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1. INTRODUCTION

Dementia, of which Alzheimer's disease (AD) is the most common cause, describes a cluster of symptoms associated with but not limited to impairments in learning, memory, language and self-care. Dementia is a global crisis, with an estimated 40-50 million people worldwide currently living with the syndrome (GBD 2016 Dementia Collaborators, 2019). While the greatest known risk factor for dementia is increasing age, it is estimated that a third of dementia is potentially modifiable (Livingston et al., 2017). The identification of modifiable risk and protective factors to prevent dementia or delay cognitive decline thus remains an important public health strategy to reduce the global burden of this condition.

Psychological stress and trauma are associated with dysregulation of the stress system, which includes the hypothalamic-pituitary-adrenal (HPA) axis (Herman et al., 2016). In response to stress, elevated levels of the primary stress hormone, cortisol is released. However, prolonged exposure to increased cortisol could be responsible for damage to cognitive brain regions (McEwen et al., 2016). Preliminary evidence suggests that this may play a role in cognitive decline with ageing, and could be a risk factor for AD (Lupien et al., 2009). It has previously been shown that alterations in the HPA axis response (elevated cortisol levels under a stressful situation) is associated with specific alterations in memory and executive function (Beluche et al., 2010). Other studies have found that raised basal cortisol levels and higher plasma cortisol levels have also been associated with faster progression of dementia (Ouanes and Popp, 2019).

People prone to psychological distress may also have an increased risk of dementia in later-life (Escher et al., 2019). There are several studies in male dominated military populations which have reported up to two-fold increased risk of dementia in older veterans with Posttraumatic Stress Disorder (PTSD), which is a severe clinical disorder that may arise in the aftermath of a life-threatening event (Mawanda et al., 2017; Qureshi et al., 2010; Yaffe et al., 2010). There are also

limited studies to suggest that PTSD may be a risk factor for dementia in community-based samples (Flatt et al., 2018; Wang et al., 2016), however further research is required.

The primary aim of this study is to determine whether lifetime exposure to severe trauma is associated with later-life cognitive function and the risk of dementia in a large population of older community-dwelling individuals. The secondary aim is to determine whether these associations vary according to whether the individual has re-experiencing symptoms or not. Lifetime trauma with re-experiencing symptoms (e.g. recurring dreams, flashbacks, hallucinations or frequent unpleasant memories of the event (Watson et al., 1991) is the most clinically relevant and unique class of symptoms within this disorder (Sareen, 2014). The third aim of this study is to determine whether there are gender-specific associations.

2. EXPERIMENTAL PROCEDURES

2.1 Study population

This study utilised data from the French-based, longitudinal ESPRIT (Enquête de Sante´ Psychologique- Risques, Incidence et Traitement) study of neuropsychiatric disorders in geriatric populations (Ritchie et al., 2004). Eligible participants who were non-institutionalised and aged over 65 years were randomly drawn from electoral rolls of the Montpellier district between 1999 and 2001.

Following recruitment, participants were administered numerous questionnaires and underwent extensive assessment by trained personnel, including nurses and neurologists with experience in psychogeriatrics, at Gui de Chauliac Neurology Hospital over the course of half a day. Ethical approval for the study was granted by the Ethical Committee of University Hospital of Kremlin-Bicêtre, France, and written consent was obtained from each participant. Of the 1,863 participants who were recruited, 1,723 participants provided information on their experience of lifetime trauma and its associated symptoms when completing the Watson's PTSD Inventory (Watson et al., 1991). Participants with prevalent dementia at baseline (n=20) and missing information about dementia

incidence (n=1) were also excluded from the analyses, and two participants had no follow-up information at all, leaving a total of 1,700 participants for analysis.

2.2 Lifetime trauma exposure – Psychiatric Interview

Lifetime and current PTSD diagnoses were assessed using a validated French self-report version of the Watson's PTSD Inventory (PTSD-I, α=0.92, test-retest reliability total score=0.95), according to the Diagnostic and Statistical Manual of Mental Disorders-III-R (DSM-III-R) criteria (Chaudieu et al., 2011; Watson et al., 1991).

