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The extent to which childhood adversity and recent stress influence all-cause mortality risk in older adults

Running title: Stress and mortality among older adults

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ABSTRACT

Background: Psychological stress is recognized as a major risk factor for a range of non-communicable diseases and possibly mortality. The extent to which the type and timing of stress exposure influences mortality, and potential differences between genders, remains unknown.

Objective: To examine the association between early-life and recent stressful experiences and mortality risk in later life, and to determine possible gender differences in these associations.

Method: Data were obtained from 2152 French community-dwelling participants (aged ≥65). Questionnaires were used to evaluate recent stress, as well as retrospective reporting of childhood adversity. Mortality status was determined through death registries. Adjusted Cox proportional hazards models were used to determine the association between stress and 16-year mortality risk.

Results: Over a mean 12.9 years, 850 people died. Having a childhood home environment with very serious conflicts was associated with a 54% increased mortality risk (95%CI:1.21-1.96), and childhood abuse/maltreatment with a 34% increased risk (95% CI:1.05-1.70). For females, specific childhood events (serious illness HR:1.91, 95%CI:1.40-2.60; war/natural disaster HR:1.47, 95%CI:1.14-1.88) and the number of events (≥5 adverse events HR:1.91, 95%CI:1.25-2.32), also increased mortality risk. In terms of recent events, mortality risk increased by 66% (95%CI:1.39-2.00) in participants reporting a recent serious illness or physical trauma and by 86% for those reporting problems with the police/justice (95%CI:1.05-3.30). Among males specifically, mortality risk also increased with major financial problems (HR:1.92, 95%CI:1.14-3.21), and when they had a relative with a serious illness (HR:1.26, 95%CI:1.01-1.55).

Conclusions: Stressful life experiences are associated with all-cause mortality however the associations varied between early-life adversities and recent stress, and were different across the genders. Among females, certain types of childhood adversity continue to predict mortality risk in later life, while in males specific recent stress significantly increased mortality risk.

Key words: Mortality, Stress; Early-life adversities; Gender-specific

1. INTRODUCTION

Psychological stress is commonly defined as mental or emotional strain in response to adverse circumstances that exceed an individual's adaptive capacity. It is normally accompanied by cognitive and behavioral changes, as well as a cascade of physiological events enabling the individual to rapidly deal with the situation (McEwen, 2002). Two endocrine systems are particularly responsive to stress. Activation of the sympathetic-adrenal-medullary system causes release of catecholamine which helps regulate the cardiovascular, immune and respiratory systems. Glucocorticoids (e.g. cortisol) are the end product of hypothalamic-pituitary-adrenal (HPA) axis signaling and influence a broad range of physiological processes, including metabolic functioning and the immune system (de Kloet et al., 2005). While under normal conditions activation of these systems is beneficial, excessive or prolonged stress can result in dysregulation of the stress response system and is maladaptive (Schneiderman et al., 2008), resulting in adverse biological effects on the body and brain (McEwen, 2017). Indeed, abnormal cortisol secretion and blunted cortisol response has been reported following early-life stress (Dong et al., 2004a), and in adults with chronic post-traumatic stress disorder (Olff et al., 2006). It is now clear that excessive or prolonged stress could be an important contributing risk factor for a range of diseases (Cohen et al., 2007).

Major stress such as illness, unemployment and relationship breakdowns have been shown to trigger first depressive episodes (Paykel, 2001) and may be causal for the onset of depression (Schneiderman et al., 2008). HPA-axis dysfunction may even be a permanent trait of depression (Beluche et al., 2009).

A number of studies have reported that excessive stress is a major risk factor for a range of non-communicable diseases (NCDs) (Fricchione, 2018), including cardiovascular disease (Brotman et al., 2007; Orth-Gomér et al., 2000), metabolic syndrome (Rutters et al., 2015) and metabolic disorders, such as obesity (Peters and McEwen, 2015) and diabetes (Marcovecchio and Chiarelli, 2012). Chronic or severe stress interferes with appropriate regulation of inflammation (Cohen et al., 2012) and has

been associated with inflammatory diseases (Caspi et al., 2007). Stress-related psychosocial factors can also have adverse effects on cancer incidence and survival (Chida et al., 2008).

Given these findings, it is surprising that only a few studies have investigated the association between stress and mortality risk. A large study in Sweden examined the impact of financial stress in 60-year old men and women and found that it was associated with increased incident CVD and all-cause mortality, particularly in men (Carlsson et al., 2014). In a Danish study of middle aged men that was focused on job loss and relationship break-downs, a weak increase in the number of fatal and nonfatal ischemic heart diseases events was observed in association with broken partnerships (Kriegbaum et al., 2008). A study of 2385 participants with a mean age of 62 years investigated the total number of stressful life events, and found an association with an increased risk of all-cause mortality (Rutters et al., 2014). However, these studies have been somewhat limited in scope, and other stress-related experiences have not been examined. Furthermore, the early-life environment is thought to play a critical role in later disease risk. Adverse experiences in early-life may have a particularly detrimental effect and could lay the foundations for increased susceptibility and sensitivity to stress occurring at a later stage (Charmandari et al., 2012). Indeed, exposure to severe and chronic stressors during the developmental years is thought to disrupt the potentially adaptive response to stress (Caspi et al., 2007) and mounting evidence suggests that early-life stress could increase the risk of a range of health problems (e.g. autoimmune disease, CVD, depression, diabetes, hypertension) which can persist into adulthood (Dong et al., 2004b; Dube et al., 2009; Goodwin and Stein, 2004; Ritchie et al., 2004).

