



Review article

Understanding the health effects of caregiving stress: New directions in molecular aging

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ABSTRACT

Dementia caregiving has been linked to multiple health risks, including infectious illness, depression, anxiety, immune dysregulation, weakened vaccine responses, slow wound healing, hypertension, cardiovascular disease, metabolic syndrome, diabetes, frailty, cognitive decline, and reduced structural and functional integrity of the brain. The sustained overproduction of proinflammatory cytokines is a key pathway behind many of these risks. However, contrasting findings suggest that some forms of caregiving may have beneficial effects, such as maintaining caregivers' health and providing a sense of meaning and purpose which, in turn, may contribute to lower rates of functional decline and mortality. The current review synthesizes these disparate literatures, identifies methodological sources of discrepancy, and integrates caregiver research with work on aging biomarkers to propose a research agenda that traces the mechanistic pathways of caregivers' health trajectories with a focus on the unique stressors facing spousal caregivers as compared to other informal caregivers. Combined with a focus on psychosocial moderators and mechanisms, studies using state-of-the-art molecular aging biomarkers such as telomere length, p16^{INK4a}, and epigenetic age could help to reconcile mixed literature on caregiving's sequelae by determining whether and under what conditions caregiving-related experiences contribute to faster aging, in part through inflammatory biology. The biomarkers predict morbidity and mortality, and each contributes non-redundant information about age-related molecular changes –together painting a more complete picture of biological aging. Indeed, assessing changes in these biopsychosocial mechanisms over time would help to clarify the dynamic relationships between caregiving experiences, psychological states, immune function, and aging.

1. Dementia caregiving and health risks

Substantial evidence points to dementia caregiving as a risk factor for health. Compared to noncaregivers, men and women who provide care to a spouse with dementia have more infectious illness episodes (Kiecolt-Glaser et al., 1991), poorer immune responses to influenza virus and pneumococcal pneumonia vaccines (Kiecolt-Glaser et al., 1996; Glaser et al., 2000; Vedhara et al., 1999), slower wound healing (Kiecolt-Glaser et al., 1995), and greater risk for depression, hypertension,

cardiovascular disease, metabolic syndrome, diabetes, and frailty (Kiecolt-Glaser et al., 1995; Vitaliano et al., 2005, 1996; Lee et al., 2003; von Kanel et al., 2011a, 2011b; Fredman et al., 2010a; von Kanel et al., 2008; Kolanowski et al., 2004; Dassel and Carr, 2016; Shaw et al., 1999; Grant et al., 2002; Vitaliano et al., 2002; Roth et al., 2019). Data from a private healthcare insurer showed that spousal dementia caregivers were treated more often for anxiety disorders, rheumatologic diseases, and diabetes than spouses of non-demented partners; they also had a higher incidence of falls, fractures, fever, urinary tract infections, and

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emergency room visits (Kolanowski et al., 2004). One systematic review found that caregivers had higher cortisol and poorer cognition, with mixed evidence for effects on cardiovascular and immune markers (Allen et al., 2017). In a recent meta-analytic review that examined the connection between interpersonal losses in older adulthood (specifically, spousal caregiving and widowhood) and cognitive decline, it was found that 90% of cross-sectional and longitudinal studies consistently showed a small, but modest relationship between spousal caregiving and a decline in cognitive functioning. The key cognitive consequences of spousal caregiving were found for the domains of episodic memory and attention (Wu-Chung et al., 2022). Furthermore, spousal caregivers of dementia patients have a greater risk of developing dementia themselves. A comparison of spouses of dementia care recipients to those with spouses who did not have dementia had a hazard ratio six times higher for developing dementia over the next 12 years (Allen et al., 2017; Norton et al., 2010).

