of your legal rights.

_____ _____

Signature of Adult Consenting & Authorizing for Self Date

Parent/Adult Legally Representing the Subject. By signing this form, you voluntarily give your permission for the person named below to participate in this study. You hereby authorize the collection, use and sharing of protected health information for the person named below as described in the sections above. You are not waiving any legal rights for yourself or the person you are legally representing. After your signature, please print your name and your relationship to the subject.

_____ _____

Consent & Authorization Signature Date

of Parent/Legal Representative

_____

Print: Name of Legal Representative of and Relationship to Participant:

Please indicate below if you would like to be notified of future research projects conducted by our research group:

_____ (initial) Yes, I would like to be added to your research participation pool and be notified of research projects in which I might participate in the future.

Method of contact:

Phone number: _____

E-mail address: _____

Mailing address: _____

APPENDIX H

Hierarchical Regression Model

Table H1

Hierarchical Regression Model: Predictors of Functioning in the Current Sample

	B	*SE B*	ß
Step 1			
(Constant)	6.46	2.29	
Age	-.110	.031	-.62**
Step 2			
(Constant)	1.79	2.81	
Age	-.08	.03	-.44**
Education Level	.24	.09	.42*
Step 3			
(Constant)	3.47	3.79	
Age	-.09	.04	-.51**
Education Level	.13	.18	.23*
Medium vs Low	.07	.69	.02
Medium vs High	.82	1.00	.23
Step 4			
(Constant)	4.03	3.59	
Age	-.09	.04	-.51**
Education level	.16	.17	.28*
Medium vs Low	.21	.67	.06

Medium vs High	.31	.96	.09
None vs Single Trauma	-.24	1.02	-.07
None vs Multiple Trauma	-1.35	1.03	-.39
Step 5			
(Constant)	3.45	4.15	
Age	-.88	0.39	-.49**
Education level	.17	.18	.29*
Medium vs Low	.35	.82	.09
Medium vs High	.40	1.05	.11
None vs Single Trauma	-.29	1.07	-.09
None vs Multiple Trauma	-1.50	1.17	-.45
Perceived Stress	.01	.04	0.8
Step 6			
(Constant)	-5.13	4.80	
Age	-.04	-.04	-.21**
Education level	.22	.15	.38*
Medium vs Low	.11	.70	.03
Medium vs High	-.65	.98	-.18
None vs Single Trauma	-.09	.90	-.03
None vs Multiple Trauma	-1.73	.99	-.51
Perceived Stress	.04	.04	.22
Resilience	.06	.02	.52*

Note. R^2 = .38 for Step 1; ΔR^2 = .15 for Step 2; ΔR^2 = .02 for Step 3; ΔR^2 = .10 for Step 4; ΔR^2 = .002 for Step 5; ΔR^2 = .12 for Step 6; * $p < .05$, ** $p < .01$.

Table H2
Diagnostic data – redundancy coefficients

	Beta in	Partial Cor.	Semipartial Cor.	Tolerance	R-Square
Age	-0.31	-0.39	-0.26	0.71	0.29
Education Level	0.31	0.40	0.27	0.75	0.25
Resilience	0.37	0.44	0.30	0.69	0.31

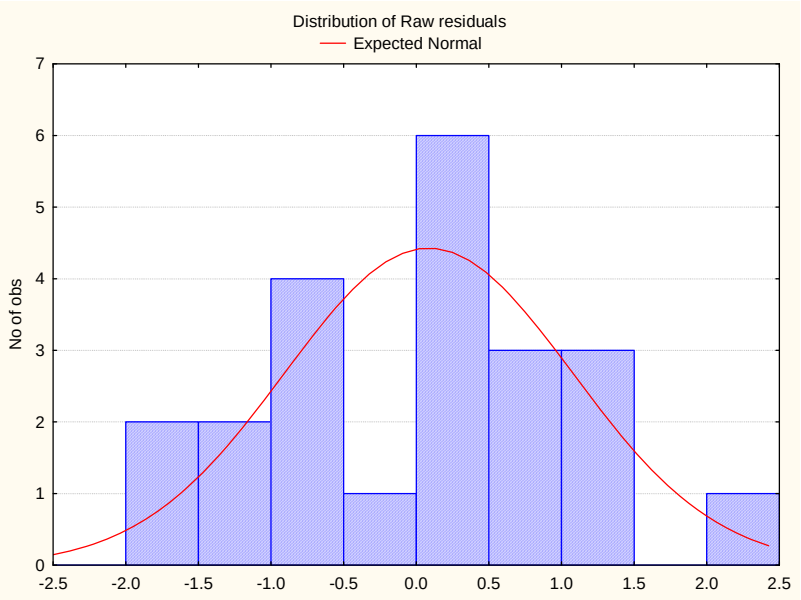

Figure H1. Distribution of raw residuals for final regression model.

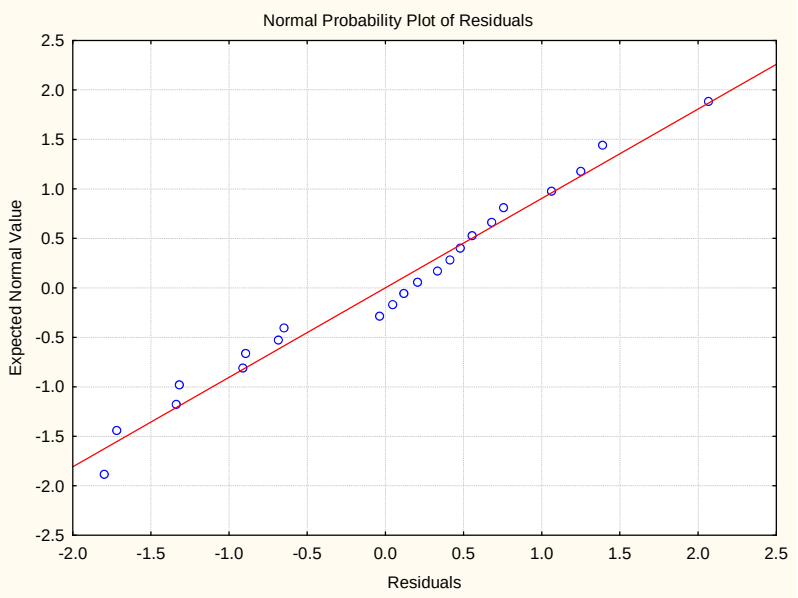

Figure H2. Normal probability plot of residuals for final regression model