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Adverse events in older adults and the risk of dementia and cognitive decline

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Abstract

Background: Increasing evidence suggests that stress could be a risk factor for dementia but this might vary by gender. This study investigated whether adverse life events were associated with cognitive decline and dementia in later-life, separately in men and women.

Methods: Participants were 12,789 community-dwelling Australians aged ≥ 70 years. Ten common adverse events in later-life were self-reported. Cognitive decline was defined as a 1.5 SD decline from participants' baseline score in tests of global cognition, psychomotor speed, episodic memory, and executive functioning, which were assessed regularly over a maximum of 10.3 years. Dementia was diagnosed according to DSM-IV criteria.

Results: An increased risk of dementia was observed in participants who experienced the death of a spouse/partner (HR: 1.72, 95% CI: 1.17 – 2.52) and for individuals who experienced major financial problems (HR: 1.53, 95% CI: 1.05 – 2.23). The latter also increased the risk of cognitive decline in men specifically (HR: 1.43, 95% CI: 1.10 – 1.86). In contrast, some events for women were associated with a reduced risk of dementia (e.g. close family or friends lost their job/retired (HR: 0.62, 95% CI: 0.40–0.95)).

Limitations: Events including major money problems may result from prodromal dementia symptoms, thus reverse causation needs to be considered.

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Contributors

RW and JM are responsible for the study conception and design of the ASPREE study. AO and CB provided major roles in the acquisition of ALSOP data. JR, CG, and RFP conceived the current study. DN drafted the manuscript, with major input from JR, and DN takes responsibility for the accuracy of analysis of data. DN, JR, CG, ZW, and RFP interpreted the data, with input from AM, AO, ZW, SGO, CB, RW, and JM. All authors read and gave final approval to the submitted manuscript.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2023.100592.

Conclusions: Adverse life events may influence dementia risk in older adults, but associations vary depending on the nature of the event, and across genders. These findings support the need for early interventions in older people who have experienced adversities, particularly for the death of a loved one.

Keywords

Stress; Older; Later-life; Bereavement; Cognition; Dementia

1. Background

Ageing is commonly associated with a myriad of transitions within interpersonal relationships (e.g. bereavement and caregiving), health (e.g. reduced mobility), finances (e.g. retirement) and living situation (e.g. moving to residential aged care) (Hardy et al., 2002). The inability to adapt to these changes can cause profound psychological distress, which is widely acknowledged to threaten physical health and wellbeing (Yaribeygi et al., 2017). While health-related issues and reduced capacity to perform daily functions are expected to cause psychological stress/distress in older adults, non-health related events, including unforeseen trauma (e.g. assaults and accidents) can also cause profound distress (Herrera and Fernández, 2020).

In comparison to their younger counterparts, older age groups may be more susceptible to negative health outcomes following an adverse event (Lavretsky and Newhouse, 2012; Lupien et al., 2009). The increase in morbidities could be attributed to the decline in physiological reserves during the ageing process, thus increasing one's vulnerability to stress (Bergman et al., 2007). Dementia is of particular interest to this study, as increasing evidence suggests that stress may influence cognitive function and an earlier onset of clinical dementia symptoms (Franks et al., 2021).

Dementia is a debilitating neurodegenerative syndrome most common in later-life. It is characterised by cognitive decline, including impairments to language, memory, learning and self-care (Collaborators, 2019). Some studies have also shown that chronic stress may influence volumetric and functional changes to brain regions, and these changes may be more pronounced during ageing when the brain is undergoing a period of rapid decline (Lupien et al., 2009). The neurological effects of psychological stress may also differ between men and women, as previous research has reported gender differences in the response to stress (Verma et al., 2011), as well as dementia risk (Niu et al., 2017).

To date, the majority of research investigating the role of stress in the etiopathogenesis of dementia have been conducted in animal-models (Devi et al., 2010; Jeong et al., 2006), with limited epidemiological studies. Amongst these, the majority measure clinical manifestations of stress (including Posttraumatic Stress Disorder) (Mawanda et al., 2017; Qureshi et al., 2010), and stress at various stages of the lifespan (including early and mid-life) (Johansson et al., 2010; Radford et al., 2017). Furthermore, only limited studies have investigated whether the associations between stress and dementia differ by gender (Nilaweera et al., 2020).

The primary aim of this study is to determine whether adverse events in later life are associated with the risk of cognitive decline and dementia, in a cohort of initially healthy, community-dwelling older adults. The secondary aim is to determine if these associations are gender-specific.