Another area which has been insufficiently investigated is the potential for gender-specific effects of stress, despite clear evidence of gender differences in how the brain responds to stress (McEwen, 2017). Gender is an important determinant in health, and there is a clear pattern for the gender-specific prevalence rates of many NCDs (Gobinath et al., 2014; Mathers et al., 2001). Sexual dimorphic responses to stress and immune and inflammatory reactions have also been shown, with females exhibiting more robust responses (Chrousos, 2010). In animal models sex-specific effects of

early-life stress on behavioural, mental and cognitive outcomes have been demonstrated (Bath et al., 2017; Goodwill et al., 2019). The effects of sex hormones are thought to explain some of these differences, however, social and cultural factors can also result in different cognitive and adaptive processes between men and women (Chrousos, 2010). Despite this, very few studies have yet assessed the influence of gender on the relationship between stress and mortality.

The aim of this study was to examine the association between stressful life experiences, specifically early life adversity and recent stress, and 16-year mortality risk in older individuals. Possible gender differences in these associations were also explored.

2. MATERIAL AND METHODS

2.1 Study population

The data are derived from the ongoing longitudinal ESPRIT study (Enquete de Sante Physchologique – Risques, Incidence et Traitement). A specific aim of the ESPRIT study was to investigate the prevalence and risk factors for late-life psychiatric disorder in non-institutionalised Caucasian elderly aged 65 years and over. Each participant was randomly recruited from electoral rolls in the Montpellier district, France (Ritchie et al., 2004). Where an individual was not willing and able to participate, a further participant was randomly selected from the same electoral division in order to maintain a representative sample. The ESPRIT study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicetre. Further details of the ESPRIT study have been reported elsewhere (Ritchie et al., 2004; Ritchie et al., 2009). Of the 2268 participants recruited to the study, nine were lost to follow-up and 107 had not completed the recent adverse life questionnaire. This left 2152 participants for the analysis of whom 1579 provided a measure of childhood adversity.

Compared with the analysed sample, those not included in the analysis were less likely to have completed at least secondary school (24.3% vs. 33.4%, p=0.05), were slightly older (mean 74.4 vs. 73.3 years, p=0.05) and were more likely to have died during follow up (52.3% vs. 39.5%, p=0.01). However, there was no significant difference in terms of gender, living alone, chronic conditions, cancer, alcohol consumption, smoking status and the prevalence of depression, ischemic pathologies and obesity (in all cases p>0.05).

Compared to the 1579 participants having provided a measure of childhood adversity, those with missing data were less likely to have completed at least secondary school (27.43% vs. 35.04%, p<0.001), were slightly older (mean 75.00 vs. 72.59 years, p<0.001) and were more likely to be obese (11.09% vs.7.82%, p=0.01), have ischemic pathologies (21.18% vs. 13.30%, p<0.001) chronic conditions (43.97% vs. 36.16%, p<0.001) and to die during follow up (56.18% vs. 33.19%, p<0.001). There was, however, no significant difference with respect to gender, depression, anxiety, living alone, recent cancer, alcohol consumption and smoking status (in all cases p>0.05).

2.2 Measures

Written and verbal consent was obtained for all investigations. Participants underwent a baseline examination and were re-examined a further six times at two-year intervals. At baseline and each follow up, participants attended a half-day examination by a neurologist and interviewer (nurse or psychologist) at the Gui de Chauliac Neurology Hospital (Montpellier, France). During examinations, participants underwent a standardised health interview, neurological examination and psychiatric interview at baseline, and responded to a childhood environment questionnaire at the second follow up. Measures used in this analysis are outlined below.

2.2.1 Childhood adversity questionnaire

A retrospective self-report questionnaire assessing adverse experiences during ‘childhood’ was administered at the second follow up (four years after recruitment). This allowed study interviewers

time to establish close relationships with the individuals to facilitate the gathering of sensitive information (Ritchie et al., 2009). Participants were also given an opportunity to discuss the content of the questionnaire with interviewers.

The questionnaire was developed based on a review of existing validated instruments containing 25 adverse and eight protective experiences. The majority of questions had yes/no responses. Full details about each of the questions has been published previously (Ritchie et al., 2009).