The questionnaire was administered at baseline and during 5 follow-up visits across a 12-year period. The PTSD-I requires participants to state their most traumatic or frightening event throughout their lifetime, which is further classified as severe trauma only if they were in accordance with PTSD criterion A1 in DSM-IV (American Psychiatric Association, 1994). The remainder of the PTSD-I consists of 17 items which examines the symptoms associated with the severe trauma. Features of this questionnaire in addition to its high internal consistency and reliability, include continuous measures regarding the severity and frequency of each symptom (Watson et al., 1991), and its ability to identify participants with sub-syndromic PTSD, who do not fully meet the criteria required for a diagnosis of PTSD. Thus, this study was able to classify individuals who reported a history of PTSD re-experiencing symptoms without a formal PTSD diagnosis, including participants who had experienced flashbacks, hallucinations, unpleasant dreams, psychological distress, intrusive thoughts and reliving of the severe trauma. However, it is important to note that the PTSD-I was initially constructed to diagnose current PTSD in male Vietnam combat veterans, thus reliability and validity data may not be as strong in other populations.

2.3 Cognitive assessments

Participants were assessed with a battery of cognitive tests administered by staff trained in psychogeriatrics. This included the Mini Mental State Examination (MMSE) to assess global

cognition (concurrent validity: $0.66 \leq r \leq 0.78$, test-retest reliability: $0.80 \leq r \leq 0.95$) (Folstein et al., 1975), Benton's Visual Retention Test (BVRT) administered using form D for visual memory (construct validity: $0.46 \leq r \leq 0.62$, test-retest reliability: $r=0.85$) (Sivan, 1992), Isaacs Set Test (IST) of verbal fluency and semantic processes (construct validity: $0.40 \leq r \leq 0.64$, $\alpha=0.90$) (Isaacs and Kennie, 1973; Oeksengaard et al., 1995), the Trail Making Test, Part A (TMTA) to assess psychomotor speed (construct validity: $-0.58 \leq r \leq -0.34$, test-retest reliability: $r=0.83$) (Corrigan and Hinkeldey, 1987; DesRosiers and Kavanagh, 1987; Kowalczyk et al., 2001), and Trail Making Test, Part B (TMTB) for executive function (construct validity: $-0.77 \leq r \leq 0.27$, test-retest reliability: $r=0.90$).

2.4 Dementia diagnosis

Dementia diagnosis was undertaken completely blinded to the participant's status in terms of lifetime trauma exposure. A preliminary diagnosis of dementia was performed by clinical investigators, according to DSM-IV revised criteria, and took into consideration participants' results on the cognitive measures as described previously (Ryan et al., 2009). Suspected cases of dementia were validated by a national panel of independent neurologists according to DSM-IV Axis 1 criteria (American Psychiatric Association, 1994). Participants with a suspected diagnosis of dementia, were referred to a physician who further monitored the development and symptoms of the disease, independently of their results on the cognitive tests (Ryan et al., 2009). Further sub-classification of possible and probable cases of Alzheimer's disease (AD) and vascular dementia was confirmed according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria, and the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences (NINDS-AIREN) criteria, respectively. Participants with a history of both AD and previously reported strokes were labelled as having mixed dementia (Carcaillon et al., 2014). This process of diagnosing dementia was repeated 6 times, every 2-3 years, at each follow-up across 14 years, with the onset of dementia recorded as the date of diagnosis.

2.5 Sociodemographic, lifestyle and physical health covariates

Participants self-reported a selected range of sociodemographic, lifestyle and physical health factors using a standardised health questionnaire, which was supplemented with additional information from general practitioners. This included age, gender, education level attained (whether individuals had completed secondary school education or not), marital status, alcohol consumption and smoking, history of vascular disease (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, arteritis, bradycardia or palpitations) and chronic illnesses (asthma, hypercholesterolemia (total cholesterol ≥ 6.2 mmol/L), hypertension (resting blood pressure ≥ 160/95 mmHg or treated), thyroid problems, cancer diagnosis in last 2 years, diabetes or fasting glucose ≥ 7.0 mmol/L or reported treatment). The diagnosis of current Major Depressive Disorder (MDD) was determined according to DSM-IV criteria (American Psychiatric Association, 1994) using the Mini-International Neuropsychiatric Interview (MINI) French Version 5.00 (as described previously (Ritchie et al., 2004)). The severity of current depressive symptoms was also assessed using the 20-item inventory: Centre for Epidemiologic Studies-Depression scale (CES-D) (Radloff, 1977), with a cut-off of 16 indicating moderate to severe depressive symptoms. Depression was herein defined as a current diagnosis of MDD or moderate/severe depressive symptoms. Genotyping of the Apolipoprotein E (*ApoE*) gene was performed at a facility in Northern France (Lille Genopole) using fasting blood samples from the participants. The restriction fragment length polymorphism bands were analysed, and positive *ApoE* ε4 status was assigned to participants carrying at least one copy of the *ApoE* ε4 allele.