2. Methods

2.1. Study population

This study utilised data from the ASPirin in Reducing Events in the Elderly (ASPREE) study, and the ASPREE Longitudinal Study of Older Persons (ALSOP) sub-study (McNeil et al., 2018a, 2018b, 2019; Ryan et al., 2020a). ASPREE was a randomised clinical trial of low-dose daily aspirin in community-dwelling older individuals who were without a diagnosis of dementia or cardiovascular disease, and had a Modified Mini-Mental State Examination (3MS) score of 78 and above. Aspirin use was found to have no significant impact on dementia, cognitive decline or cognitive change, over a median of 4.7 years (McNeil et al., 2018a, 2018b; Ryan et al., 2020a). Following the conclusion of the clinical trial in 2017, ongoing observational follow-up of participants continued (ASPREE-XT study).

In Australia, 16,703 participants aged 70 years and over were recruited through partnership with their general practitioners (GPs) between March 2010 and December 2014. Most participants were also invited to enrol in the ALSOP sub-study 3–6 months post-baseline (randomisation into the ASPREE trial) (McNeil et al., 2019), which comprised of two questionnaires which collected medical and social health data respectively. Invitation was delayed up to 15 months for some participants (<15%) as the recruitment of the ALSOP study was asynchronous with the early stage of the ASPREE (ASPREE began two years prior to the commencement of ALSOP). This study analyses data collected from the ALSOP social health questionnaire, which was administered to the majority of participants approximately 6–9 months after baseline, and was returned by 90% of invitees. Participants were also without a diagnosis of dementia at the time the questionnaire was administered.

The present study is a secondary data analysis of 12,896 participants who returned the social health questionnaire, and were followed for a median follow-up time of 6.4 years. Of these participants, 107 individuals did not have information regarding one or more of the four cognitive tests, and thus were excluded from further analyses, leaving a total of 12,789 participants.

Ethical approval for the ASPREE-XT and ALSOP (project numbers CF11/1100 and CF11/1935) studies were granted by the Monash University Human Research Ethics Committee, or the Alfred Hospital Human Research Ethics Committee, and written consent was obtained from each participant for each study. ASPREE was registered at Clinicaltrials.gov (NCT01038583).

2.2. Adverse events

Participants reported whether they had experienced any of ten adverse life events over the year prior to completing the ALSOP social health questionnaire (McNeil et al., 2019)

(Appendix A). The events were related to interpersonal relationships (e.g. death of a spouse), finances (e.g. major money problems) and external factors (e.g. major accident or disaster). The list of stressful events was adapted from other commonly used life stress inventories such as Holmes-Raye, with removal of events not related to an older age group (e.g. pregnancy) and a modification of other published work (Kershaw et al., 2014).

2.3. Cognitive assessments

Cognition was measured as part of the main study using validated tests administered by trained personnel at baseline, year one, and then approximately every two years until 2017 and then annually. Global cognition was measured with the 3MS (Teng and Chui, 1987), episodic memory with the Hopkins Verbal Learning Test-Revised (HVLT-R) Delayed Recall task (Benedict et al., 1998), executive functioning with the Controlled Oral Word Association Test (COWAT) (Ross, 2003) and psychomotor speed with the Symbol Digit Modalities Test (SDMT) (Smith, 1982).

Incident cognitive decline was defined as those whose cognitive score dropped by >1.5 SD from their own baseline value on any of the four cognitive tests (Ryan et al., 2019, 2020b, 2021), However, this did not apply to those who only experienced a transient decline – a drop of >1.5 SD at one wave followed by a rise above this threshold at subsequent waves (Ryan et al., 2020a).

2.4. Dementia diagnosis

Participants with suspected dementia (triggers included a 3MS score below 78 or a greater than 10.15 point drop from the 5-year predicted score during follow-up, cognitive issues reported to a specialist as indicated by self-report or medical reports, or prescription for cholinesterase inhibitors), were referred for additional cognitive and functional assessments (McNeil et al., 2018b; Ryan et al., 2020a). Information from these additional tests were reviewed by an expert adjudication committee, consisting of neurologists, neuropsychologists and geriatricians, who validated the suspected diagnoses according to criteria listed in the *Diagnostic and Statistical Manual for Mental Disorders (*fourth edition; *DSM-IV)*. Additional documentation including laboratory tests (i.e. blood tests) and neuroimaging reports (brain CT or MRI) were also obtained from health providers in order to adjudicate a dementia diagnosis.

For participants with confirmed dementia, the date of diagnosis was recorded as the date of original trigger, or specialist diagnosis.

2.5. Covariates

Covariates included the following baseline sociodemographic factors: age, binary gender, and highest level of education (McNeil et al., 2017). The following clinical factors were also included (McNeil et al., 2017): hypertension (yes/no), diabetes mellitus (yes/no), smoking status (current/former/never), alcohol consumption (current/former/never), current depressive symptoms (score of ≥8 ascertained from ten-item Centre for Epidemiologic Studies Depression Scale (CES-D 10)) (Radloff, 1977). Additionally, we adjusted for socioeconomic status using the Socio-Economic Indexes for Areas-Index of Relative

Socioeconomic Advantage and Disadvantage (SEIFA-IRSAD index) which summarises the economic and social situations of people and households within an area (e.g. employment, household income and cost of rent).

