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Is Stress an Overlooked Risk Factor for Dementia? A Systematic Review from a Lifespan Developmental Perspective

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Abstract

Stress exposure and stress reactivity may be potent factors associated with increased risk of dementia. The 2017 Lancet Commission on Dementia and its 2020 update reviewed modifiable risk factors associated with dementia, but stress was not addressed directly. The present study provides a focused review of the association between stress and dementia across the lifespan, with measures of stress including stress exposure, psychological stress, posttraumatic stress disorder (PTSD), and biological markers of stress. Published research articles were identified in the American Psychological Association PsycINFO database (1887–2021), Web of Science database, and Google Scholar. A total of 53 samples from 40 studies published from 1985 to 2020 met inclusion criteria. Results suggest that stressful life events that occur earlier in the lifespan, such as loss of a parent, psychological stress experienced in midlife, and extreme stress responses, i.e., PTSD, correlate with higher risk of dementia. Although results generally are mixed, a consistent theme is that stress experienced earlier in the lifespan and chronic stress portend the greatest risk of dementia. Reducing stress exposure and improving stress management when stress exposure cannot be changed are thus relevant strategies in dementia risk reduction.

Keywords Stress exposure · Stress reactivity · Dementia · Alzheimer's disease · Lifespan development · Risk factors

Dementia is a worldwide health challenge that has devastating effects on people's quality of life, family and caregivers, and finances, as well as on social services. Dementia entails loss in multiple cognitive functions sufficient to interfere with ability to take care of daily needs. The first disease-modifying treatment for Alzheimer's disease (AD), which is the most common cause of dementia, has just been approved by the US Food and Drug Administration, albeit with conditions for use and based on mixed evidence (Selkoe, 2021). Given the discouragingly slow development of drugs and history of failed clinical trials, research has turned to identifying modifiable factors that might reduce dementia risk or delay the onset of dementia. Although inconsistencies exist, summaries and reviews suggest that cardiovascular factors (e.g., diabetes, mid-life obesity, mid-life hypertension), low formal education, lifestyle factors (e.g., physical inactivity, smoking, diet), and other psychosocial factors (e.g., depression, social isolation) are important modifiable risk factors for dementia (Baumgart et al., 2015; Livingston et al., 2020; World Health Organization, 2019). Increasingly, these reviews are adopting lifespan developmental models, resulting in recommendations for individual and population interventions across the lifespan to mitigate dementia risk (Livingston et al., 2020). A number of multi-domain prevention trials are in progress, which are targeting vascular factors, physical exercise, diet, and cognitive training. Results indicate some improvement in cognitive performance attributable to these programs (Bott et al., 2019).

Missing from both risk factor summaries and prevention trials is consideration of the role of stress. Although

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stress was not identified as a risk factor for dementia (e.g., Livingston et al., 2020), previous research indicates well-established associations between stress and the risk factors for dementia cited above (e.g., cardiovascular disease and depression, see Gawlik et al., 2019; Hammen, 2005; Johns, 1973; Monroe et al., 2009; Stanley & Burrows, 2008). We further suggest that stress may be a risk factor for dementia in its own right, including aspects of stress exposure and response that might be amenable to established interventions for stress developed for other health conditions or stressful situations (Chiesa & Serretti, 2009; Forneris et al., 2013).

Stress may influence development of dementia via cellular aging, as well as structures involving hippocampus and amygdala (McEwen & Sapolsky, 1995; Miller & Sadeh, 2014), brain regions that are most affected by processes associated with dementia. Prior reviews have summarized evidence for the associations between a diverse range of stress-related constructs, including neuroticism, psychological distress, stressful events, perceived stress, and posttraumatic stress disorder (PTSD) and various cognitive outcomes, including dementia of different types, and AD in particular (Epel, 2020; Greenberg et al., 2014; Stuart & Padgett, 2020). However, the evidence has been mixed, and no review has included a comprehensive summary of stress and dementia.

Stress is a process involving multiple dimensions, including both stress exposure and stress response. Figure 1 displays the stress dimensions, as well as the life stages in which the stress experiences occurred, that were examined in the current review. Stress exposure refers to objective experience of stress (i.e., occurrence of stressors or putatively stressful life events). Stress response encompasses psychological reactions to stressors (i.e., perceived stressfulness of one's life) and changes in biomarkers (e.g., cortisol, alpha-amylase, pro-inflammatory cytokines) that are commonly measured as indicators of physiological responses to stressors (Nater et al., 2013). Stress exposure and stress response can be further differentiated. Stress exposure may differ according to duration (e.g., chronic vs. episodic) and intensity (e.g., PTSD-qualifying traumatic events vs. stressful events). Stress response may also vary in intensity, with PTSD located at the extreme end of stress response intensity. As different dimensions of stress may differentially correlate with dementia development, we separately consider stress exposure and stress response.

It is likely as well that there are differential effects of stress on the development of dementia depending on the life stages in which the stress is experienced (Grande et al., 2020). There may be lasting effects of early life adversity or deprivation on a variety of later life cardiometabolic risk factors for dementia, as well as for dementia (Deighton et al., 2018; Ehrlich et al., 2016; Hughes et al., 2017). More proximal stress exposures have also been suggested to be consequential (e.g., Peavy et al., 2012).

The purpose of the present report is to provide a systematic review of associations between different dimensions of stress and dementia from a lifespan developmental perspective. Specifically, we examined how stress experienced at different stages of life (e.g., early life vs. midlife vs. late adulthood) was associated with the risk of dementia. Both stress exposure and stress response were examined. Because the literatures are separate, we separately reviewed the relations between PTSD diagnosis and dementia. Consistent with extant reviews, we refer to risk factors for dementia and potentially modifiable factors that might reduce dementia risk, while recognizing that