The nine individual adverse experiences considered in this study were those which could be classified as moderate-to-severe, for example physical/sexual abuse, severe illness, death or illness of parents, poverty, war or natural disaster. A combined variable 'abuse/maltreatment' was also examined, which included at least one of the following nine experiences: neglect, verbal abuse from parents, humiliation, harassment, mental cruelty, physical/sexual abuse and excessive physical punishment for misbehaviour. A summary variable was created for the total number of childhood adversity experiences, and a three-category variable generated for the analysis. Cut-offs were based on the distribution, such that approximately equal numbers of participants were in each of the three groups.

Protective experiences included maternal and paternal affection, availability of an adult friend, impression of having had a happy childhood, parents perceived as doing their best, feeling happy at school, and having been raised by both parents. For the analysis, we created a composite variable by summing the responses to the eight positive items (paternal affection, maternal affection, raised by both parents, parental support, support of other adults, happy childhood and school environment and a normal education), and then created a binary variable for individuals with five or fewer positive responses.

2.2.2 Recent stress

The standardised health interview at baseline assessed exposure to stressful life events in the past two years using the Gospel Oak Life Events Schedule (Harwood et al., 1998). This schedule listed 12-

items of major stressful life events including illness, bereavement, breakdown of close relationships, severe illness and serious financial or judicial problems. One item, 'Professional Dismissal' was not considered here as too few participants (0.3%) experienced this. A summary variable was created as the total number of experiences excluding physical illness (which is a risk factor for mortality beyond the potential effect of stress). A three-category variable was generated with cut-offs based on the distribution, such that approximately equal numbers of participants were in each of the three groups.

2.2.3 Mortality

All-cause of mortality was the primary outcome of this analysis. The follow-up time for this analysis was 16 years with a median follow up of 12.9 years. For the participants who died during this period, information on the exact date was determined respectively from medical records and death registries, as detailed previously (Carriere et al., 2013; Ryan et al., 2008).

2.2.4 Other characteristics

At baseline, information was collected on participants' health, individual and family medical history, medication use and socio-demographic and lifestyle characteristics. The Mini International Neuropsychiatric Interview (MINI, French version 5.00) was used to diagnose major depressive disorder and anxiety disorders, according to DSM-IV criteria (as described previously (Ritchie et al., 2004)). Cases identified by the MINI were reviewed by an international panel of three psychiatrists and a psychologist, to validate the initial diagnosis (Ancelin et al., 2017). A detailed interview was used to obtain information on history of ischemic pathologies (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, arteritis, vascular disease), chronic conditions (high blood pressure, high cholesterol, diabetes, thyroid problems, asthma), recent cancer, body mass index

(BMI, kg/m^2), smoking status (pack years), education level, living situation (alone versus with others) and age (continuous).

2.3 Statistical analysis

All statistical analyses were performed using Stata 15.1 (StatCorp, College Station, TX). Binary variables were created to define obesity (BMI≥ 30 kg/m^2), completed at least secondary school education (yes/no), chronic conditions (≥ 1 chronic condition), high consumption of alcohol (≥ 24 grams per day) and smoking status (>10 pack years).

Descriptive statistics were used to describe the frequencies or means (±SD) of baseline characteristics. Cox proportional hazards regression models were used to determine the hazard ratio (HR), 95% confidence interval (CI) and P-values for the association between stressful experiences and mortality. To avoid the problem of non-proportionality in mortality risk with age, age was used as the time scale and baseline age was used as the time origin (Thiébaut and Bénichou, 2004).

The first step of the analysis involved investigating each of the stress experiences individually, in models adjusted for age, education and gender. Step 2 of the analysis was to consider the stressful experiences from step 1 together in the one model, to determine if they remained significantly associated with mortality risk. The potential effect modification of gender (e.g. gender specific effects of the association between stress and mortality) was then investigated by including an interaction term in the models (step 3). Where appropriate (interaction p-value ≤0.10), gender-stratified analyses were then performed to determine any differences between males and females (step 4)

Finally, additional multivariable analysis was also carried out to determine the extent to which other factors could help account for these associations. Anxiety, depression, ischemic pathologies, chronic

conditions, recent cancer and obesity could all be considered to be on the causal pathway from stress to mortality, and thus as mediators, rather than confounders of this association. As such, we adjusted for these covariates post-hoc, as well as living alone, to determine their effect on the associations reported.

3. RESULTS

3.1 Participant characteristics

Selected sociodemographic, lifestyle and clinical characteristics of the 2152 participants included in the analysis are reported in **Table 1.** Participants ranged in age from 65-96, with a mean age of 73.3 (SD 5.7) years. Over the 16-year follow up period, there were 850 deaths (446 males and 404 females).