Researchers have documented a number of behavioral risk factors for caregivers' health, including diminished social support, heightened loneliness, deteriorating mental health, disrupted sleep, reduced physical activity, and poorer medication adherence compared to non-caregivers (Vitaliano et al., 2003). Nearly half of dementia caregivers reported not being able to keep appointments with physicians, and almost a third said they frequently or occasionally missed medication doses (Wang et al., 2015). Dementia caregiving also adversely affects dietary intake; 37.5% of dementia family caregivers had a "compromised" nutritional status, compared to 21.1% of family caregivers for unspecified medical conditions (Rullier et al., 2014; Torres et al., 2010). Higher depressive symptoms elevated the risk for poor nutritional status. Caregiving for a family member with dementia is a chronic stressor because of the physical and psychological strain that can occur over extended, often indeterminate, time periods, as well as the secondary financial, occupational, and social stressors; in addition, high levels of vigilance may be necessary because of care recipients' unpredictable and uncontrollable behaviors, a notable source of stress (Schulz and Sherwood, 2008).

One core pathway behind many of the diverse health risks associated with caregiving is chronic inflammation, and more specifically, sustained overproduction of a proinflammatory cytokines (Kiecolt-Glaser et al., 2003; Gouin et al., 2012; Lutgendorf et al., 1999; Mausbach et al., 2019; von Kanel et al., 2006a, 2006b). In a 30-study meta-analysis (Roth et al., 2019), caregivers had significantly higher baseline inflammation levels compared to controls, and the differences were even more consistent when limited to dementia caregivers. Overall, the effects were small in magnitude; even so, many small-but-significant effects carry practical significance, e.g., the benefits of healthy eating and exercise are small but significant (He et al., 2007; Gillison et al., 2009; Robles et al., 2014). In addition, most of the studies included in the meta-analysis were cross-sectional, which can obscure complex dynamics that unfold over time. For example, in a systematic review of dementia caregiving and stress-related biomarkers that included a wider array of study designs, dementia caregiving was more consistently associated with impaired immune responses to challenge than with the resting baseline levels, among the 54 studies featuring immune outcomes (Allen et al., 2017). Likewise, IL-6 increases with age in as part of a process termed inflammaging (Franceschi et al., 2000; Maggio et al., 2006). As such, longitudinal studies are uniquely suited to tease apart the effects of caregiving from the correlation with age (Allen et al., 2017). Indeed, we previously found that spousal dementia caregivers' IL-6 levels increased four times faster than non-caregivers across a six-year period (Kiecolt-Glaser et al., 2003). Importantly, these effects were not due to premorbid differences between the demographically matched caregivers and controls; both groups excluded individuals with a wide variety of health problems. The few differences between the groups fell in opposing directions: caregivers smoked less (in a marginally significant trend) but drank more than controls. Caregivers' IL-6 trajectories remained steeper after accounting for health behaviors

and all other potential confounds. Surprisingly, even after their spouse died, former caregivers' IL-6 levels kept pace with current caregivers, suggesting that caregiving's immunological impact continues to reverberate for years beyond the caregiving experience.

In turn, higher levels of proinflammatory cytokines have been linked to a spectrum of major health problems associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, certain lymphoproliferative diseases or cancers (including multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia), periodontal disease, and Alzheimer's disease (Ershler and Keller, 2000; Bradburn et al., 2017). Elevated levels of peripheral inflammation, including CRP, IL-6, and TNF- α , in older adults have been identified as a risk factor for future cognitive decline, specifically in the domains of global cognition, episodic memory, executive functioning, and attention (Chi et al., 2017; Sartori et al., 2012; Randolph et al., 2005; Beydoun et al., 2018; Bowman et al., 2018; Teunissen et al., 2003). Markers of peripheral inflammation have been associated with reductions in total brain volume, gray matter volume, hippocampal volume, and white matter integrity (Marsland et al., 2015, 2008). Furthermore, one study found that the observed neurodegeneration in gray matter volume mediated the association between peripheral inflammation and cognition (Marsland et al., 2015). The impact of these pathological changes in brain structure, resulting from systemic inflammation, extends to metrics of brain functioning as well. For example, a meta-analytic review of 24 studies highlighted a strong association between peripheral inflammation and brain activity in the hypothalamus, striatum, insula, midbrain, brainstem, as well as the prefrontal and temporal cortices. Peripheral inflammation has also been linked with functional connectivity of canonical networks such as the default-mode network and the dorsal attention network, known to support cognitive performance (Dev et al., 2017; Kraynak et al., 2018; Marsland et al., 2017).