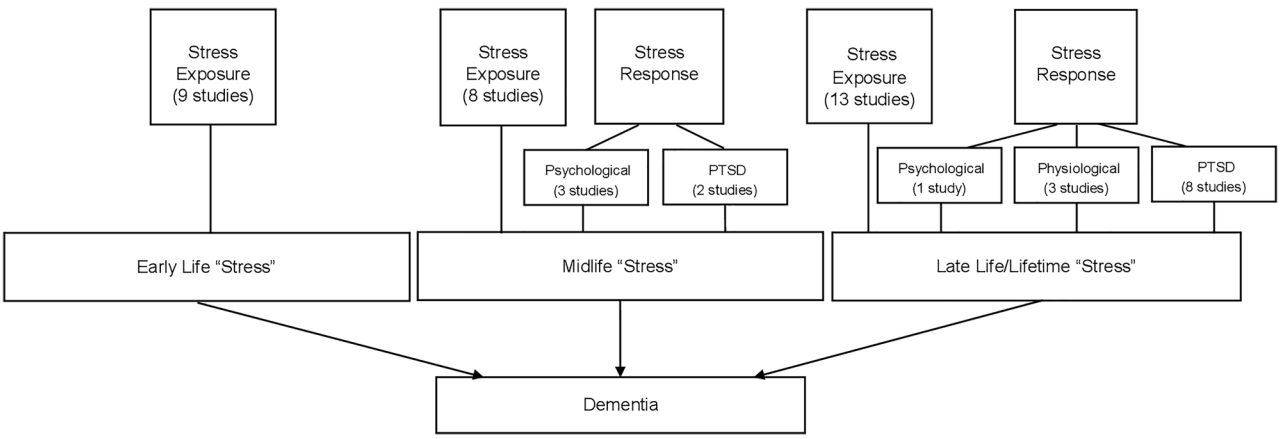

Fig. 1 Diagram for the dimensions of stress and the life stages in which the stress experiences occurred. Within each life stage, we show only those dimensions where there was available to be examined in the current review. Conceptually, stress exposure and stress responses take place across the life span. The current review includes 40 studies. Some studies are included multiple times in the figure as they encompassed multiple life stages

these variables represent correlational rather than causal evidence.

We reviewed both prevalence and incidence studies of dementia. Dementia encompasses a variety of etiologies or subtypes, the most common of which is AD type dementia. The next most common types of dementia include vascular dementia and dementia with Lewy bodies. Most studies separately present results for total dementia or for AD alone, or for one outcome and not the other. As AD comprises about 75% of all dementia cases, results for all dementias combined are driven in large part by AD. Only a very limited number of studies specify other subtypes of dementia. We therefore focus on total dementia, but separately evaluate AD where possible or where that is the only outcome presented.

Methods

The initial pool of relevant studies was obtained by conducting keyword searches in the American Psychological Association's PsycINFO database (1887–2021), Google Scholar, and Web of Science database for journal articles and unpublished dissertations and theses. Search terms included combinations of "stress," "stressor," "life events," "adversity," "adverse childhood experiences (ACEs)," "PTSD," "cortisol," "alpha-amylase," "cytokines" and "dementia" and "AD." We excluded studies that tested health-related life events (e.g., heart attack, cancer) as stressors. Citations within included studies were inspected for additional studies. We continued this iterative process until no new study could be found. The primary criterion was that each study assessed at least one dimension of stress (stress exposure, psychological or physiological stress responses) or PTSD diagnosis and assessed dementia status using a standardized assessment procedure (clinical diagnosis or validated classification based on measures of cognitive status). A small number of studies focused only on AD, which we include in the supplement. Studies that included generic cognitive impairment or cognitive decline as the primary outcome were excluded. Literature on risk and protective factors for dementia is sparse prior to the early 1990s, possibly reflecting a general absence of research on non-genetic or environmental risk factors for dementia. As shown in Fig. 2, 135 full-text articles were assessed for eligibility. Table S.1 presents the PRISMA checklist. Based on our inclusion criteria, 40 studies with a total of 53 samples published between 1985 and 2020 were included in the current study.

We included both dementia prevalence and dementia incidence studies. Prevalence studies took a case–control design and compared previous stress exposure or retrospective reports of stress exposure in those with and without diagnosed dementia. Incidence studies used a prospective cohort design such that stress and dementia status were assessed at baseline, and only participants who were initially dementia-free were included. Dementia status was then evaluated during follow-up assessments.

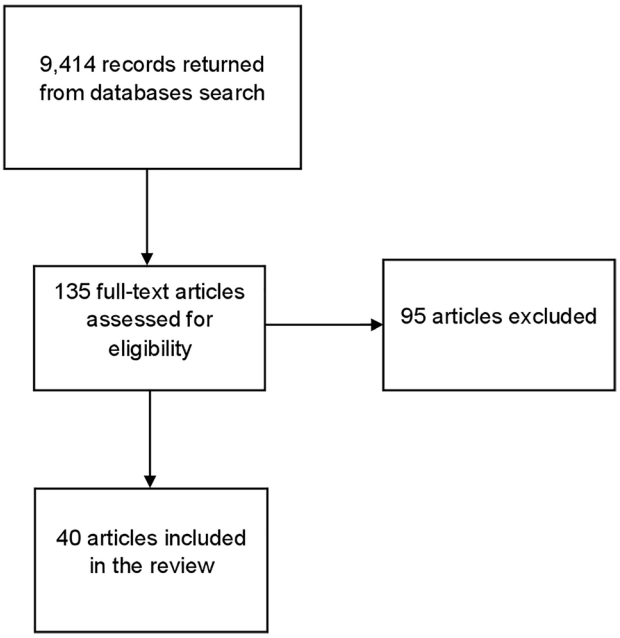

Fig. 2 Flowchart outlining retrieved, excluded, and evaluated articles

The lifespan period in which stress experiences occurred was coded based on ages at baseline assessment (e.g., age means, ranges, and variances). Studies examined different dimension of the stress process (e.g., stress exposure, biomarkers of stress) in different domains (e.g., interpersonal stress, financial stress). Thus, multiple effect sizes for the relationship between stress and dementia were reported for a given sample of subjects, resulting in a total of 285 effect sizes reported for the 53 samples. To optimize comparability across included studies, we extracted results estimated from models that were adjusted for the least number of covariates. An estimated odds ratio (OR), hazard ratio (HR), or incidence rate ratio (IRR), and respective 95% CIs and *p* values were extracted from the univariate or multivariate model reported in each study. ORs were reported in prevalence studies, whereas HRs and IRRs were reported in incidence studies (Sedgwick, 2010; Stare & Maucort-Boulch, 2016). When the value of the statistic is larger than 1.0, those exposed to stress are more likely to be classified as demented than those not exposed. When the applicable statistic equals 1.0, those exposed and those not exposed to the measured stress are equally likely to be classified as demented. To compare results across studies and identify patterns across results, we considered results to be significant if the probability value was less than 0.05. The reported test statistic (OR, HR, or IRR) can be considered an effect

size. Effect sizes smaller than 1.5 were considered small; between 1.5 and 4.9, moderate; and larger than 5.0, large (Chen et al., 2010).