3.2 Association between adverse experiences during childhood and mortality

Four individual adverse experiences during childhood were significantly associated with mortality in age, education and gender-adjusted analysis (**Table 2** and **Figure 1**). Childhood abuse/maltreatment, serious childhood illness and war/natural disaster increased mortality risk by 34%, 47%, and 25%, respectively. Participants who experienced very serious conflicts at home in childhood also had a 54% increased risk of mortality. A higher number of adverse childhood experiences was also associated with increased mortality risk (**Table 2**). Compared to individuals with 0-2 adverse experiences, participants with five or more adverse experiences had a 38% increased risk of mortality

Investigating the possibility of gender-specific associations, there was some evidence of potential interaction for two of the experiences and the total number of experiences, which were subsequently found to only be significant for females. The risk of mortality was 91% higher among

female participants who experienced serious childhood illness and 47% higher for experiencing war/natural disaster.

Based on the significant findings in Table 3, we then examined whether further adjustment for chronic conditions, current anxiety and depression, ischemic pathologies, recent cancer, obesity and living alone, influenced the association between childhood adversity and mortality. In the overall sample, abuse/maltreatment (HR=1.23, 95% CI: 0.93, 1.63, p=0.14) and serious childhood illness (HR=1.32, 95% CI:1.00, 1.74, p=0.05) were no longer significantly associated with mortality risk, but very serious conflicts at home (HR=1.48, 95% CI: 1.12, 1.95, p=0.006) and the overall number of experiences were (HR=1.32, 95% CI:1.03, 1.70, p=0.03). Likewise, in females, the three significant associations remained, even after adjustment for additional lifestyle and health factors (serious childhood illness HR=1.76, 95% CI: 1.20, 2.59, p=0.004; war/natural disaster HR=1.36, 95% CI:1.02, 1.82, p=0.04; ≥5 experiences HR=1.56, 95% CI: 1.10, 2.23, p=0.01).

3.3 Association between recent stressful events and mortality

Table 3 reports results from the Cox proportional hazards model for the association between recent stressful experiences and mortality adjusted for age, gender and education level. The risk of mortality was increased by 66% in participants who experienced a recent serious illness or physical trauma and by 86% in individuals who reported problems with the police or justice. When these two stress experiences were included in the same model, serious illness remained significantly associated with an increased risk of mortality (HR=1.65, 95% CI: 1.37, 1.98, p<0.001), however problems with the police/justice was no longer significant (HR=1.67, 95%CI: 0.94, 2.96, p=0.08).

The next step involved gender-stratified analysis where there was some evidence of gender-specific associations. For both males and females, serious illness/physical trauma was significantly associated with the risk of mortality, however it was stronger for males compared to females (90% vs. 45% increase risk) (**Table 3**). No other significant associations were observed for females. However

among males, the risk of mortality was also increased by 92% in participants who experienced major financial problems, and by 26% in individuals who had a relative with a serious illness. When combining these three significant experiences together in the one mode, both serious illness or physical trauma (HR:1.86, 95% CI: 1.44, 2.40, p<0.001), and major financial problems (HR: 1.75, 95%CI: 1.03, 2.95, p=0.04) remained significantly associated with mortality risk, but serious illness of a relative did not (HR=1.19, 95% CI:0.96, 1.47, p=0.11).

Based on the significant findings in Table 3, we then examined whether further adjustment for other characteristics, including chronic conditions, anxiety, depression, ischemic pathologies, recent cancer, obesity and living alone, influenced the association between recent stress and mortality. Serious illness/physical trauma remained associated with a higher risk of mortality, in the overall sample (HR=1.41, 95% CI: 1.13, 1.75, p=0.002) and in men (HR: 1.84, 95% CI: 1.37, 2.45, p<0.001) but was no longer significant in females (HR: 1.05, 95% CI:0.75, 1.46, p=0.79). Inclusion of depression accounted for most of this reduction in significance, although this factor itself was not associated with mortality risk (p=0.44). Among males, having relatives with a serious illness and major financial problems, remained associated with increased mortality risk, even after multivariate adjustment (HR: 1.30, 95% CI: 1.03, 1.66, p=0.03 and HR: 2.47, 95% CI: 1.41, 4.33, p=0.002, respectively).

3.4 Childhood experiences adjusting for recent stress in women

Given the previous findings in women, that a number of adverse childhood experiences were associated with increased mortality risk (**Table 2**), we also examined whether these associations remained after accounting for recent serious illness/physical trauma (based on the results in Table 2). The results in **Table 4** indicate that childhood adverse experiences were associated with mortality risk, even after accounting for recent serious illness/physical. There was no statistically significant interaction term in the Cox regression models (p>0.10 for the interaction between recent serious

illness/physical trauma and childhood adverse experiences) suggesting that recent serious illness/physical trauma was not an effect modifier of the association between childhood adversity and mortality risk.

3 DISCUSSION

The main findings of this large population-based study were that specific stressful experiences in childhood and a higher number of events, were significant predictors of mortality in later life, especially for women. These associations remained even after considering recent stressful experiences including serious illness. In contrast, recent stress was not a strong risk factor for mortality in either men or women.