More globally, chronic inflammation may mechanistically connect caregiving with frailty, disability, and, ultimately, death (Taaffe et al., 2000; Hamerman, 1999). Many lines of evidence now indicate that IL-6 may function as a "global marker of impending deterioration in health status in older adults" (Ferrucci et al., 1999). Indeed, although other risk factors like cholesterol, hypertension, and obesity have lower predictive validity among the very old, chronic inflammation continues to be an important marker (Ferrucci et al., 1999). Epidemiological evidence among those 65 and older indicate that IL-6 levels above 3.19 pg/ml had twice the risk of death compared to those in the lowest quintile (Harris et al., 1999). In our study, caregivers would have crossed that line around age 75, compared to age 90 for controls (Kiecolt-Glaser et al., 2003). In short, caregiving-related upticks in systemic inflammation may pave the way for accelerated aging, morbidity, and early mortality.

Heightened inflammation is also a cause and consequence of depression (Kiecolt-Glaser et al., 2015). In fact, the two can reinforce one another in a vicious cycle of treatment-resistant, immune-mediated depression characterized by anhedonia and somatic symptoms (Jokela et al., 2016; Haroon et al., 2018). Even relatively modest levels of anxiety and depressive symptoms can boost proinflammatory cytokine production (Lutgendorf et al., 1999; Fagundes et al., 2013a; Irwin, 2002), fueling the cycle. Across 74 studies, caregivers with more depressive symptoms suffered poorer health outcomes (Pinquart and Sorensen, 2007). Multiple laboratories have reported that the stresses of providing care for a husband or wife with dementia put the caregiving spouse at greater risk for depression and anxiety than well-matched noncaregivers, including a recent analysis of pooled data from 3927 caregivers and matched with 129,798 controls from the Health and Retirement Study (Dura et al., 1990, 1991; Vitaliano et al., 1997; Schulz et al., 1990; Light and Lebowitz, 1989; Gallagher et al., 1989; Liu et al., 2023). The median rate for major and minor depression in dementia caregivers was twice that in community-dwelling older adults (Schulz et al., 1995). A recent meta-analytic review found large effect size differences between dementia caregivers and noncaregivers in depressive symptoms, Hedges' $g = 1.01$, and even greater effects among women, g

= 1.58 (Ma et al., 2018). Critically, elevated depressive symptoms carry physical health risks. After adjusting for sociodemographic data, prevalent clinical and subclinical disease and health risk factors, the risk for mortality was 25%– 43% higher among those with high levels of depressive symptoms (Schulz et al., 2000). The close tie between inflammation and depression may help to explain the elevated health risks.

Of importance, anxiety and depressive symptoms are highly comorbid and, particularly among dementia caregivers. For example, among 181 spousal dementia caregivers without a clinical depression or anxiety disorder at baseline, 60% developed a depressive and/or anxiety disorder within the 24 month follow-up; 37% depression, 55% anxiety, and 32% with both (Joling et al., 2015). Similarly, in a study of 553 dementia caregivers, Barrera-Caballero and colleagues reported a 54.79% presented with significant symptoms of both depression and anxiety, with higher rates of comorbid symptoms in women (Barrera-Caballero et al., 2021). Such comorbidity has been linked with both exacerbated inflammation (Mikocka-Walus et al., 2016) as well as greater resistance to psychological treatments (Romero-Moreno et al., 2021). Thus, assessment and consideration of comorbid mood and anxiety disorders is critical for understanding the impact of psychological functioning on health, particularly in this population.

For dementia caregivers, one question is the extent to which the care recipient's disease severity affects the spouse's mental and physical health, a key mechanism that may explain the risks. In a 176-study meta-analysis, more severe cognitive impairment and behavioral problems in care recipients predicted greater burden, more severe depression, and poorer physical health among caregivers, even after accounting for other key factors such as age, living arrangement, caregiving time, and socioeconomic status (Pinquart and Sorensen, 2007). These associations were robust: 217 studies with null findings would be needed to reduce the results to non-significance. In addition, the link between more time spent caring and poorer health was stronger in dementia caregivers compared to those caring for individuals with other conditions (Pinquart and Sorensen, 2007). These patterns have since been replicated in inflammatory data, with a longer time spent in the dementia caregiver role and more severe dementia linked to higher CRP and IL-6 (Allen et al., 2017).