Table S.2 describes each sample as well as each subsample separately (e.g., men and women). Figures 3, 4, 5, 6, 7 and 8 show plots of study effect sizes and 95% CIs reported for the relations between stress and dementia for each stress variable by life stage. Only full sample results are portrayed. Where there were multiple measures of stress in one study, all are plotted in the respective figure. If a study included multiple life stages, the relevant stress variables were plotted in the figure corresponding to that stage. Studies were not included in the figure if insufficient information was supplied. For example, some effects were not plotted due to lack of information for effect sizes and confidence intervals (e.g., Persson & Skoog, 1996; Sperling et al., 2011; Umberson et al., 2020). Figures for AD are presented in the supplementary information.

Results

Stress in Early Life and Dementia

Stress Exposure Eight studies (24 effect sizes plotted in Fig. 3) tested the relations between stress exposure that occurred before age 16 or 18 and dementia risk, seven prevalence studies and one incidence study. Among the four studies that tested the associations between the endorsement of multiple stressful or traumatic life events before age 18 and dementia risk, three of them reported significant links between cumulative stress exposure and prevalence (Persson & Skoog, 1996; Radford et al., 2017) or incidence (Donley et al., 2018) of dementia, but one did not (Pilleron et al., 2015). Five studies reported the associations between different specific ACEs and prevalent dementia. The strongest association was found between

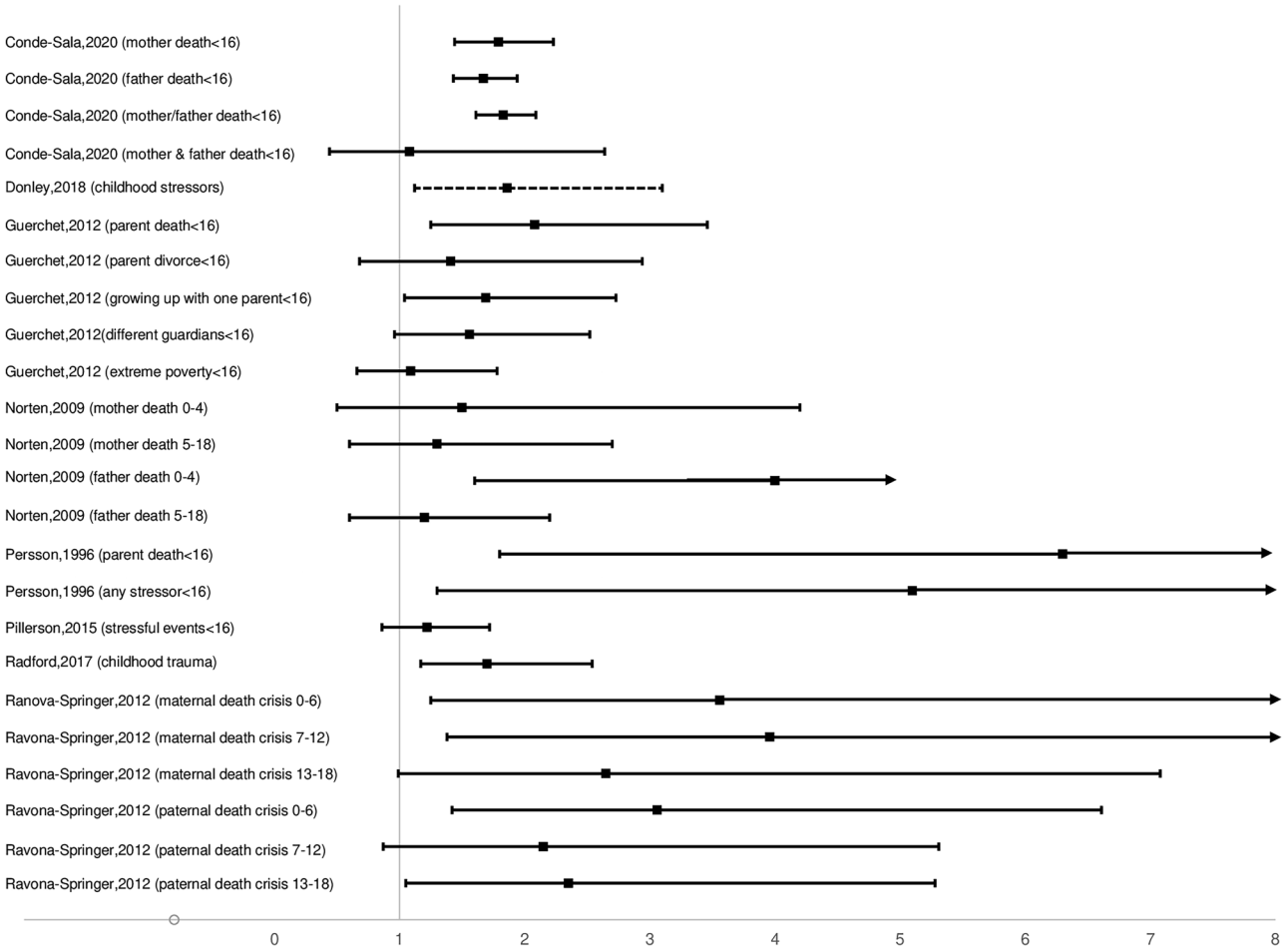

Fig. 3 Associations between stress exposure at early life stage and total dementia. Seven prevalent studies and 1 incident study are plotted. Some effects reported in Persson and Skoog (1996) were not plotted due to lack of information for effect sizes and confidence intervals. Notes: Rows show study and specific measures evaluated. OR is indicated by a black square and 95% CIs by a solid line for prevalent studies and a broken line for incident studies