2.6 Statistical analysis

All analyses were completed using Stata 15 (StataCorp, 2017). Initial analyses were conducted using a two categorical variable, which defined participants as either having experienced lifetime major trauma according to DSM-IV criteria or not. Further investigations were then conducted with a three

group categorical variable; no major trauma versus participants with a lifetime major trauma with or without re-experiencing PTSD symptoms.

To determine the univariate association between lifetime major trauma and low cognition at baseline, univariate logistic regression models were used. A series of multivariate logistic regression models were then used to adjust for age, gender, education, morbidity (presence of at least one of: vascular disease, chronic illness or recent cancer in the last two years) and current depression. Multivariate associations with significant gender interactions were further investigated in a gender-stratified manner to determine any differences between men and women. Results for the univariate and multivariate analyses were presented as odds ratios (95% CI) and P-values.

Survival analysis was performed using a Cox proportional hazards regression model to determine the association between major lifetime trauma and incidence of dementia across a 14-year observation period. The time participants became at risk of dementia was defined as the age at study recruitment (baseline) and the time of failure was defined as the age when participants were diagnosed with dementia or the age at which they were last assessed (censored). Person-years were calculated from the date of baseline examination to the time of dementia incidence/last follow-up visit. To factor in the non-proportional risk of dementia with age, age was used as the time scale and baseline age was used as the time origin, as detailed previously (Ryan et al., 2014).

Univariate analyses were performed initially, followed by multivariate analyses which adjusted for age, gender, and education, and potential gender interactions were investigated. Further adjustments for global cognition (assessed by MMSE cut-off), morbidity, depression, marital status, smoking status, alcohol consumption, and *ApoE* ε4 allele were also considered, to ensure these factors did not confound the associations.

Similar analyses were also conducted investigating the incidence of possible and probable Alzheimer's disease, rather than dementia overall. Results for the univariate and multivariate analyses were presented as hazards ratios (95% CI) and P-values.

3. RESULTS

3.1 Characteristics of study population

Selected characteristics of participants are displayed in Table 1. The majority of participants were women, married, and were generally healthy. Approximately one-third of participants completed at least secondary school education. Participants' ages at baseline ranged from 65 to 96 years, with a right skewed distribution given that 65 years was the minimum age for recruitment to ESPRIT.

Table 1 about here

In ESPRIT the median age at the time of the traumatic event was 25.0 years, and the median duration between exposure to the traumatic event and administration of the PTSD-I was 54.6 years. The frequency of lifetime and current PTSD were 2.4% and 1.2% respectively (Chaudieu et al., 2011). The lifetime prevalence of PTSD in French adults has previously been reported as 3.9% (Husky et al, 2015), thus a higher rate was expected in this older cohort, due to the possibility of increased exposure to traumatic life events. As a result of the low number of participants with a clinical diagnosis of PTSD, the study was underpowered to examine this exposure. Therefore, this this study focused on the secondary aim, analysing individuals who had experienced a major lifetime trauma with or without re-experiencing symptoms.

Approximately half of participants (54.3%) had experienced a lifetime major trauma that met PTSD criterion A1 in DSM-IV (Table 2), with 16.8% reporting a history of having re-experiencing symptoms following the event, and 37.5% who did not. Of the participants exposed to a major trauma, the majority were men (58.4%), however almost twice as many women reported re-experiencing symptoms, than men (20.3% vs 11.8%) (Tables 3 and 4).

3.2 Association between trauma and cognitive function

In comparison to no trauma exposure, lifetime major trauma was associated with a 21% decreased risk of low global cognition (OR: 0.79, 95% CI: 0.63-0.98, p=0.03), and a 30% decreased risk of low executive function (OR: 0.70, 95% CI: 0.55-0.91, p=0.007) in the univariate analysis (Appendix A.1).