Among the general population, prior work has linked loss of control, unpredictable negative events, and spousal loss with depressive affect (Pagel et al., 1985); dementia caregivers may commonly experience these scenarios, especially as the care recipient's disease advances. One systematic review found that the care recipients' behavioral problems (inclusive of "neuropsychiatric symptoms", "behavioral and psychological symptoms of dementia BPSD", and "behavioral problems or disturbances") were the most important care recipient-related variable in determining caregiver burden and depressive symptoms; however, care recipients' cognitive function did not play as much of a role in caregiver mental health as might be expected (van der Lee et al., 2014). Anger and hostility are other putative psychological mechanisms. One meta-analysis found significant correlations between dementia caregivers' hostility and their chronic low-grade inflammation, as well as cognitive decline (See et al., 2022). Inconsistencies in the cognitive batteries used to assess care recipients' status, as well as those used to assess caregiver mental health may contribute to these discrepancies. Further, single time-point, cross-sectional studies may not fully capture the relationships between care recipient cognitive status and caregiver burden because it is likely within-subject change in cognitive status over time, rather than between-subject differences, that track with changes in caregiver burden and depressive symptoms over time (Coen et al., 1997; Gallicchio et al., 2002; Leinonen et al., 2001). Indeed, in one large study of dementia caregivers, the relationship between care recipient cognitive function and caregiver distress only emerged longitudinally – not cross-sectionally (Mohamed et al., 2010). Therefore, additional longitudinal research examining relationships between changes in specific facets of care recipient cognition and changes in caregiver mental health

could provide additional insight.

2. Reconciling inconsistent findings: evidence for beneficial effects of caregiving

In contrast to the data detailed above, others have reported little or no harm, or even benefits from caregiving (Bertrand et al., 2006; Freedman et al., 2010b, 2008; Brown et al., 2009; Roth et al., 2018, 2015, 2013; Ramsay et al., 2013; O'Reilly et al., 2015). The healthy caregiver hypothesis asserts that caregiving-related behaviors can serve to maintain caregivers' health, and that this beneficial association can be detected when the effects of caring are appropriately teased apart from the risks associated with exposure to the care recipient's health problems (Brown et al., 2009). Evidence supporting this hypothesis includes seven epidemiological studies that reported greater longevity among caregivers (Bertrand et al., 2006; Freedman et al., 2010b, 2008; Brown et al., 2009; Roth et al., 2018, 2015, 2013; Ramsay et al., 2013; O'Reilly et al., 2015; McCann et al., 2004). For example, short-term mortality was lower among caregivers than noncaregivers (O'Reilly et al., 2015), even among those providing 50 or more hours of weekly care when caregiving was defined by the census question "Do you look after, or give any help or support to family members, friends, neighbors, or others because of either long-term physical or mental ill health/disability or problems related to old age?" In the population-based REGARDS study, 3580 family caregivers who provided care for at least 5 h per week (to those with dementia and a variety of other conditions) were individually matched to 3580 noncaregivers using 15 demographic, health history, and health behavior variables (Roth et al., 2018). Although caregivers had substantially higher depressive symptoms and greater perceived stress than noncaregivers—putative mediators thought to link caregiving-related distress to poor health outcomes—caregivers showed larger inflammatory increases compared to noncaregivers only in one of six inflammatory markers (Roth et al., 2020); and caregivers' seven-year mortality rates were 16.5% lower than noncaregivers (Roth et al., 2018). These paradoxical patterns underscore the need track biopsychosocial mechanisms over both proximal and distal time frames.