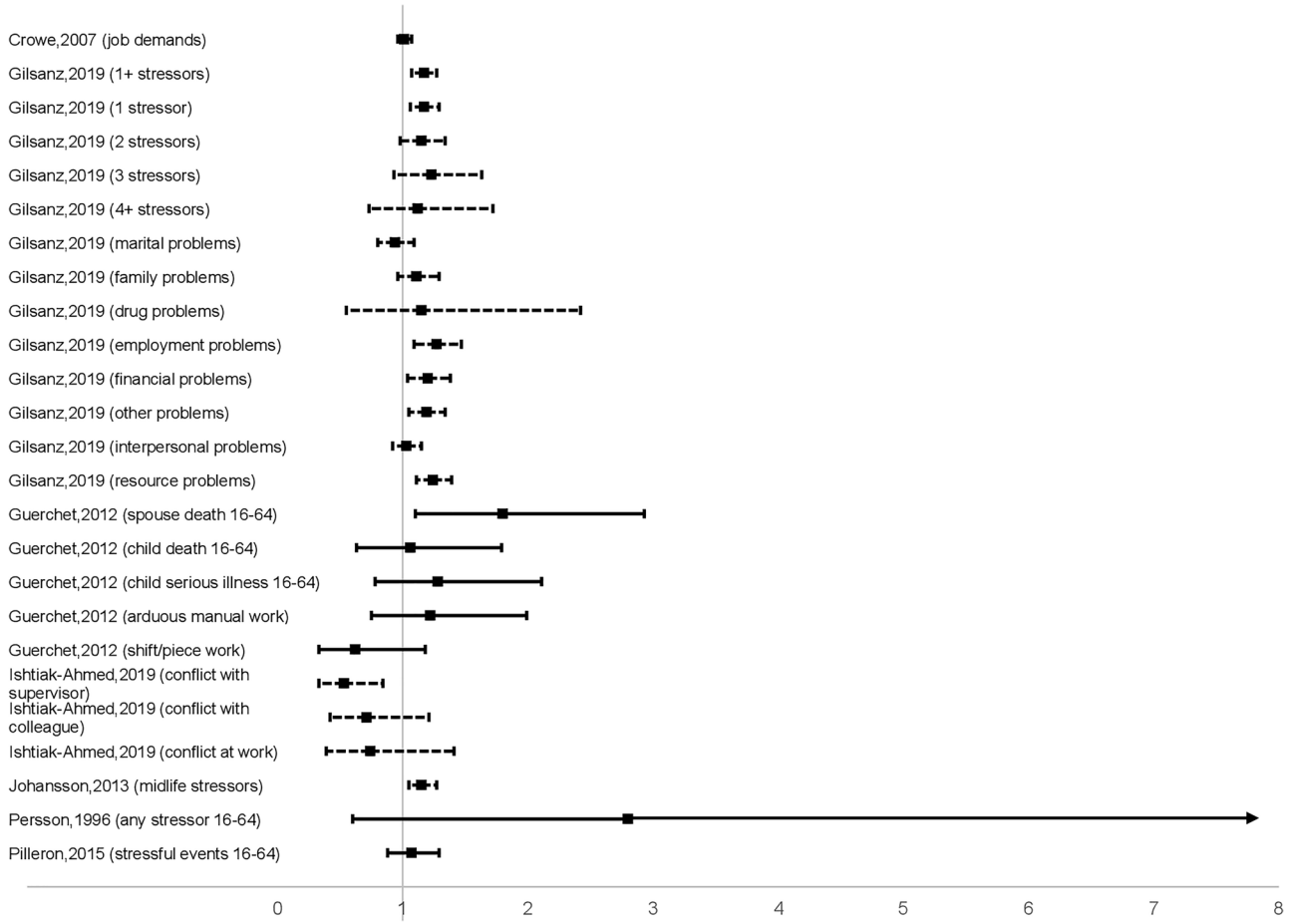

Fig. 4 Associations between stress exposure at midlife stage and total dementia. Four prevalent studies and three incident studies are plotted. Umberson et al. (2020) was not plotted due to the lack of information for confidence interval. Some effects reported in Persson and Skoog (1996) were not plotted due to lack of information for effect sizes and confidence intervals or extremely large effect size. Notes: Rows show study and specific measures evaluated. OR is indicated by a black square and 95% CIs by a solid line for prevalent studies and a broken line for incident studies

parental death and greater rates of dementia (Conde-Sala & Garre-Olmo, 2020; Guerchet et al., 2012; Norton et al., 2009; Persson & Skoog, 1996; Ravona-Springer et al., 2012), as effect sizes ranged from moderate to large. Other stressful life events rarely displayed significant effects. Three studies examined the associations between multiple ACEs and risk of AD (Broe et al., 1990; Donley et al., 2018; Radford et al., 2017; Fig. S.1), but only one study showed a significant association (Radford et al., 2017).

Stress in Midlife and Dementia

Thirteen studies examined the associations between stress and dementia risk roughly between ages 16 and 64. Figures 4, 5 and 6 display the effect sizes and 95% CIs reported for total dementia, with separate plots for stress exposure, psychological stress, and PTSD, respectively.

Stress Exposure Among the four studies that tested the relations between stress exposure in midlife and dementia prevalence (8 effect sizes plotted (solid lines) in Fig. 4), no significant relation was consistently reported. There was a moderate correlation between death of a spouse and dementia risk (Guerchet et al., 2012). Arduous manual work also significantly correlated with dementia risk (Persson & Skoog, 1996, not plotted). No other specific stressful life events, nor total number of events in midlife, significantly correlated with dementia (Crowe et al., 2007; Guerchet et al., 2012; Persson & Skoog, 1996; Pilleron et al., 2015).

In contrast, for incident dementia (17 effect sizes plotted in Fig. 4), cumulative stressors were found to significantly predict incident dementia in both men and women (Gilsanz et al., 2019) and in a sample of women (Johansson et al., 2013), although effect sizes were small. There was no statistically significant evidence of a dose–response relationship between number of stressors and increased incidence. Death