The early-life environment is thought to play a critical role in the programming of disease risk across the lifespan (Ryan et al., 2016). Stress during critical periods of development can result in long-term alterations in brain structures (Lupien et al., 2007) and stress signaling (Doom et al., 2014), and previous research has shown that childhood stress can influence overall health (Garcia et al., 2016). Findings from our study showed that among females specifically, those who had experienced serious childhood illness, war/natural disaster or five or more adverse experiences, had an increased mortality risk. Very serious conflicts at home and abuse or maltreatment were risk factors for mortality in the overall sample. There has also been some previous evidence of a dose response relationship between early-life adversities and mortality risk (Brown et al., 2009), and our findings suggests a possible cumulative effect from multiple adverse experiences. Adversities also cluster in the home (Green et al., 2010; Kessler et al., 2010).

The gender specific impact of early-life stress reported in our study could be due in part to the nature and intensity of childhood stress. Females specifically were found to have a great risk of mortality with serious childhood illness and war/natural disaster, but no significant associations were found in men. War has previously been shown to have a disproportional effect on women, during and after war, and is thought to be a result of gender biases and inequalities becoming intensified (McKay, 2006; Under-Secretary-General, 2003). Such biases may have resulted in men being prioritised in food allocation and medical attention, as observed in other countries. It has also been reported that females are more vulnerable to abuse or maltreatment in childhood (Olff, 2017), but we found no evidence for a gender interaction in terms of this exposure.

The differential influence of early-life stress on females and males, could also in part be a consequence of biological differences between the sexes. The hippocampus and frontal cortex which are thought to undergo rapid growth over childhood and adolescence respectively are target sites for the stress hormone cortisol. Early life trauma has been associated with structural changes in these brain regions (Lupien et al., 2007), but with evidence of sex-specific differences (Wellman et al., 2018). Epigenetics could be a mechanisms which helps account for the long-term effects of early-life stress on mortality risk (Ryan et al., 2016) and could differentially impact males and females (Mansell et al., 2016). Female sex hormones have been shown to influence the HPA-axis response to stress, while a more potent inflammatory reaction to stress has also been observed in females (Chrousos, 2010). Similarly, findings from mouse models have shown that early life stress has differential effects, with females more likely to develop stress-related disorders such as depression (Bondar et al., 2018; Goodwill et al., 2019).

Some studies of the impact of stressful life experiences have highlighted the importance of examining individual stressors rather than summing all experiences (Kriegbaum et al., 2008; Ritchie et al., 2009; Rutters et al., 2014). The impact of stress on mortality, however, is thought to depend on the severity and accumulation of stress. One study of 2385 older men and women found that having three or more stressful life experiences is associated with increased risk for all-cause and

cardiovascular mortality during a 20 year follow up (Rutters et al., 2014). Further, the death of a child or partner, financial problems, and moving house were significantly associated with all-cause mortality, while other stressful experiences, such as serious problems with a child, relationship problems with partner, or death of a friend, only revealed a trend for an association with all-cause mortality (Rutters et al., 2014). Early childhood experiences and gender-specific differences were however, not examined.

Our findings support this, indicating that it is not just the number of experiences but also the type of experience that may have the greatest effect. Importantly, we have also shown that the associations differ for men and women. Of the 11 recent stressful life events examined, an overall increased mortality risk was found for serious illness/physical trauma and problems with the police/justice. However, illness would increase mortality risk through mechanisms unrelated to stress itself, and this finding thus needs to be interpreted with caution. The only other significant risk factor was major financial problems in men specifically and this finding is supported by another large study that focused on financial stress specifically, and also reported an increased risk of all-cause mortality in men, but not women (Carlsson et al., 2014). Older men have usually lived their life in a breadwinner role and could be more susceptible to stress experiences that threaten their ability to support the household (Carlsson et al., 2014; Davis and Mantler, 2004). Major financial problems could be a measure of social economic status and therefore be directly related to mortality due to lower access to health care and quality of life. However, such an effect is likely to be spread across the household and consequently, gender, rather than only having an effect among males, as our findings suggest. It may also be related to the consequences of a health issue, and thus could influence mortality risk independently of stress itself.

This study has several limitations, the most important of which is the healthy survivor effect (survival bias). Espirt study participants were aged 65 years and over at inclusion and were living in the community, and thus are a relatively healthy cohort who have survived until this age. If early-life stress does have a negative effect on survival, individuals at the greatest risk would not have bene

included in this study (hospitalised or having died). The overall effect is that our estimate of the true association between early-life stress and mortality may be estimated. Furthermore, it's also possible that individuals having survived to this age, are less susceptible to the effects of stress that than population more generally. In a similar manner, the exclusion of institutionalized or homeless elderly people as well as underrepresentation of the oldest age group, in which effects of war may have been greatest. Another limitation to consider is the retrospective reporting of childhood experiences, which is subject to recall bias and under-reporting, given the sensitivity of the questionnaire and the long time since its occurrence. Similarly, the data concerning recent stress were also self-reported and may also be subject to recall bias. However, participants with possible dementia were excluded which minimised the potential for recall bias. The analysis shown here is explorative in nature and further validation and replication of these findings in an independent study is warranted. A large number of statistical tests were performed which has increased the risk of a type 1 error (false positive). Therefore, it is possible that some of the findings reported may be chance rather than true associations. Likewise, some experiences were rare resulting in insufficient power to detect differences in some gender stratified analyses, despite the relatively large sample size. Lastly, the results of this study cannot make inferences about cause and effect. While our hypotheses was centred around the effects of stress, with strong biological a prior rationale, it is possible that the associations were driven by other factors apparat from stress itself, which were no considered here.