The study had over 80% (alpha 0.05) to detect an odds ratio of 0.70 for lowest quintile of cognitive decline, comparing individuals with and without trauma.

When age, gender, education, morbidity and depression were adjusted for in the models, these associations remained, yet decreased in significance (particularly with global cognition) (global OR: 0.83, 95% CI: 0.67-1.04, p=0.11; executive OR: 0.72, 95% CI: 0.55-0.94, p=0.01) (Table 2). When a three categorical variable was examined, a significant association was observed with these two cognitive domains, even after adjustment, but only in those without re-experiencing symptoms (Table 2). Indeed, compared to participants without lifetime trauma, trauma without re-experiencing symptoms was associated with a more than 30% decreased risk in low global cognition (OR: 0.67, 95% CI: 0.52-0.87, p=0.002) and low executive function (OR: 0.69, 95% CI: 0.51-0.93, p=0.01). Non-significant trends were also observed for higher visual memory and verbal fluency.

Table 2 about here

There was evidence that some of these associations were modified by gender ($p<0.05$ for interaction terms), so gender-stratified analysis was undertaken (Table 3). In a multivariate model, men with lifetime trauma had a 39% decreased risk of low global cognition (OR: 0.61, 95% CI: 0.42-0.88, p=0.008), and more specifically, a 43% reduced risk in men without re-experiencing symptoms (OR: 0.57, 95% CI: 0.38-0.84, p=0.005). Women without re-experiencing symptoms had no significantly decreased risk of low global cognition, but this was not statistically significant. In contrast, in women with re-experiencing symptoms, there was a 46% increased risk of low global cognition (OR: 1.46, 95% CI: 1.03-2.09, p=0.04) (but no significant association was observed in men with re-experiencing symptoms).

Table 3 about here

3.3 Association between trauma and incident dementia

After 14 years there were 164 (9.7%) incident cases of dementia, with 103 (62.8%) of these women. The total time at risk was 17,306.9 years, and the average years from baseline to the diagnosis of

dementia was 10.18 years. The most frequent dementia sub-classification was probable Alzheimer's disease (AD), 40.9% of all dementia cases, followed by possible AD (19.5%) and mixed dementia (15.2%).

There was no significant association between lifetime trauma overall, versus no trauma, and the incidence of dementia in unadjusted (Appendix B.1) and adjusted models (Table 4). Gender was not a significant effect modifier of this association (p=0.24), although in stratified analysis, women experiencing trauma had a 35% decreased risk of dementia compared to individuals without severe trauma (HR: 0.65, 95% CI: 0.43-0.96, p=0.03).

Using a three group categorical variable which separated trauma into those with re-experiencing symptoms or not, there was a 37% decreased risk in the incidence of dementia amongst those who had lifetime trauma without re-experiencing symptoms, at the unadjusted level (HR: 0.63, 95% CI: 0.44-0.91, p=0.01) (Appendix B.1), and when adjusting for age, gender, education, global cognition, morbidity and depression (HR: 0.63, 95% CI: 0.43-0.90, p=0.01) (Table 4). On the other hand, there was no significant difference in dementia risk between individuals exposed to trauma with re-experiencing symptoms and individuals without lifetime trauma. Gender was an effect modifier of these associations (p=0.04); only women without re-experiencing symptoms had a 51% decreased incidence of dementia compared to non-trauma exposed women (HR: 0.49, 95% CI: 0.29-0.80, p=0.005) (Table 4). This finding remained when adjusting for other potential confounding factors (marital status, smoking status, alcohol consumption, *ApoE* ε4 allele, diabetes) (HR: 0.51, 95% CI: 0.30-0.87, p=0.01)

Table 4 about here

Probable or possible Alzheimer's disease was the most common dementia sub-classification, thus this group were also investigated separately. No significant associations were found between trauma exposure and the incidence of probable/possible Alzheimer's disease (Appendix B.2).