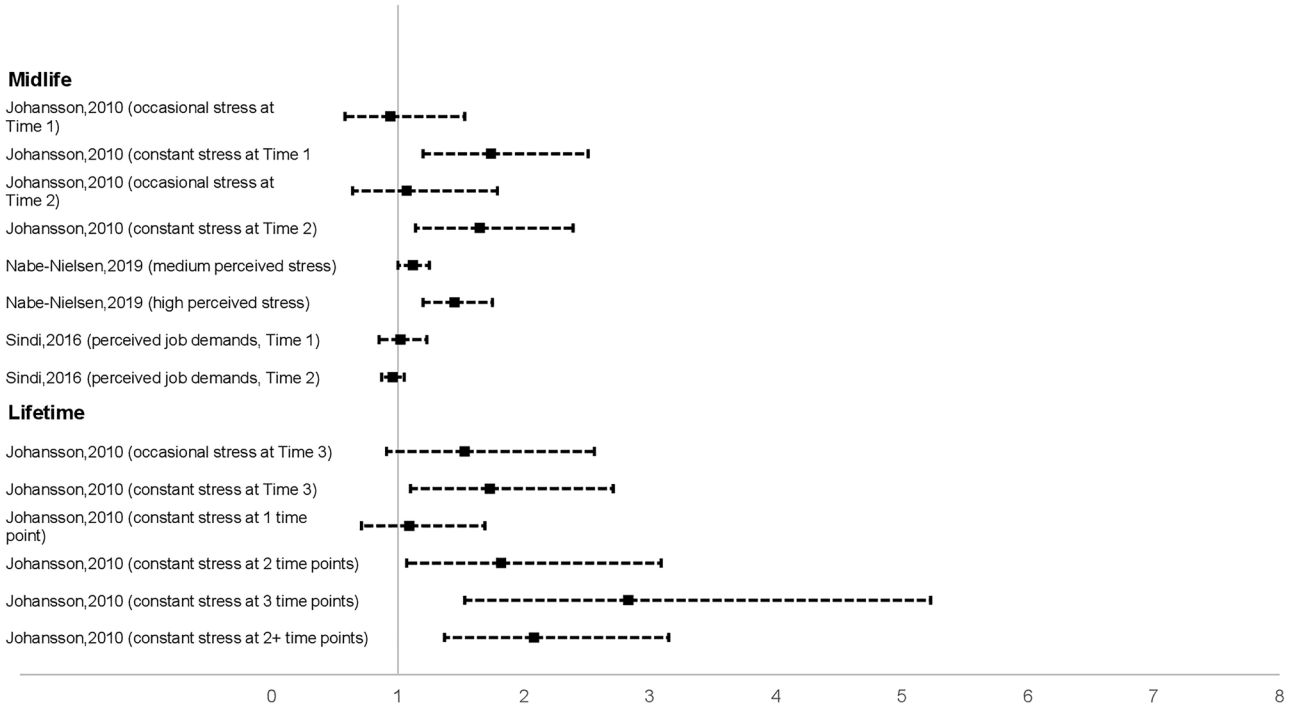

Fig. 5 Associations between psychological stress in midlife and lifetime/others and total dementia. Three incident studies are plotted. Notes: Rows show study and specific measures evaluated. OR is indicated by a black square and 95% CIs by a solid line for prevalent studies and a broken line for incident studies

of a child before age 40 significantly increased incidence of dementia (Umberson et al., 2020, not plotted). Job-related stressors inconsistently correlated with incident dementia (Gilsanz et al., 2019; Ishtiak-Ahmed et al., 2019).

For AD, significant positive association between total number of stressors and AD incidence was observed in one study (Johansson et al., 2013).

Psychological Stress Among three studies that investigated the association between psychological stress in midlife and incident dementia risk (8 effect sizes plotted in the upper part of Fig. 5), small to moderate effect sizes were found between high levels or constant psychological stress and dementia incidence (Johansson et al., 2010; Nabe-Nielsen et al., 2019). Lower or occasional stress was not significantly correlated with dementia. Perceived work-related stress in midlife was not found to correlate with dementia incidence (Sindi et al., 2017). Similar results were reported for AD incidence (Johansson et al., 2010; Sindi et al., 2017; see Fig. S.1).

PTSD As shown in the upper part of Fig. 6 (2 studies; 2 effect sizes plotted), evidence for significant correlations in moderate effect sizes between PTSD diagnosed in midlife and incident dementia was provided by both studies (Roughead et al., 2017; Wang et al., 2016). We note, however, that one study consisted of veterans with a documented hospital admission with a primary diagnosis of PTSD (Roughead et al., 2017). The association was not significant when the service record indicated PTSD but no record of hospitalization.

Stress in Late Life and Dementia

Stress Exposure Four studies examined the associations between stress exposure in late life (age 65 and older) and dementia prevalence (12 effect sizes plotted in Fig. 7), with positive associations reported in three studies (Guerchet et al., 2012; Peavy et al., 2012; Persson & Skoog, 1996). Although mixed results were reported for total number of stressors (Peavy et al., 2012; Pilleron et al., 2015), the occurrence of "any stressor" (non-specified) was not significantly related to prevalent dementia (Persson & Skoog, 1996). Specific stressful life events, such as physical illness of a spouse, serious illness of a child, change of residence, and financial status deterioration, were not associated with dementia risk consistently (Guerchet et al., 2012; Persson & Skoog, 1996).

Lifetime Stress and Dementia

Nineteen studies tested the association between lifetime stress and dementia, meaning that stress could have been

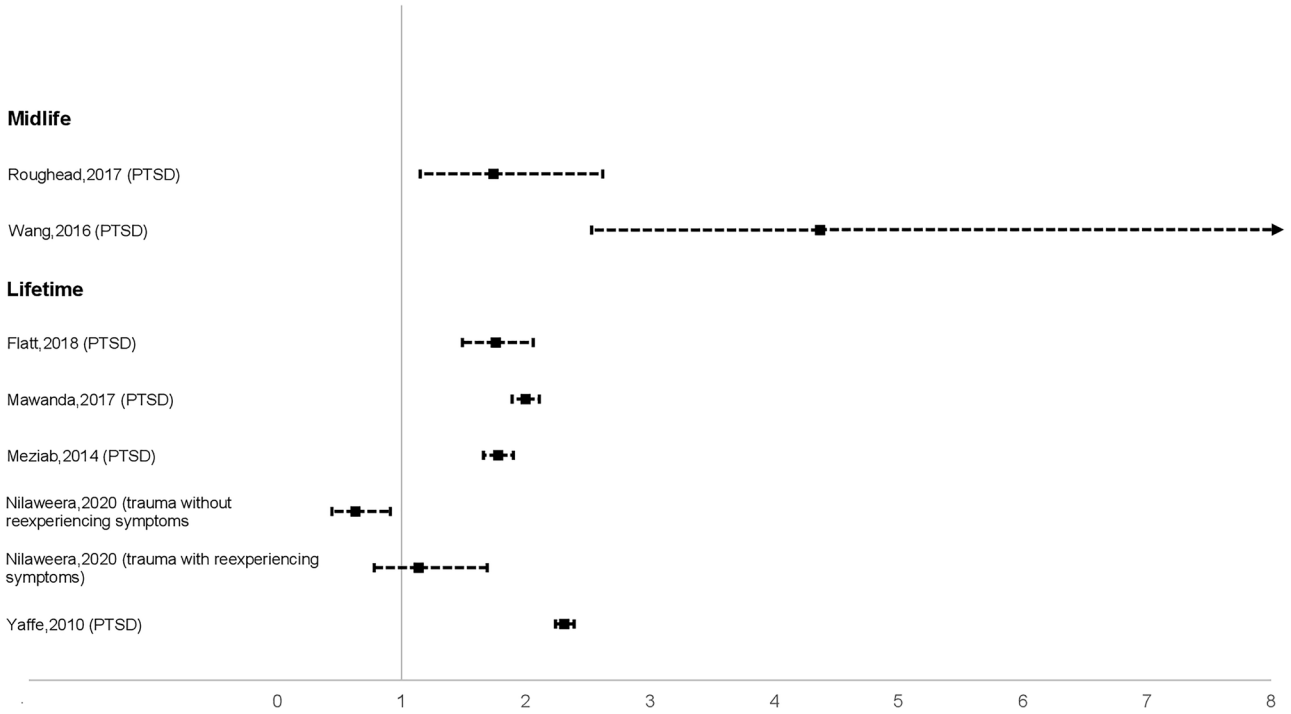

Fig. 6 Associations between PTSD in midlife and lifetime/others and total dementia. Seven incident studies are plotted. Bonanni et al. (2018) and Sperling et al. (2011) were not plotted as they provided descriptive statistics only. Notes: Rows show study and specific measures evaluated. OR is indicated by a black square and 95% CI by a solid line for prevalent studies and a broken line for incident studies

experienced across multiple life phases or not have specified the specific period in the lifespan when it occurred.