2.6. Statistical analysis

All analyses were conducted using Stata 17 (StataCorp, 2021). Longitudinal associations between adverse life events, and the outcomes of incident dementia or incident cognitive decline, were determined using Cox proportional hazards regression adjusted for age, gender and education. Further adjustments for hypertension, diabetes, smoking status, alcohol consumption, and current depressive symptoms were made. To test whether these associations differed between men and women, gender interactions were determined, followed by age and education-adjusted gender-stratified analysis. To help account for the potential period between when participants were recruited to ASPREE and when the ALSOP social and behavioural questionnaire was given, sensitivity analyses were conducted by censoring participants with a diagnosis of dementia during the first two years of follow-up. The results were presented as hazard ratios (HRs), 95% confidence intervals (CIs) and two-sided p-values. A threshold of 0.05 was applied to determine significance.

3. Results

3.1. Characteristics of study population

Participants' age at baseline ranged from 70 to 95, with a mean age of 75.2 (4.3) years, and a higher proportion of women (n = 6949) (Table 1). The sample reflected a wide spread in formal education level, with approximately 48% having less than 12 years of schooling, 26.8% with 12–15 years, and 25.0% with more than 16 years. More women than men reported depressive symptoms (10.1% vs 7.4%). The frequency of adverse events experienced ranged from 2.1% (divorce or breakup) to 42.2% (death or serious illness of a family member or close friend). A greater percentage of women reported experiencing a serious illness or death of a spouse, partner, family member or close friend than men (Table 1). Participants displayed a mean 3MS score of 93.71 (SD: 4.40; maximum possible score = 100) (Ryan et al., 2019), aligning with previously reported normative data (Jones et al., 2002).

Incident cognitive decline across a maximum duration of 10.3 years was observed in 21.3% (N = 2698) of participants, and 4.1% (N = 530) individuals were diagnosed with dementia. A total of 48 participants were diagnosed within two years post-baseline, 149 within two-four years, 197 within four-six years, 111 within six-eight years, and 25 after eight years and until the maximum duration of 10.3 years. The number of men with incident dementia (N = 263, 4.5%) was similar to the number of women (N = 267, 3.8%).

3.2. Association between adverse life events and incident dementia

In adjusted analysis, individuals whose spouse or partner died had an increased risk of dementia (HR: 1.72, 95% CI: 1.17 – 2.52, P = 0.006), as did those experiencing major money problems (HR: 1.53, 95% CI: 1.05 – 2.23, P = 0.03) (Appendix B). On the other hand, death or serious illness of a family member or close friend was associated with a

decreased risk of dementia (HR: 0.83, 95% CI: 0.69 – 0.99, $P = 0.04$) (Appendix B). Some of the associations were attenuated after further adjustments for other covariates including health status and behaviours, and current depressive symptoms, all of which could be potential mediators on the putative causal pathway between adverse events and dementia/cognitive decline (Appendix B and C, Model 2).

In gender-stratified analyses (Fig. 1), both genders were more likely to develop incident dementia following the death of a spouse or partner (men HR: 1.85, 95% CI: 1.03 – 3.32, $P = 0.04$; women HR: 1.63, 95% CI: 0.98 – 2.71, $P = 0.06$), or major money problems (men HR: 1.91, 95% CI: 1.16 – 3.12, $P = 0.01$; women HR: 1.20, 95% CI: 0.67 – 2.14, $P = 0.54$). A decreased risk of dementia was observed in both genders who experienced the death or illness of a close family member or friend (men HR: 0.92, 95% CI: 0.72 – 1.19, $P = 0.54$; women HR: 0.74, 95% CI: 0.57 – 0.95, $P = 0.02$). In contrast, for lost job/retired of a close family/friend, there was a statistically significant gender interaction ($p = 0.03$, Appendix D), and only in women was a significant association with increased risk of dementia observed (HR: 0.62, 95% CI: 0.40 – 0.95, $P = 0.03$). These results were not altered in sensitivity analyses censoring the 48 participants who were diagnosed with dementia during the first two years of follow-up, nor when additionally adjusting for socioeconomic status (Appendix E).

3.3. Association between adverse life events and incident cognitive decline

A 27% increased risk of cognitive decline was observed in participants who experienced the death of a spouse or partner (HR: 1.27, 95% CI: 1.03 – 1.56, $P = 0.03$), but this was not significant after adjustment (HR: 1.11, 95% CI: 0.90 – 1.37, $P = 0.34$) (Appendix C), notably with the inclusion of age in the model. The risk of cognitive decline increased by 27 to 45% in participants with a divorce or break up (albeit these results were not statistically significant). On the contrary, experiencing a divorce or break up of close family or friends appeared to be a protective factor for later-life cognitive function (multivariate HR: 0.89, 95% CI: 0.79 – 1.00, $P = 0.04$) (Appendix C). In addition, participants whose family member or close friend died or were seriously ill had a reduced risk of cognitive decline in the adjusted model (HR: 0.92, 95% CI: 0.85 –1.00, $P = 0.04$). Further adjustments for hypertension, diabetes, smoking status, alcohol consumption, and current depressive symptoms had no substantial influence on these results.