However, this study has a number of strengths. The data used in the analysis come from a large population-based prospective study. Information on the mortality status of the participants was obtained, using death registries and medical records, with only nine participants lost to follow-up. Data was collected on a number of childhood adversity experiences, as well as recent stress experiences, and these were embedded within the larger Esprit study so that participants were unaware of the objectives of this analysis. By assessing stressful life experiences, rather than the individuals' perception of how stressful they regard their life, stress was measured objectively,

reducing the risk of misclassification. Lastly, we controlled for a large number of covariates, particularly measures of physical health and mental health, which were either assessed by trained staff or validated by medical records.

4 CONCLUSION

Consistent with previous studies, we conclude that certain stressful life experiences are associated with all-cause mortality in a population-based cohort of older men and women. However, our findings indicate gender-specific associations. In females, certain types of adverse childhood experiences continue to predict mortality risk in later life, independent of recent stress. Among males, however, specific recent stressful experiences and serious conflicts at home during childhood increased mortality risk. Our study highlights the importance of identifying individuals who have experienced early life and recent stress during routine medical assessments and the necessity for appropriate prevention strategies. It also highlights the importance of informed care, which would ensure the health and welfare settings are responsive to an individual's needs based on their history (Higgins and McCabe, 2001; Knight, 2014). Further research should consider not just early-life adversity but other major stress experiences across the lifetime, including major psychological trauma and post-traumatic stress disorder. Investigating further the cause of death would also help provide a better understanding of the possible biological mechanisms driving these associations, particularly in relation to possible gender differences. This would be essential to target preventative interventions to the individuals most at risk.

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Figure 1. The association between early-life adversity and mortality risk in later-life.

Hazard ratios with 95% confidence intervals are shown.

Table 1: Baseline characteristics of the participants (n=2152)

Characteristic	**Total n (%)**	**Males n (%)**	**Females n (%)**
		902 (41.9%)	1250 (58.1%)
Age			
65-74	1373 (63.8)	581 (64.4)	791 (63.3)
≥ 75	780 (36.3)	321 (35.6)	459 (36.7)
Living alone	589 (27.4)	76 (8.4)	513 (41.1)
Completed at least secondary school education	719 (33.4)	392 (43.6)	327 (26.2)
High alcohol consumption (≥24 grams per day)	382 (18.1)	314 (35.2)	68 (5.6)
Smoking (>10 pack years)	868 (41.1)	588 (67.9)	280 (22.5)
Chronic conditions[1]	824 (38.3)	358 (39.7)	466 (37.3)
Recent cancer	59 (2.7)	29 (3.2)	30 (2.4)
Cardiovascular ischemic pathologies	335 (15.6)	196 (21.7)	139 (11.1)
Current major depressive disorder	57 (3.1)	14 (1.8)	43 (4.0)
Current anxiety disorder	326 (16.6)	92 (11.2	234 (20.6)
Obese (BMI ≥ 30 kg/m^2)	185 (8.7)	70 (7.8)	115 (9.3)

[1] *Includes cerebro- and cardio-vascular disease, more than one chronic illness (high blood pressure, high cholesterol, diabetes, thyroid problems, asthma)*

Table 2: The association between childhood adversity and all-cause mortality (n=1579)