Stress Exposure Among five studies that tested the relations between stress exposure and prevalent dementia (11 effect sizes plotted in Fig. 8), two studies suggest that stress exposure correlates moderately to highly with increased dementia risk (Persson & Skoog, 1996; Tsolaki et al., 2010). For specific stressful life events, financial difficulties were found to be connected to prevalent dementia (Chaudhry et al., 2014). Other stressful life events, such as job demands, family problems, and death and illness of beloved ones, were inconsistently associated with dementia (Andel et al., 2012; Chaudhry et al., 2014). Family problems, child loss, and financial difficulties were associated with increased risk of dementia whereas family illness, loss of grandchildren, spousal loss, and job strain were not.

Among four studies that tested the association between stress exposure and incident dementia (7 effect sizes plotted in Fig. 8), mixed results were found. Cumulative stressors moderately significantly predicted incident total dementia (Gerritsen et al., 2017). Specific measures of stress exposure did not correlate with total dementia incidence (Wang et al., 2012).

Regarding AD (Fig. S.2), one study found a significant association between total stressors and prevalent AD (Tsolaki et al., 2010). Grief events were not significantly associated with increased AD risk (Amaducci et al., 1986, not plotted; Chandra et al., 1987, not plotted; French et al., 1985; Jorm et al., 1991), although death of a spouse and endorsement of any of three stressors was associated with increased AD prevalence in a Dutch sample (Jorm et al., 1991). Incident AD was not significantly correlated with stress exposure (Gerritsen et al., 2017; Nilaweera et al., 2020; Sundstrom et al., 2014; Wang et al., 2012).

Psychological Stress When psychological stress experienced in late phases of midlife and/or early stages of older adulthood was tested (6 effect sizes plotted at the bottom of Fig. 5), constant but not acute psychological stress moderately correlated with incident dementia. Constant psychological stress accumulated across two or three time points correlated with increased risk of incident total dementia (Johansson et al., 2010). When AD cases were considered alone (Johansson et al., 2010), constant psychological stress across two or three time points was associated with incident AD (see Fig. S.2).

PTSD As shown at the bottom of Fig. 5 (6 effect sizes plotted), there was a significant moderate association between diagnosis of PTSD and incident dementia in four of the five studies (Flatt et al., 2018; Mawanda et al., 2017; Meziab et al., 2014; Nilaweera et al., 2020, Yaffe et al., 2010). No significant association was observed for AD (Fig. S.2). Two

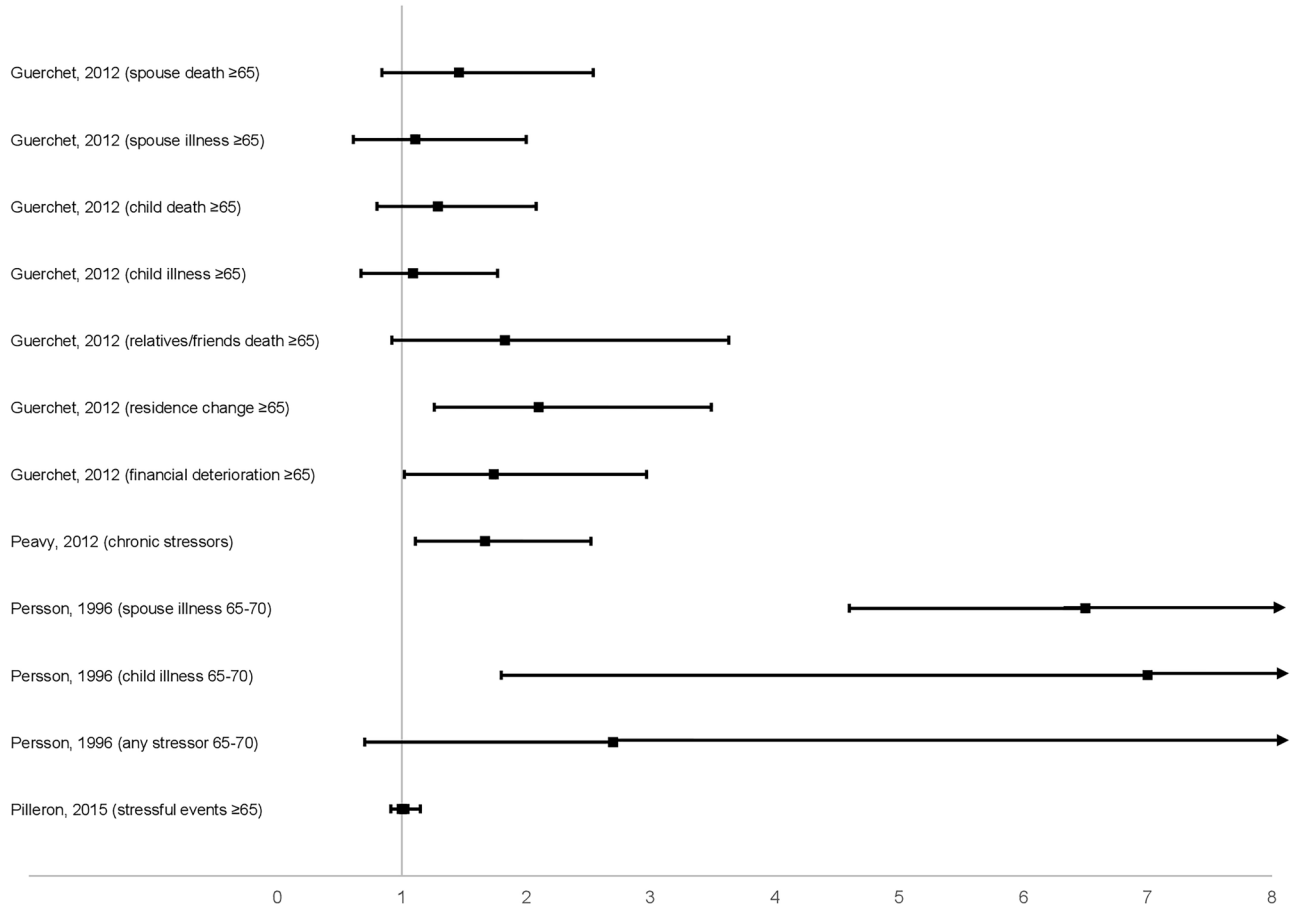

Fig. 7 Associations between stress exposure at late life stage and total dementia. Four prevalent studies are plotted. Some effects reported in Persson and Skoog (1996) were not plotted due to lack of information for effect sizes and confidence intervals. Notes: Rows show study and specific measures evaluated. OR is indicated by a black square and 95% CI by a solid line for prevalent studies and a broken line for incident studies

other studies offered descriptive statistics only. For example, in a sample of dementia patients, 4.5% were evaluated as having a history of PTSD (Bonanni et al., 2018), which was associated with the development of frontotemporal dementia only. A study that tracked a sample of Holocaust survivors who suffered from PTSD reported a diagnosis of dementia in 14% of the subjects (Sperling et al., 2011).