Caregiving is thought to provide benefits in part by strengthening connections to family and friends, and by providing caregivers with a sense of meaning and purpose (Freedman et al., 2014). At the same time, large population-based studies include caregivers in widely diverse situations: Those who live with the care recipient versus not, those with varying degrees of burden, those who care for someone with dementia versus another chronic disease in which the care recipient may retain their mental capacities, as well as diverse relatives or friends of the care recipient (spouse, offspring, other relatives, and friends). With broad measures that are not tailored to any one subgroup, some population-based studies may lack the granularity needed to tease apart caregiving from social connection; in many cases decisions to volunteer or offer social support are not obligatory and may cost the helper little (Brown et al., 2009). Such prosocial, time-limited, and voluntary acts of kindness are in stark contrast to more intensive, prolonged caregiving roles, which can be all-consuming and sometimes obligatory. Recent experimental evidence among healthy adults suggests that prosocial acts of kindness enhance leukocyte gene expression by reducing proinflammatory gene expression and boosting innate antiviral gene expression (Nelson-Coffey et al., 2017). Epidemiological literature that includes a large number of secondary, non-obligatory, part-time caregivers or those caring for other types of diseases that do not require as much hypervigilance on the part of the caregiver may simply mirror these experimental findings showing prosocial immune enhancement. By contrast, because dementia care recipients may require around-the-clock supervision, primary caregivers may become housebound and unable to maintain other social relationships. As compared to other types of informal caregivers, spousal caregivers are more likely to be the sole care provider, especially in later life stages, resulting in more substantial burden and related health risks (Chen et al., 2020; Ornstein

et al., 2019). Indeed, dementia spousal caregivers have smaller support networks and report greater loneliness than noncaregivers (Kiecolt-Glaser et al., 1991; Vitaliano et al., 2003; Kiecolt-Glaser et al., 2003; Pinquart and Sorensen, 2007; Moritz et al., 1989). In fact, one study showed that dementia caregivers lost about a third of their support network over a five-year period (Clay et al., 2008). These interpersonal losses are consequential; we found that caregivers who had the greatest immune function decline over a 13 month period had lower levels of social support and were most distressed by care recipients' dementia-related behaviors at study entry (Kiecolt-Glaser et al., 1991). In this study, immune decline was defined by three measures of cellular immune function, blastogenesis with two mitogens (concanavalin A and phytohemagglutinin) as well as antibody titers to latent Epstein-Barr Virus (EBV).

Importantly, the association between caregiver burden and poor physical health was stronger among spousal caregivers compared to other caregiving relationships. Spouses provide more hours of care, they are more likely to live with the care recipient, and 78% report that they are the only care provider for their spouse (Persons NAfCAFR, 2015; Zivin and Christakis, 2007). Compared to offspring caregivers, spousal caregivers also report greater financial and physical burden, as well as higher levels of depressive symptoms (Pinquart and Sorensen, 2011). Potential health effects were highlighted in the large Nurses' Health Study: the risk for coronary heart disease was almost two-fold higher among female spousal caregivers compared to those caring for a parent or friend, with the highest risk among those providing care ≥ 9 h/week (Lee et al., 2003). Additionally, at-home caregivers rate their health more poorly, their subjective burden higher, and they have more depressive symptoms and functional limitations than those who do not co-reside (Pinquart and Sorensen, 2007; Caputo et al., 2016). In an exception, data from the Health and Retirement Study showed that dementia spousal caregivers had higher 12-year survival rates compared to married non-caregivers (Leggett et al., 2020). However, results were qualified by a nuanced interaction, wherein the dose-response association between poorer self-rated health and higher risks for mortality was stronger among non-caregivers than dementia caregivers. This resulted in a survival advantage for spousal dementia caregivers, specifically among participants who rated their health as 'poor' at the initial assessment. Nevertheless, the authors noted that dementia caregivers may have inadvertently had shorter follow-up periods, as widows showed the same apparent survival advantage. Also, models adjusted for depressive symptoms and functional limitations, which are viable mechanisms that contribute to dementia caregivers' risks for earlier mortality.

Furthermore, although increased closeness to the care recipient is an oft-cited benefit of caregiving (Pinquart and Sorensen, 2003), the memory and behavior problems that accompany worsening dementia can change the relationship and impede closeness. More broadly, certain features of dementia caregiving can make it considerably more challenging and less rewarding than non-dementia caregiving. For example, compared to individuals with other diseases, persons with dementia are more likely to exhibit difficult behaviors such as wandering, paranoia, repetitive questions, nighttime agitation, aggression, property destruction, and comprehension problems, among other unsafe or distressing behaviors (Ory et al., 1999). Adding to these difficulties, dementia caregivers can anticipate that the care recipient's functioning will worsen, and the changes will be unpredictable and uncontrollable (Ory et al., 1999). Accordingly, a landmark 84-study meta-analysis found greater depression and stress, as well as poorer physical health, self-efficacy, and well-being among caregivers compared to non-caregivers, with the starker disparities between dementia caregivers and noncaregivers (Pinquart and Sorensen, 2003). Thus, understanding and integrating the broader caregiving literature requires a nuanced focused on the specific features of the caregiving experience.