In gender-stratified analysis adjusted for age and education (Fig. 2), both genders had an increased and decreased risk of cognitive decline respectively, following a divorce/break-up of the participant themselves or of their family/friend. Statistically significant gender interactions were observed for major money problems ($p = 0.04$) and death of a pet ($p = 0.05$; Appendix D). Only men with major money problems had an increased risk of cognitive decline by 43% (HR: 1.43, 95% CI: 1.10 – 1.86, $P = 0.007$), while for women this was not significant (HR: 0.98 (0.76 – 1.26), $P = 0.87$). However, women who experienced the death of a pet had a greater risk of cognitive decline (HR: 1.25, 95% CI: 1.06 – 1.49, $P = 0.009$), while men with this event did not have an increased risk (HR: 0.97, 95% CI: 0.80 – 1.17, $P = 0.73$). These gender-specific findings also remained significant in sensitivity

analyses which excluded 48 participants who were diagnosed with dementia during the first two years of follow-up.

4. Discussion

4.1. Summary of findings

This prospective study across a maximum duration of 10.3 years, conducted in a cohort of 12,789 older community-dwelling participants, demonstrated that specific adverse events were associated with the risk of cognitive decline and dementia. In particular, the death of a spouse or partner was associated with a 72% increased risk of dementia. Some gender differences were observed in this study, with a 43% increased risk of cognitive decline amongst men with major money problems. Women who experienced the death of a pet had a 25% increased risk of cognitive decline. Surprisingly, women whose family or friends lost their job/retired appeared to be protected against dementia, with a 38% decreased risk. Our findings suggest that the events with stronger impacts on the core components of life situations may impose a greater neuropathological burden, regardless of categories. For example, the death of a spouse/partner, which is arguably the most adverse event in this study, marks a major change in the proximal networks and the loss of a primary social role. Likewise, financial problems and major accidents, which are often associated with unemployment, also largely influence the social status and living conditions. In contrast, the events that are less connected to an individual's daily life, such as changes in distal networks, appear to have weaker associations.'

4.2. Comparison to previous literature

To date, very few studies have investigated the role of adverse events in later-life as a risk factor for dementia and those that have, report mixed findings. While one study which comprised of 2462 adults aged over 55 years at baseline did not report any association between later-life adversity and dementia after a mean follow-up time of 11.4 (5.6) years amongst those diagnosed with dementia (Sundström et al., 2014), a case-control study demonstrated that dementia patients had a greater than two-fold risk of experiencing a range of adverse events in the last year before the onset of symptoms, in comparison to healthy subjects (Tsolaki et al., 2010). Furthermore, it was shown that the majority of these adverse events are likely to be causally related to dementia (including health problems such as stroke) (Fountoulakis et al., 2011). The interpretation of the previous study's results should also consider the possibility of recall bias, since the assessment of adverse events relied on caregiver reports. Also, due to the retrospective nature, findings from that study lack evidence regarding the temporality between stressful events and dementia. In comparison, our present study was prospective and assessed the individual impact of adverse events in participants without major cognitive impairment (3MS score of 78 and above) at study entry.

4.3. Main findings

A main finding in this study involves the increased risk of dementia in participants who have experienced the death of a spouse or partner. This finding is supported by a meta-analysis of samples where at least half of the participants were aged 65 years or more when diagnosed with dementia (N = 812 047), which showed that the risk of dementia in widowed

individuals increased by 20% (95% CI: 1.02 to 1.41), in comparison to married individuals (Sommerlad et al., 2018). Two included studies considered gender differences (Beard et al., 1992; Sundström et al., 2016), but these differences were not statistically significant. Interestingly, the present study showed that the associations between death of a spouse or partner and dementia were similar between men and women.