Biomarkers The majority of studies assessed biomarkers and dementia risk on a concurrent basis because biomarker tests were part of the clinical workup for dementia (e.g., Csernansky et al., 2006). We located two prospective studies (Fig. S.2). In a study that tested the prospective effects of cortisol dysregulation on AD risk, urinary free cortisol (UFC) and creatinine (Cr) were measured at multiple points over an average interval of 10.56 years. Results indicated that UFC/Cr level but not UFC/Cr slope significantly predicted AD incidence (Ennis et al., 2017). Serum levels of cortisol, however, were uncorrelated with incidence of total dementia or AD in another study (Schrijvers et al., 2011).

Discussion

The current study reviewed the association between stress exposure and stress response and increased risk of dementia from a lifespan developmental perspective. Although results were not uniform across all studies, three reliable findings emerged. First, in case–control studies, respondents with dementia more often reported ACEs compared to those without dementia. Second, exposure to a greater number of stressors and persistent exposure was associated with higher prevalence and incidence of dementia. Third,

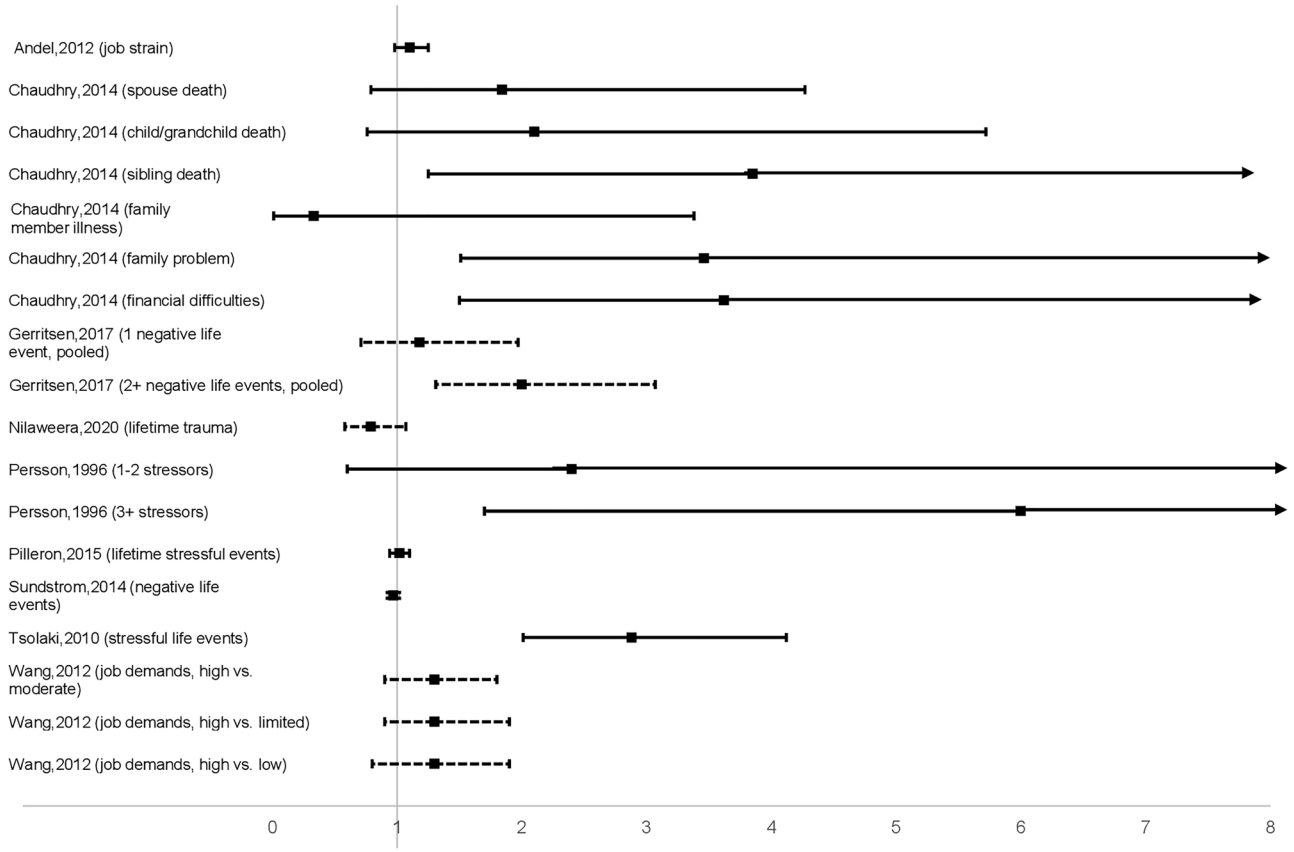

Fig. 8 Associations between lifetime stress exposure and total dementia. Five prevalent studies and four incident studies are plotted. Notes: Rows show study and specific measures evaluated. OR is indicated by a black square and 95% CI by a solid line for prevalent studies and a broken line for incident studies

constant or persistent psychological stress, typically measured in midlife, and PTSD correlated with dementia risk.

The Long Arm of Early Exposure

Consistent with previous research on stress and health (Epel, 2020; Grande et al., 2020), cumulative or severe ACEs were found to demonstrate substantial associations with the development of dementia. Mixed results were common for most specific stressors. However, parental death in childhood was generally related to greater dementia prevalence whereas the death of other relatives was only associated with dementia risk occasionally. For studies examining incidence of dementia, effects were also found to vary on the basis of number of stressors experienced and length of follow-up time. Previous research indicates that ACEs may exert lifelong effects on health. One potential mechanism may be interference with good brain development (Epel, 2020), which may put people at risk of earlier onset of metabolic disease, lower cognitive reserve capacity, and poorer health behaviors, in turn elevating risk for developing dementia.