4. DISCUSSION

4.1 Main findings

This study investigated the association between lifetime major trauma exposure, cognitive functioning, and dementia, considering whether an individual had re-experiencing PTSD symptoms, and their gender. The novel, yet consistent results shown here, suggest that in some circumstances, trauma may be associated with increased later-life cognitive function and reduced incident dementia in older community dwelling individuals. Overall, lifetime trauma *without* re-experiencing symptoms was associated with a 31% decreased risk of low executive function (OR: 0.69, 95% CI: 0.51-0.93, p=0.01), 43% decreased risk of low global cognition in men (OR: 0.57, 95% CI: 0.38-0.84, p=0.005), and a 51% decreased risk of incident dementia across a 14-year observation period in women (HR: 0.49, 95% CI: 0.29-0.80, p=0.005), in comparison to individuals without lifetime trauma. However, findings pertaining to lifetime trauma *with* re-experiencing symptoms revealed a 46% increased risk of low global cognition in women (HR: 1.46, 95% CI: 1.03-2.09, p=0.04). These findings are also supported by prior work with the ESPRIT cohort which showed an increased risk of psychiatric disorders, as well as other comorbidities such as hypertension and thyroid dysfunction only in individuals *with* re-experiencing symptoms versus no trauma (Chaudieu et al., 2011). In addition, they showed an association between lifetime major trauma and a higher rate of cardio-ischemic diseases. Importantly in the analysis shown here however, the associations persisted even after accounting for these factors.

4.2 Comparison to previous literature

There have been several recent studies which have sought to address the relationship between PTSD and dementia in older people, mainly in male dominated veteran populations. All but two of these studies (Roughead et al., 2017; Weiner et al., 2017) found that older veterans with PTSD, compared to those without PTSD, had a two-fold increased risk of dementia (Mawanda et al., 2017; Qureshi et al., 2010; Yaffe et al., 2010). Similar positive trends were also observed in the only two civilian-based studies identified; men and women from a national health insurance database in Taiwan (Wang et al., 2016), and members of a large integrated healthcare delivery system in Northern California (Flatt et

al., 2018). Both of these studies used a physician's diagnosis of PTSD within a limited period of 5-8 years, obtained from electronic medical records. As a result, these studies had a relatively low number of participants with PTSD, which is as expected in a community-based sample. In comparison, the present study used a self-report questionnaire to capture a wider range of participants who not only have a formal diagnosis of PTSD, but have also reported re-experiencing symptoms at any point during the lifespan. In addition, both studies based their diagnoses of PTSD and dementia according to International Classification of Diseases, Ninth Revision (ICD-9) codes, which are less sensitive and more prone to reporting bias than the DSM-IV used in this study (Aboraya et al., 2006). This may have resulted in misclassification of outcome diagnosis.

4.3 Gender differences

It is important to also acknowledge the gender differences in the present results. Despite there being very limited studies assessing PTSD and dementia in women, the studies identified all reported a positive association (Flatt et al., 2018; Wang et al., 2016; Yaffe et al., 2019). Amongst these studies include the aforementioned civilian studies conducted in Taiwan and Northern California (which were both predominantly female participants), in addition to a large cohort study of older female veterans by Yaffe *et al* 2019 which reported a 78% increased risk of dementia in women with PTSD (versus women without PTSD) (HR: 1.78, 95% CI: 1.34–2.36) (Yaffe et al., 2019). The present study found significant associations predominantly in women rather than men. These were in a similar direction to that of past literature for global cognition at baseline, but a reversed direction in terms of dementia incidence. These gender differences may be driven by biological, social and/or behavioral differences in how men and women respond to PTSD (Tekin et al., 2016). Relatively few studies have yet explored the biochemical differences in how men and women respond to chronic stress, but there is some evidence to suggest interplay with systems regulating the stress response (hypothalamic-pituitary-adrenal (HPA) axis) and sex hormones (hypothalamic-pituitary gonadal (HPG) axis) (Oyola and Handa, 2017).