Some bereaved individuals may experience a severe, prolonged, and pathological form of grief – termed 'complicated grief' (Nakajima, 2018). Complicated grief is diagnosed in approximately 7% of bereaved individuals, with a greater risk in those over the age of 61y when compared to younger age groups (Kersting et al., 2011). Furthermore, complicated grief has previously been linked to worse cognitive functioning than typical bereavement (Saavedra Pérez et al., 2015). The present study did not measure a diagnosis of complicated grief; therefore, it is yet unclear whether the distress associated with typical grief following the death of a spouse or partner, or complicated grief, may be associated with dementia incidence. This finding may also be mediated by other risk factors of dementia which are likely to increase following bereavement, and were not considered for in this study. Widowhood is associated with poor sleep quality (which could be intensified if the bereaved individual has lost their bed partner) (Monk et al., 2008), nutritional risk and alcohol consumption (Stahl and Schulz, 2014). The likelihood of a psychiatric diagnosis also increases after bereavement in older people, including Posttraumatic Stress Disorder (O'Connor, 2010), which has previously been linked to dementia incidence (Flatt et al., 2018). It is also important to consider aspects of social health, such as loneliness, which can increase following spousal death, particularly in older men (Freak-Poli et al., 2022a). Indeed, the present study demonstrated a slightly increased risk in dementia amongst men who experienced the death of a spouse or partner, in comparison to women. However, the present study did not adjust for loneliness as 92% of these participants reported good social health, and very few were categorised as being socially isolated (2%), with low social support (2%) or lonely (5%) (Joyce et al., 2021). Finally, these findings might also be explained by possible 'unmasking' of dementia, given that partners can often naturally compensate for the functional decline of their partner in the early stages of dementia. Our sensitivity analysis, excluding participants diagnosed with dementia in the first few years, however, has attempted to minimise this as a possible cause for the results.

4.4. Gender differences

Some adverse events appeared to be stronger risk factors for dementia in men, and in women, some events decreased dementia risk. These gender-specific findings could be attributed to the unique biopsychosocial factors in men and women. Psychosocial factors related to gender roles in the historical context may also apply to our findings, as this study measured gender as a binary construct (whether participants identified as a man or woman). In particular, gendered social roles may explain the increased risk of cognitive decline in men with major money problems in comparison to women. In Australia, fathers are more likely to undertake full-time paid employment than mothers (Baxter, 2013), and could be assumed to be responsible for their family's finances. Thus, men may be more affected by financial difficulties than women. It is also possible that decreased financial resources limits

the opportunity to socialise, contributing to greater feelings of loneliness, and subsequent risk of low cognition and incident dementia (Freak-Poli et al., 2022b; Sutin et al., 2020).

Our study reported an increased risk of cognitive decline in women who had experienced the death of a pet. It could be that women have greater emotional attachment to their pets than men (Winefield et al., 2008), hence eliciting a stronger stress response. The psychological stress and grief of losing an animal companion could be comparable to that in human bereavement literature, however may not be as universally understood (Mohanti, 2017). Anecdotal reports of women comparing the loss of a pet with experiencing a miscarriage have been noted, in that the extent of their grief was not acknowledged by their community, particularly within support services such as pastoral care (Brown, 2006). In addition, a qualitative study of older women who experienced the death of a companion animal reported losses in pet-related physical activity, such as neighbourhood walks (Wilson et al., 2021), which may also contribute to poor cognitive health (Mandolesi et al., 2018).

Our study also revealed unexpected findings in women, with the retirement/loss of job of their family or friends being a protective factor against dementia. It is difficult to interpret how these events could be beneficial to one's cognitive health, but it may be due to the indirect increases in social health (Penninkilampi et al., 2018), through meaningful interactions with their various networks. For example, an adult child who has lost their job may reach out seeking emotional support, or a close friend who has retired may now have additional time to socialise. Indeed, providing support, as opposed to receiving, may have greater importance in promoting well-being amongst older adults (Kim et al., 2020; Thomas, 2010), possibly by contributing to the individual's sense of purpose. Prior work has also shown that enhanced positive social interactions in later-life may be closely linked to the individual's sense of purpose (Pfund et al., 2022), which could be important in maintaining cognitive health and preventing dementia risk in ageing (Boyle et al., 2010). Older mothers in particular may be more involved in the relationships with their adult children than fathers (Fingerman et al., 2020), and cross-cultural research suggests that women may be more likely to favour dyadic and intimate friendships than men (David-Barrett et al., 2015). However further research is required to elucidate the specific nature of the relationship which is providing a beneficial effect.

This is the first study examining gender differences in the influence of stressful events on dementia risk, but our findings still echo some theories on stress response. For example, prior studies (Kendler et al., 2011) observed a greater vulnerability to problems in employment, working situation and marriage, while women were more emotionally affected by disruptions of interpersonal networks, such as problems in getting along with or the death of a friend or relative.

4.5. Biological mechanisms supporting hypothesis

While the causal link between stress associated with adverse events and dementia is yet to be elucidated, several biological mechanisms have been proposed. The first includes the body's endocrine response to stress, which is regulated by the Hypothalamic-Pituitary-Adrenal (HPA) axis. Psychological distress may increase the activation of the HPA axis, leading to dysregulated levels of glucocorticoids such as cortisol (hormonal mediators in the stress