The Weight of Chronicity

Chronic psychological stress, or psychological stress reported at multiple time points in midlife, correlated with greater incident dementia. These effects were observed more consistently than effects of individual stress exposures that occurred in midlife. Unfortunately, there were no studies of psychological stress self-reported in early life or self-reported in later life.

Congruent with previous reviews (e.g., Elias et al., 2020), a prospective link was supported between PTSD and dementia incidence. Diagnosis of PTSD was associated with increased subsequent risk of dementia. PTSD is an indicator of both exposure to traumatic stressors and intensive and chronic psychological responses to the traumas.

Modifiability of Stress

Literature on risk factors for dementia has focused on identifying potentially modifiable risk factors where timely interventions might mitigate dementia risk. Many of the

exposures reviewed here, such as the occurrence of certain traumatic or very severe stressors, like death of a parent, may not be modifiable. Nonetheless, psychological responses to those experiences can be modified to help people better cope with the effects of stress.

There is a large literature on the beneficial effects of stress management for various health conditions. These approaches include mindfulness-based stress reduction (Grossman et al., 2004), progressive muscle relaxation, cognitive behavioral methods, and psychosocial education (Chiesa & Serretti, 2009; Forneris et al., 2013). There has been some application of mindfulness-based stress reduction in improving memory performance and cognitive function (Haddad et al., 2020), but such modules are not typically included in multicomponent dementia prevention programs.

Stress reduction and stress management may be relevant interventions at any age. For example, widowhood was associated with a threefold increased risk of dementia (Gerritsen et al., 2017), suggesting the utility of grief interventions to process the stress associated with spousal loss. In studies of later life stress exposures, the temporal sequence between stress and onset of dementia always is a concern for inferring a causal association. However, even if stress responses stem from prodromal or early dementia, stress reduction may be a useful intervention to slow or interrupt cognitive change (Wong et al., 2017).

Further Consideration for Dementia Risk Reduction

Among risk factors for dementia most often cited in the literature, several may be considered proxies for stress exposures or stress responses. In particular, both the WHO risk reduction guidelines (World Health Organization, 2019) and the Lancet Commission (Livingston et al, 2020) include depression on their lists of modifiable risk factors even though depression may be a prodromal symptom of dementia. Although stress and depression share a bidirectional association (Hammen, 2015), it seems plausible that the association between depression and dementia, especially when depressive symptoms are not part of the dementia prodrome, may in part reflect a greater history of stress exposure, psychological response to stress, and associated biological stress responses in those who develop dementia. Stress is plausibly the fundamental risk factor, with depression a manifestation of psychological stress.

Effects of stress on dementia may also index important lifestyle factors, such as smoking and physical inactivity (Stubbs et al., 2017; Todd, 2004), that could be modifiable. Established associations between stress and hypertension (Spruill, 2010) or other cardiovascular disease (Assadi, 2017) suggest that these recognized risk factors for dementia may also reflect the role of stress. Finally, early life stress exposures include some of the same variables considered indicators of early life socioeconomic disadvantage, which has in turn been associated with poorer cognitive outcomes in later life (Greenfield & Moorman, 2019).

Interventions designed to help people lower stress and improve coping skills to regulate psychological stress, thus, may have a synergistic place in programs to reduce dementia risk. Indeed, addressing multiple risk factors simultaneously may be the most effective strategy to reduce the risk of dementia (Rosenberg et al., 2020). We recommend that multi-component lifestyle programs for preventing or delaying the development of dementia in later life might include stress reduction and regulation in addition to such interventions as vascular monitoring, physical exercise, nutrition counseling, and cognitive training (Kivipelto et al., 2020). Because many of the stress-related risk factors for dementia occur relatively early in life, and because they are not specific to dementia but also are risks for other negative health outcomes, prevention programs do not need to be advertised as specific to dementia. For example, support programs for children who have lost a parent may reduce children's distress (Bergman et al., 2017) but also provide a longer-term benefit in reducing risk of dementia. Mindfulness-based stress reduction programs targeting hypertension (Lee et al., 2020) may have secondary benefits for dementia.

Beyond strategies targeted on individuals, population-wide dementia risk reduction strategies offer further opportunities (cf., Livingston et al., 2020). Currently recommended population-wide strategies include reducing population exposure to air pollution and improving levels of education. We recommend targeting social determinants of health that would reduce stress and modulate stress response at a population level, especially with minoritized groups who are at elevated dementia risk (Chin et al., 2011).

Limitations and Future Directions

First, due to the limited number of available studies, we were not able to systematically review how the association between stress and dementia may vary across different sampling characteristics (e.g., education level, SES) and study design features (e.g., prospective self-reported stress measures vs. retrospective other-reported measures vs. documented records of life experiences). Because it is prohibitive for any single researcher to follow a birth cohort prospectively until some begin to develop dementia, design compromises are inevitable. Second, limited evidence was available about the prospective association of biomarkers of stress on dementia risk, permitting no conclusion whether elevated stress biomarkers contribute to subsequent development of dementia. Such evidence would be useful in pointing to mechanisms underlying persistent exposure to stress or chronic psychological stress. Third, there is a lack of literature testing the effects of stress in broader societal

context (e.g., a financial recession) on the development of dementia. Fourth, our model of stress for purposes of this review does not show all of the factors that may exacerbate or buffer stress such as stress appraisals, social support, coping skills, and socioeconomic resources. As implied by the notion of stress proliferation (Pearlin et al., 2005), acute and chronic stressors occur in concert with one another, making it impossible to identify a single stressor that exerted determinative effects on the development of dementia. The dynamic interplay between stressful events and stress reactions that unfold over people's lifetime likely puts people at greater risk of dementia (Wheaton & Montazer, 2010). Examining the associations among distinct stress experiences across the life course in combination with contextual factors may help achieve a better understanding of the possible additive, cumulative, and interactive effects of stress experiences on the development of dementia.

Conclusions

The current study provided a systematic review of the relations among different types of stress and dementia. This review suggests that chronic stressful events and reactions experienced earlier in life (e.g., childhood and midlife) have the strongest effect on dementia risk. Although findings appear to depend on sampling characteristics and study design features, dementia risk increases as the number or severity of experienced stressors increases or the stress is perceived as chronic. Integration of these studies highlights the importance of examining different dimensions of the stress process from a lifespan developmental perspective. According to the findings, stress reduction interventions should be included in programs for preventing or delaying the development of dementia.

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Data, Materials and/or Code Availability All data and materials were drawn from publicly available reports found via common academic search engines.

Declarations

Ethics Approval Ethics approval was not required for this review/theoretical manuscript.

Consent of Participant Not applicable–not human subject research.

Conflict of Interest The authors declare no competing interests.

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