4.4 Biological mechanisms supporting hypothesis

There are several theories which have been proposed to explain the biological mechanisms as to how lifetime major trauma and chronic stress could be a risk factor for dementia. Chronic stress is associated with an increase in reactive oxygen species and neuroinflammation, which may promote increased deposition of brain amyloid and neuronal death, which are typical neuropathologies of AD (Greenberg et al., 2014). In addition, chronic stress results in dysregulation of the HPA axis, and abnormal secretion of the primary stress hormone cortisol, which may lead to structural brain changes including decreased hippocampal and prefrontal cortex volume (McEwen et al., 2016). There is some evidence to suggest that the association between stress and dementia may be mediated by genetics. Within the ESPRIT cohort, major trauma with re-experiencing symptoms has been associated with lower cortisol levels and an increased stress response in the evening, although this was also driven by underlying genetic vulnerability (Ancelin et al., 2017). Nievergelt *et al* 2019 demonstrated that a polygenic risk score for PTSD also predicted re-experiencing symptoms in a veteran cohort (Nievergelt et al., 2019). There is also some evidence of common genetic vulnerability underlying both PTSD and neurodegenerative diseases. For example, Nievergelt *et al* 2019 also found that evidence for several genetic loci associated with PTSD in large multiethnic cohorts, including *PARK2* and *SH3RF3*, which are also associated with neurodegenerative disease, i.e. Parkinson's Disease and dementia respectively. There is also previous evidence to suggest that epigenetic mechanisms, such as DNA methylation, may influence regulation of the stress response (Wrigglesworth et al., 2019). As it has been previously reported that the median duration between trauma exposure and administration of the PTSD-I is 54.6 years, stable changes in DNA methylation may help explain the association between severe lifetime trauma and cognitive function in later-life, many decades after the initial exposure has occurred (Ryan et al., 2016).

4.5 Novel findings

A novel finding of this study involves the decreased risk of low cognition and incident dementia in individuals with lifetime major trauma *without* re-experiencing symptoms. A potential explanation for

these results may be due to the process of posttraumatic growth, which is the process of self-development following extreme trauma, including re-evaluation of core beliefs, to attain a heightened level of functioning than prior to experiencing the event (Tedeschi and Calhoun, 1996). In comparison, resiliency does not focus on psychological transformation, and rather a constant trajectory of healthy functioning across time in response to trauma (Bonanno et al., 2011).

Within this process of posttraumatic growth, cognitive rebuilding may occur to cause a shift in thinking, and more positive psychological change, which often includes an appreciation for smaller details in life (Malhotra and Chebiyan, 2016). The process of cognitive rebuilding is not well understood, however limited studies suggest that this process may improve cognitive function. One study by Anders *et al* (Anders et al., 2015) found a positive association between self-reported posttraumatic growth in veterans without PTSD and neural network decorrelation, the process of a neural network being freed from a particular input (e.g. intrusive thoughts following a traumatic event) so it is able to encode new information. Decorrelation may be most prominent in the prefrontal cortex (Rossi et al., 2009), thus the process of breaking and building neural connections in this region may be protective against structural brain changes associated with dementia pathology (McEwen et al., 2016). Another possible explanation could be the level of social engagement, which was not taken into consideration in our analyses. Several studies have indicated that the presence of social support from the community is associated with resilience and increased PTSD recovery, and a decreased level of social support may be an important risk factor for the disorder (Clapp and Gayle Beck, 2009). Undergoing a traumatic event may have prompted participants to reach out to members of their community for support, who in turn may have provided resources to resist and not develop PTSD symptoms, and thus had a positive impact on their cognition. Several epidemiological studies have suggested that the cognitive stimulation involved in complex social interactions may increase neural connectivity, and subsequently protect individuals from neuropathology associated with dementia and cognitive decline (Holwerda et al., 2014). However, it is also important to note that increased psychosocial support is also associated with an increase in self-reported posttraumatic growth, thus

having a greater support network may also play an important role in the growth process (Roepke, 2015).

4.6 Strengths, limitations and future directions

There are several strengths which should be acknowledged in this study, including the large sample size, longitudinal design across 14 years, and a validated dementia diagnosis. Unlike similar studies in civilian general populations, the present study also used a validated questionnaire based on DSM-IV criteria to identify individuals with lifetime major trauma rather than relying on medical records. In addition, this study also distinguishes the effects of trauma exposure from symptom expression, by capturing individuals with re-experiencing symptoms.