response), which bind to brain regions involved in both HPA axis activity and cognitive functions (de Souza--Talarico et al., 2011). This may lead to alterations in cognitively relevant brain regions such as the hippocampus, prefrontal cortex and amygdala, thus accelerating the progression of dementia (McEwen et al., 2016). While a small increase in cortisol levels can occur naturally in older age, contributing to the normal cognitive decline in ageing, further elevations have been observed in patients with Alzheimer's Disease (Zheng et al., 2020). Furthermore, these cognitive regions may be more susceptible to the effects of cortisol in later life, due to natural rapid decline and regression of the brain in the ageing process (Lupien et al., 2009). Other theories relating stress with dementia pathology focus on oxidative stress and neuroinflammation, both of which are increased with the chronically stressed (Agostinho et al., 2010), including bereaved individuals (Fagundes et al., 2019). Overactivation of these mechanisms can affect the regular process of neurons, and influence cell death and damage to brain regions. In addition, they may impact neuropathology involved in advancing Alzheimer's Disease, such as increased amyloid plaque deposition (Guglielmotto et al., 2010; Ismail et al., 2020).

4.6. Strengths

To our knowledge, this is the first study to investigate the effects of adverse events on dementia risk in older adults, separately in men and women. Strengths of this study include its large sample size of healthy men and women without overt disease, thus limiting the influence of other potential risk factors of dementia on the observed associations. Unlike similar studies (Sundström et al., 2014; Tsolaki et al., 2010), the present study was conducted prospectively in initially cognitively heathy individuals at baseline when assessing stressful events, to minimise the possibility of recall bias. Furthermore, adverse events were considered as individual items in this study, rather than a grouped variable, thus providing more clinically relevant information regarding dementia risk factors.

4.7. Limitations

However, there are some limitations to consider. A key barrier in the interpretation of these findings, is the low number of participants experiencing some of the adverse events, including only 2.6% of individuals in the study experiencing a major accident or disaster. Thus, reduced power in this study, and larger variability in the results, could mean that we were unable to detect smaller effects, particularly for rarer events. In addition, there is likely some exposure misclassification arising from assessing adverse events at a single point in time. The stressful events that occurred after the one-year assessment period were not recorded, so the 'exposed' participants may have been underestimated. Overall, this may have attenuated some of the associations. Therefore, future studies should expand the assessment to a longer timeframe. However, a pre-specified period for data collection, which is not uncommon in epidemiological studies, permits the standardised measurement and minimises potential recall bias, and in particular reverse causation. The cohort may also not be representative of all older Australians, especially individuals who are not Caucasian or community-dwelling. As future demographic trends in older Australians are expected to shift, with greater representation of non-Australian born migrants, the current results may be even less generalisable in the coming decades (Wilson et al., 2020). Dementia also has a relatively long preclinical phase (Parnetti et al., 2019), and as such, some participants may

have had asymptomatic dementia during enrolment. It is also possible that due to the long preclinical phase, associations which have been reported elsewhere (Norton et al., 2010) may have been observed given a longer follow-up period. Some events, including major money problems, could also result from prodromal symptoms of dementia (Triebel et al., 2009), thus the possibility of reverse causation need to be considered in the interpretation of some of the observed associations. Furthermore, this study could have been improved upon by using a validated tool to measure adverse events, such as the Life Events Inventory (Jackson, 2009), which provides weightings to each event based on the level of distress they are likely to cause. As the questionnaire in the present study did not assign weightings to each event, we are unable to create a summative measure of stress to investigate if there was a dose-response relationship. It is likely that individuals with greater distress and challenges following an event would experience more severe impact to somatic health, than individuals who are less affected by the same event. While this study did adjust for various sociodemographic and health factors, there may be potential residual confounding, thus limiting the causal inferences from these findings.

5. Conclusions

This study provides evidence that experiencing adverse events in later-life, in particular death of a spouse or partner, may increase the risk of dementia. Our findings highlight not only the importance of counselling and support for older adults following a major adverse event, but that clinicians should also be aware of the potential for cognitive decline in response to this stress. Increased screening and possible intervention strategies could be particularly beneficial for this group of individuals.

Furthermore, our results suggest gender has a role in the associations between stressful life events and dementia risk, thus highlighting the importance of gender-based interventions to improve social health amongst older populations, could be beneficial. As causal relationships cannot be ascertained from this study, further research into the biological pathways underpinning these associations is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

Any requests for data can be sent to the corresponding author.