	Childhood adversity							
	No	**Yes**	**Overall**		**Men[3]**		**Women[3]**	
Experience during childhood	**% died (n total)**	**% died (n total)**	**HR (95% CI)** [3]	**P-value**	**HR (95% CI)** [3]	**P-value**	**HR (95% CI)** [3]	**P-value**
Low number, ≤5 of 8 positive responses[2]	33.06 (1,331)	33.87 (248)	1.08 (0.86-1.37)	0.65				
Abuse or maltreatment[1]	32.53 (1,362)	37.33 (217)	1.34 (1.05-1.70)	0.02				
Physical and/or sexual abuse	33.25 (1,549)	30.00 (30)	1.15 (0.59-2.23)	0.69				
Death of a parent	32.78 (1,318)	35.25 (261)	0.95 (0.76-1.20)	0.69				
Death of a parent or attempted suicide	33.01 (1,224)	1,224 (355)	0.96 (0.79-1.17)	0.66				
Parents hospitalised for a long duration	33.08 (1,330)	33.73 (249)	1.16 (0.92-1.47)	0.22				
Serious illness of a parent	32.81 (1,335)	35.25 (244)	0.96 (0.76-1.21)	0.75				
Serious childhood illness	31.89 (1,389)	42.63 (190)[2]	1.47 (1.15-1.87)	0.001	1.08(0.74-1.58)	0.68	1.91(1.40-2.60)	<0.001
Poverty or financial difficulties	32.69 (1,199)	34.74 (380)	0.96 (0.78-1.18)	0.71				
Strict education	33.91 (814)	32.42 (765)	1.00 (0.85-1.19)	0.96				
War event or natural disaster	36.54 (717)	30.39 (862)[5]	1.25 (1.05-1.49)	0.01	1.07(0.84-1.37)	0.59	1.47(1.14-1.88)	0.003
Conflicts at home								
None/few (reference	-	33.16 (1,318)	1.00					
Frequent	-	20.00 (30)	0.55 (0.25-1.23)	0.15				
Very serious	-	35.06 (231)	1.54 (1.21-1.96)	<0.001				
Total adverse experiences								
0-2 (reference)	-	34.07 (725)	1.00		1.00		1.00	
3-4	-	30.62 (503)[5]	1.09 (0.89-1.34)	0.38	1.02 (0.77-1.36)	0.87	1.17 (0.87-1.56)	0.31
≥5	-	35.04 (351)[5]	1.38 (1.11-1.72)	0.004	1.11(0.81-1.52)	0.51	1.71(1.25-2.32)	0.001

[1] *Reported having at least one of the following experiences: neglect, verbal abuse from parents, humiliation, harassment, mental cruelty, physical/sexual abuse and excessive physical punishment for misbehaviour.*

[2] *Composite score comprising the eight 'positive' questions about paternal affection, maternal affection, raised by both parents, parental support, support of other adults, happy childhood and school environment and a normal education.*

[3] *Adjusted for education and gender (with age as time scale in model*

[4] *Where there was evidence of gender-specific associations*

Table 3: The association between recent stressful events and all-cause mortality (n=2152)