There are also several limitations to consider. Firstly, both PTSD and dementia observe similar structural changes to the brain such as hippocampal and prefrontal cortex atrophy (Greenberg et al., 2014). It is not yet determined if structural changes in both conditions are due to common risk factors. This study adjusted for some known risk factors e.g. low education levels and health factors (Livingston et al., 2017), however there likely remains residual confounding and a causal link cannot be determined. It is also important to note that stronger associations with diagnosable PTSD as the exposure may have been observed, had this study not been limited by the lack of power due to the low number of PTSD diagnoses. Had a formal diagnosis of PTSD been used as an outcome, this study may have observed similar results to previous studies, with stronger evidence to suggest that PTSD may increase the risk of dementia in later-life (Flatt et al., 2018; Wang et al., 2016; Yaffe et al., 2019). In addition, this study was conducted with a French population of European of West Asian ancestry, thus the extent to which these findings could apply to other populations is uncertain. As dementia is a global issue, these findings are likely to be generalizable to other geriatric populations, in particular those of similar ancestry to the study's sample. However, it is important to note that there is a need to better understand risk factors for dementia onset in more diverse populations. In particular, it would be beneficial to explore similar associations in low-income and middle-income countries (i.e. countries in Latin America and Africa), as the majority of research pertaining to dementia risk factors

occurs in high-income countries (Ferri and Jacob, 2017). In addition, dementia prevalence is increasing in low-income and middle-income countries, thus highlighting the need for further research within these populations.

Furthermore, there are limitations in using self-report questionnaires and retrospective data. This includes recall bias, as the median duration between trauma exposure and administration of the PTSD-I was greater than 50 years, which may lead to an underestimation of the associations discussed. It has also been suggested that people who are less satisfied with their life in adulthood, may overestimate the number of stressful events during their earlier life and childhood (Susser and Widom, 2012). Survival bias should also be considered, as individuals with the most severe forms of trauma may be underrepresented in an older cohort, given the link between stress/trauma and premature mortality (Johnson et al., 2020). In addition, this study may have been impacted by recruitment bias, due to over-recruiting participants who are less likely to develop trauma-related disorders, e.g. more optimistic individuals. Future studies could consider using prospective data from longitudinal cohort studies. In addition, the biological mechanisms as to how trauma in resilient participants may improve cognition is yet to be determined, however this study suggests that gender may have a role. Further research into these mechanisms may not only improve psychotherapy available for PTSD, but also benefit later-life health.

This study presented findings supported by pre-existing literature, in addition to novel findings. Lifetime major trauma without re-experiencing symptoms was associated with higher later-life cognitive performance and a reduced incidence of dementia. Some hypotheses have been postulated to help account for these findings but no direct causal relationships can be ascertained from this analysis. This study will provide the basis of future research which includes investigating in more detail the association between lifetime major trauma without re-experiencing symptoms and increased later-life cognition/reduced dementia risk, as well as potential biological mechanisms mediating this relationship.

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Table 1: ESPRIT sample characteristics at baseline (n = 1700*)

		Mean (±SD)
Sociodemographic	Age, y 65-96	72.63 (5.22)
		%(n)
	65-69	33.00 (561)
	70-79	56.06 (953)
	80-89	10.41 (177)
	90-99	0.53 (9)
	Female gender	59.00 (1,003)
	Married	68.16 (1,158)
	Completed at least secondary school education	35.65 (606)
Lifestyle	High alcohol consumption (≥ 24 grams per day)	18.14 (302)
	Ever smoking (>1 pack years)	41.27 (690)
Physical health	Morbidity (vascular disease[†] and orchronic illness[‡])	17.53 (298)
	Diabetes	8.42 (142)
Genetic	*ApoE* ε4 allele	19.07 (320)
Psychological	Major Depressive Disorder/severe depressive symptoms [§]	28.26 (477)

* Marital status had 1 missing participant. Current MDD/severe depressive and diabetes had ≤ 13 missing participants. Smoking status and ApoE ε4 allele had ≤ 28 missing participants. Alcohol consumption had 35 missing participants.

[†] Vascular disease defined as answering 'yes' to at least one of the following: angina pectoris, myocardial infarction, stroke, cardiovascular surgery, bradycardia or palpitations.

[‡] Chronic illness defined as answering 'yes' to at least one of the following: asthma, hypercholesterolemia (total cholesterol ≥ 6.2 mmol/L), hypertension (resting blood pressure ≥ 160/95 mmHg or treated, thyroid problems, cancer diagnosis in last 2 years, diabetes or fasting glucose ≥ 7.0 mmol/L or reported treatment.