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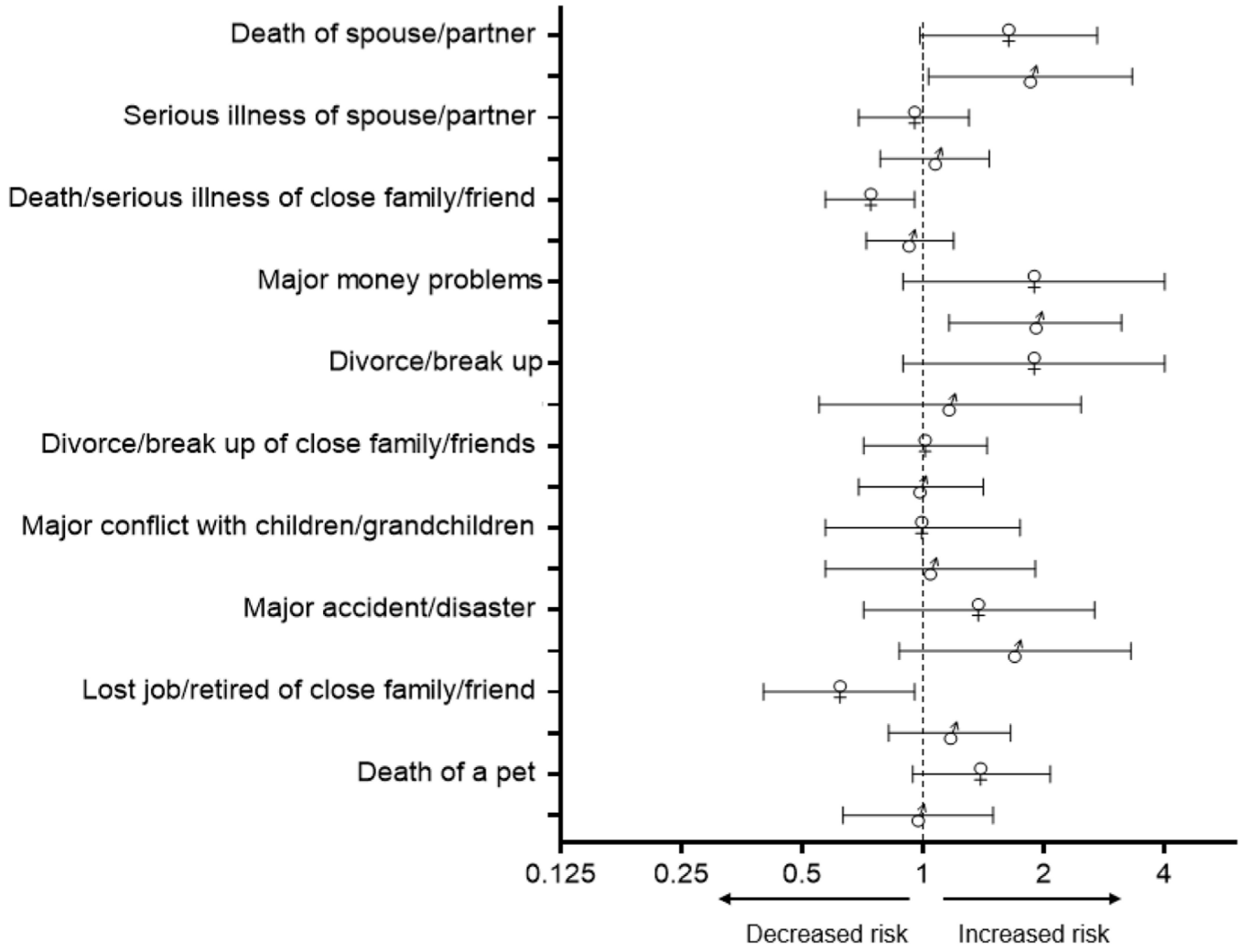

Fig. 1.

Gender-stratified association between recent adverse events and incident dementia (*N* = *12,596*), adjusted for age and education. Hazard Ratio (HR) and 95% CI were reported, where ♀ denotes women and ♂ denotes men.