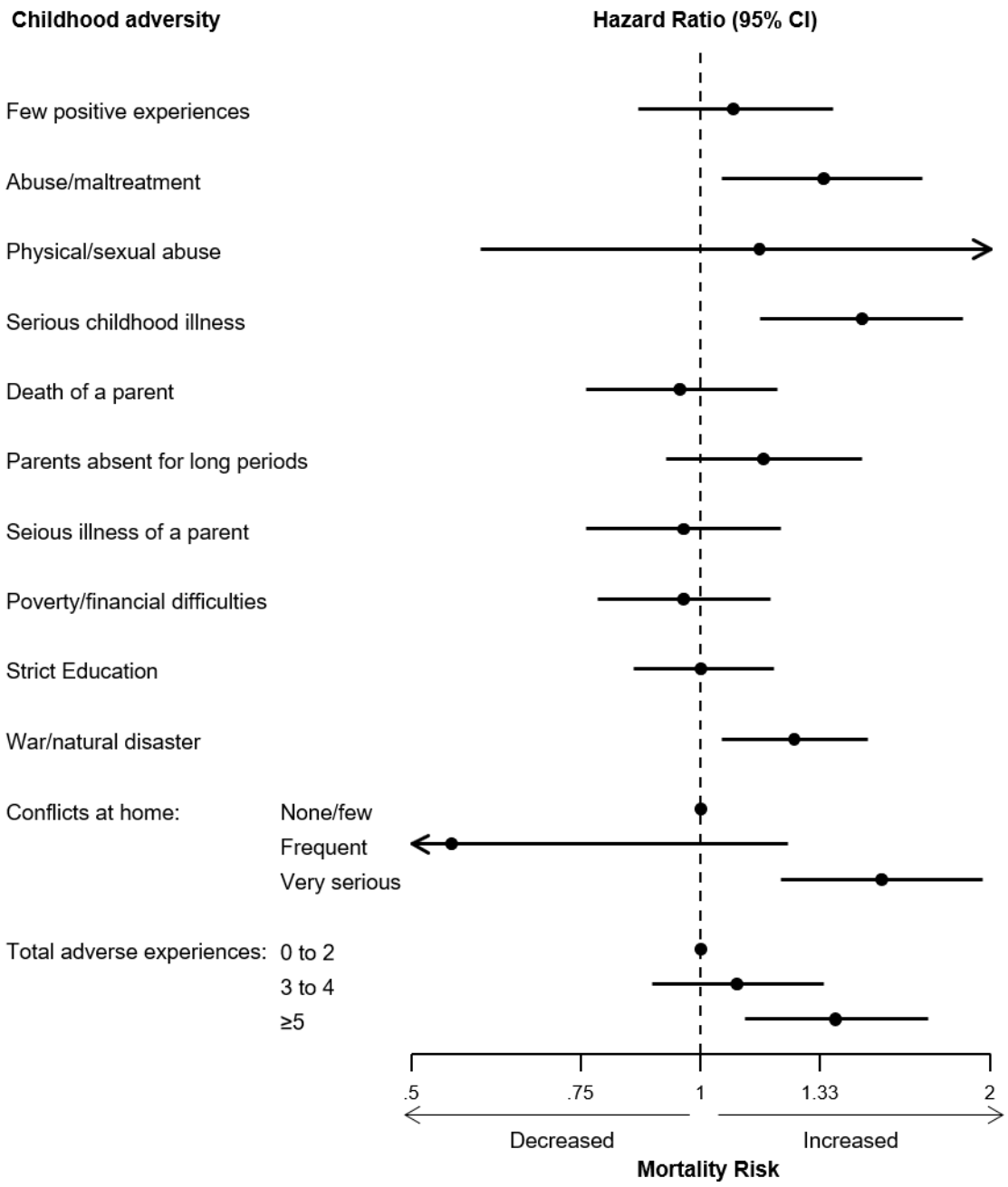
	No event	Experienced event	Overall		Men[4]		Women[4]	
Recent stressful events[1]	**% died (n total)**	**% died (n total)**	**HR (95% CI)** [3]	**P-value**	**HR (95% CI)** [3]	**P-value**	**HR (95% CI)** [3]	**P-value**
Serious illness or physical trauma[2]	36.98 (1,917)	60.00 (235)[3]	1.66 (1.39-2.00)	<0.001	1.90 (1.47-2.45)	<0.001	1.45 (1.12-1.88)	0.01
Serious illness of a relative[2]	38.38 (1,626)	42.97 (526)[3]	1.09 (0.94-1.27)	0.25	1.26 (1.01-1.55)	0.03	0.97 (0.78-1.21)	0.79
Death of first degree relative	39.97 (1,919)	35.62 (233)	0.95 (0.76-1.19)	0.65				
Death of close friend	38.34 (1,526)	42.33 (626)	1.04 (0.90-1.2)	0.62				
Marital separation	39.51 (2,126)	38.46 (26)	1.26 (0.68-2.36)	0.47				
Breakdown of another regular relationship	39.51 (2,116)	38.89 (36)	1.18 (0.70-2.02)	0.52				
Serious problem with a close friend or relation	39.22 (1,958)	42.27 (194)	1.10 (0.87-1.38)	0.44				
Unemployment	39.56 (2,136)	31.25 (16)	1.43 (0.59-3.45)	0.43				
Major financial problems	39.53 (2,077)	38.67 (75)[3]	1.30 (0.90-1.89)	0.17	1.92 (1.14-3.21)	0.01	0.96 (0.57-1.64)	0.89
Problems with the police/justice	39.38 (2,128)	50.00 (24)	1.86 (1.05-3.30)	0.03				
Loss/theft of something valuable	39.26 (2,058)	44.68 (94)	0.98 (0.71-1.34)	0.89				
Total recent events, excluding personal illness								
None (reference)	-	37.02 (967)	1.00					
1-2	-	40.90(731)	1.07 (0.92-1.25)	0.37				
≥3	-	42.60 (453)	1.15 (0.96-1.37)	0.12				

[1] *Not included here was a question related to 'Professional Dismissal' as too few participants (0.3%) reported having experienced this.*
[2]*Serious illness or physical trauma (men=99, women=136); serious illness of a relative (men=203, women=323); major financial problems (men=22, women=53)*
[3]*Adjusted for education and gender (with age as time scale in model)*
[4]*Where there was evidence of gender-specific associations*

Table 4: The association between adverse childhood experiences and mortality in women, adjusted for recent serious illness/physical trauma

	HR (95% CI)	**P-Value**
Serious childhood illness[1]	2.04(1.48-2.83)	<0.001
War event or natural disaster[1]	1.43(1.10-1.85)	0.007
Abuse or maltreatment[1]	1.48 (1.07-2.06)	0.02
Conflicts at home[1]		
None/few (reference		
Frequent	0.32 (0.05-2.32)	0.26
Very serious	1.71 (1.22-2.41)	0.002
Total adverse experiences during childhood[1]		
0-2 (reference)	1.00	-
3-4	1.17(0.86-1.59)	0.32
≥5	1.81(1.33-2.49)	<0.001

[1] *Adjusted for recent serious illness/physical trauma and education (with age as timescale in model)*


Childhood adversity
Hazard Ratio (95% CI)
Few positive experiences
Abuse/maltreatment
Physical/sexual abuse
Serious childhood illness
Death of a parent
Parents absent for long periods
Seious illness of a parent
Poverty/financial difficulties
Strict Education
War/natural disaster
Conflicts at home:
None/few
Frequent
Very serious
Total adverse experiences:
0 to 2
3 to 4
≥5
.5
.75
1
1.33
2
Decreased
Increased
Mortality Risk