[§] Severe depressive symptoms defined by Centre for Epidemiologic Studies Depression scale >=16

Table 2: Adjusted association* between lifetime major trauma, with and without re-experiencing symptoms and low cognition† at baseline

		Global (MMSE) *n* = 1,680		Visual memory (BVRT) *n* = 1,676		Verbal fluency (IST) *n* = 1,658		Psychomotor speed (TMTA) *n* = 1,664		Executive function (TMTB) *n* = 1,619	
	Freq.	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	
No trauma (ref.)	45.71	1.00		1.00		1.00		1.00		1.00	
Lifetime major trauma	54.29	0.83 (0.67-1.04)	0.11	0.87 (0.68-1.11)	0.25	0.88 (0.69-1.13)	0.32	1.04 (0.79-1.35)	0.80	0.72 (0.55-0.94)	0.01
No trauma (ref.)	45.71	1.00		1.00		1.00		1.00		1.00	
Trauma without re-experiencing symptoms	37.47	0.67 (0.52-0.87)	0.002	0.78 (0.59-1.02)	0.07	0.79 (0.60-1.04)	0.10	0.89 (0.66-1.21)	0.46	0.69 (0.51-0.93)	0.01
Trauma with re-experiencing symptoms	16.82	1.22 (0.91-1.65)	0.19	1.07 (0.77-1.49)	0.68	1.09 (0.78-1.52)	0.61	1.35 (0.95-1.91)	0.10	0.78 (0.54-1.14)	0.20

*Results adjusted for age, gender, education, morbidity and depression (X^2, *d.f.*=1).

†Low cognition as measured by ≤ 26 Mini Mental State Examination (MMSE), ≤ 10 Benton's Visual Retention Test (BVRT), ≤ 40 Isaacs' Set Test (IST)l, ≥ 65 Trail Making Test Part A (TMTA), ≥130 Trail Making Test Part B (TMTB).

Table 3: Gender-stratified association* between lifetime major trauma, with and without re-experiencing symptoms and low global cognition at baseline[†] (*n* = 1,680)

		Males *n* = 688			Females *n* = 992		
	Gender interaction *P*	Freq.	OR (95% CI)	*P*	Freq.	OR (95% CI)	*P*
No trauma (ref.)	0.04	41.61	1.00		48.55	1.00	
Lifetime major trauma		58.39	0.61 (0.42-0.88)	0.008	51.45	1.01 (0.76-1.33)	0.97
No trauma (ref.)	<0.001	41.61	1.00		48.55	1.00	
Trauma without re-experiencing symptoms		46.63	0.57 (0.38-0.84)	0.005	31.11	0.75 (0.54-1.05)	0.10
Trauma with re-experiencing symptoms		11.76	0.77 (0.43-1.39)	0.39	20.34	1.46 (1.03-2.09)	0.04

*Results adjusted for age, education, morbidity and depression. (X^2, *d.f.*=1).
[†]Low global cognition as measured by ≤ 26 Mini Mental State Examination (MMSE)

Table 4: Adjusted association* between lifetime major trauma, with and without re-experiencing symptoms and incidence of dementia (n = 1,700)

				Males n = 688			Females n = 992		
	HR (95% CI)	*P*	Gender-interaction *P*	Freq.	HR (95% CI)	*P*	Freq.	HR (95% CI)	*P*
No trauma (ref.)	1.00			41.61	1.00		48.55		
Lifetime major trauma	0.77 (0.56-1.05)	0.10	0.24	58.39	1.04 (0.61-1.77)	0.89	51.45	0.65 (0.43-0.96)	0.03
No trauma (ref.)	1.00		0.04	41.61	1.00		48.55	1.00	
Trauma without re-experiencing symptoms	0.63 (0.43-0.90)	0.01		46.63	0.90 (0.51-1.60)	0.72	31.11	0.49 (0.29-0.80)	0.005
Trauma with re-experiencing symptoms	1.06 (0.72-1.58)	0.76		11.76	1.60 (0.77-3.31)	0.21	20.34	0.88 (0.55-1.42)	0.61

*Results adjusted for age, gender and education, global cognition, morbidity and depression. (X^2, *d.f.*=1).