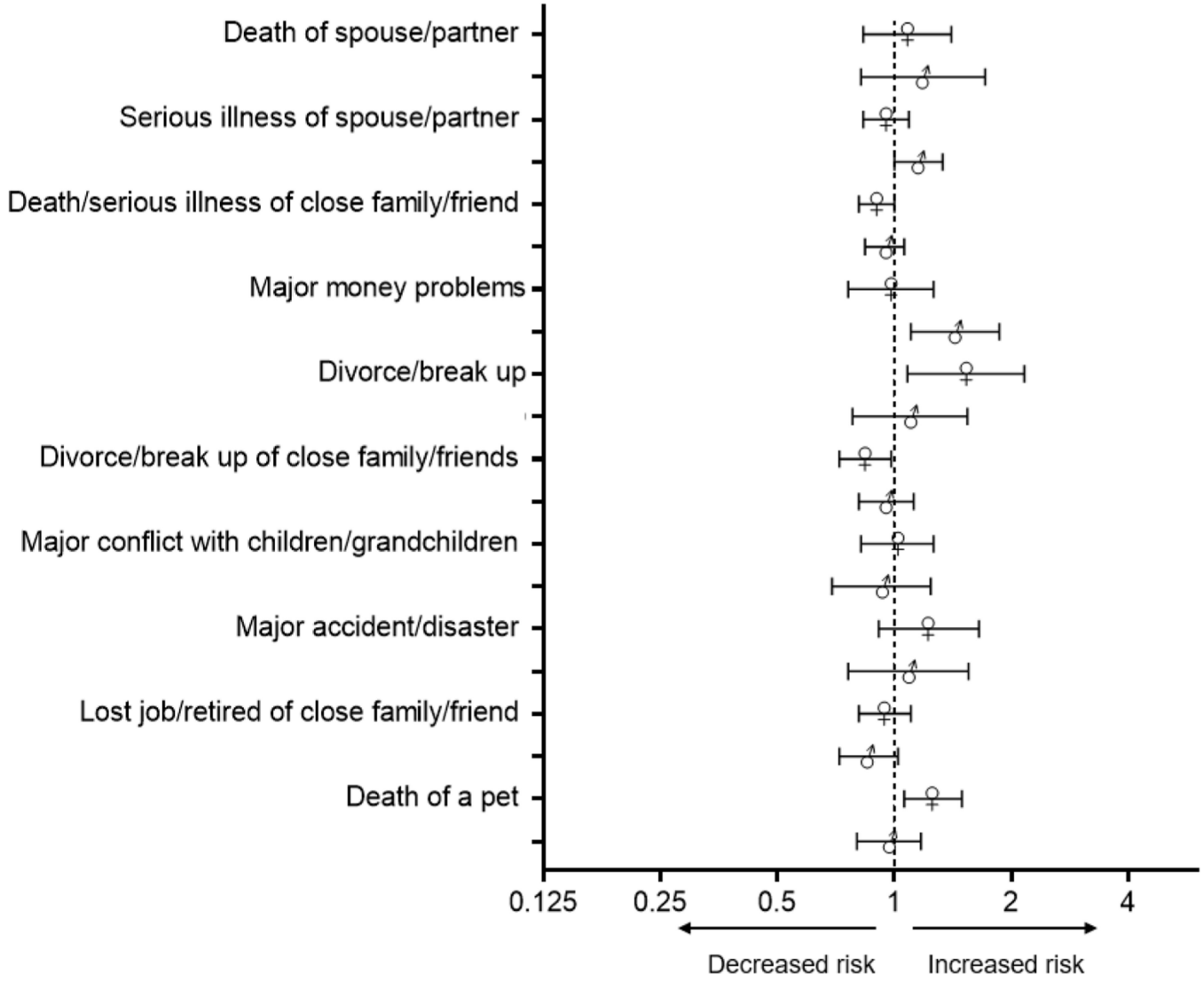

Fig. 2.

Gender-stratified association between recent adverse events and cognitive decline* (*N* = *12,454*), adjusted for age and education. Hazard Ratio (HR) and 95% CI were reported, where ♀ denotes women and ♂ denotes men.

Table 1

Participants' characteristics at baseline (*N = 12,789*).

		WOMEN (*N* = 6949) Mean (±SD)	MEN (*N* = 5840) Mean (±SD)
SOCIODEMOGRAPHIC	*Age, y*	75.3 (4.3)	75.1 (4.34)
		% (N)	**% (N)**
	Years of education		
	<12	50.8 (3531)	45.2 (2640)
	12–15	27.4 (1902)	26.0 (1521)
	16+	21.8 (1516)	28.8 (1679)
HEALTH	*Hypertension*[*]	50.1 (3480)	44.1 (2576)
	Diabetes[†]	6.5 (449)	9.6 (560)
	Smoking status		
	Current	2.3 (160)	3.3 (195)
	Former	30.9 (2149)	53.5 (3125)
	Never	66.8 (4640)	43.2 (2520)
	Alcohol use		
	Current	74.7 (5193)	85.9 (5018)
	Former	3.9 (271)	5.5 (322)
	Never	21.4 (1485)	8.6 (500)
	Depressive symptoms[‡]	10.1 (704)	7.4 (430)
RECENT ADVERSE EVENTS	*Death of spouse or partner*	3.5 (242)	2.2 (128)
	Serious illness of spouse or partner	19.2 (1335)	16.7 (975)
	Death or serious illness of a family member of close friend	43.9 (3051)	40.3 (2353)
	Major money problems	4.3 (298)	3.8 (219)
	Divorce or break up	1.6 (112)	2.6 (152)
	Divorce or break up of close family or friends	14.2 (983)	13.9 (812)
	Major conflict with children or grandchildren	6.0 (414)	4.7 (274)
	Major accident, disasters	2.69 (187)	2.6 (150)
	Lost job or retired of close family or friend	13.53 (940)	12.4 (725)
	Death of a pet	9.27 (644)	9.5 (553)

[*] Hypertension as defined by the receipt of treatment for high blood pressure or a blood pressure of more than 140/90 mm Hg at trial entry.

[†] Diabetes as defined by participants' report of diabetes mellitus, a fasting glucose level of at least 126 mg per decilitre (≥7 mmol per litre) or receipt of treatment for diabetes.

[‡] Depressive symptoms as defined by 10-item Centre for Epidemiologic Studies Depression scale score of ≥8.