Consideration of psychosocial moderators may help to explain variation in caregiver outcomes. Psychosocial factors, such as perceived

self-efficacy, may help to determine caregiving's immunological effects. For example, in one study among dementia caregivers, self-efficacy moderated the relationship between caregiving stress and IL-6 (Mausbach et al., 2011). That is, only among caregivers with low self-efficacy was higher stress associated with higher IL-6; this relationship did not exist among those with high self-efficacy. Another factor that may dampen caregiving's inflammatory impact is satisfaction with personal mastery, or the belief that life circumstances are under their control (Mausbach et al., 2011). Harmell and colleagues have written a more comprehensive review on potential resilience factors among dementia caregivers (Harmell et al., 2011). Note that this line of research primarily reports factors that modulate caregiving's effect only among caregivers; that is, although it is possible that caregivers with these resilience factors may fare better than those without, these studies say nothing about how non-caregivers fare in comparison. Among non-caregiving samples, meta-analytic evidence has consistently demonstrated that objective stressors have a greater immunological toll than subjective or perceived stress levels (Herbert and Cohen, 1993; Segerstrom and Miller, 2004). If the same is true in this domain, it would mean, for example, that although caregivers with greater self-efficacy may have better immune function than their caregiving peers with lower self-efficacy, both may have poorer immune function and health outcomes than non-caregivers – even non-caregivers with low self-efficacy (von Kanel et al., 2014).

3. New directions: molecular aging biomarkers

State-of-the-art molecular aging markers could provide additional context needed to reconcile inconsistencies in the current literature. In particular, telomere length, p16^{INK4a}, and epigenetic age are unique biomarkers predictive of morbidity and mortality (Kiecolt-Glaser et al., 2010; Cawthon et al., 2003; Epel et al., 2009; Cohen et al., 2013; Brouilette et al., 2003; Demissie et al., 2006; Gardner et al., 2005; Weng, 2012; Steer et al., 2007; Marioni et al., 2015; Breitling et al., 2016; Epel et al., 2010; Hannum et al., 2013; Teyssier et al., 2012). Together, they provide a more complete assessment of biological aging because they track different age-related molecular changes. For example, even though telomere length and epigenetic age were unrelated, both were independently associated with chronological age (Marioni et al., 2016). A one standard deviation (SD) increase in baseline epigenetic age was associated with a 22% increased risk for mortality. However, in the same cohort, a one SD longer baseline telomere length predicted an additional 11% decrease in mortality risk (Marioni et al., 2016). In another study, epigenetic age was similarly unrelated to telomere length, and frailty was associated with epigenetic age, but not telomere length (Breitling et al., 2016). Up-regulation of p16^{INK4a} expression also appears to be independent of telomere length (Herbig et al., 2004). Accordingly, data on each of these three biomarkers would provide novel, nonredundant aging information; in fact, their combined actions lead to an aging phenotype. Only telomere length has been examined in dementia caregiver research (Damjanovic et al., 2007); however, it has several limitations (discussed below). Thus, additional, more comprehensive data on biomarkers of molecular aging would help to clarify discrepancies in the broad caregiver literature..

Each of these biomarkers can change within two years or less (Epel et al., 2009; Liu et al., 2009; Verhoeven et al., 2015; Puterman et al., 2015; Boks et al., 2015), each has associations with inflammation (Liu et al., 2009; Carrero et al., 2008; O'Donovan et al., 2011; Beach et al., 2015), each is related to decline in cognitive functioning and brain volume (Bussian et al., 2018; Gampawar et al., 2022; Proskovec et al., 2020), and each has been tied to negative emotional responses (depression, anxiety, and/or stress) (Teyssier et al., 2012; Liu et al., 2009; Verhoeven et al., 2015). Thus, combined with data on caregivers' psychosocial experiences, these markers can address, critically, whether and under what conditions dementia caregiving might shorten lifespan and health span.

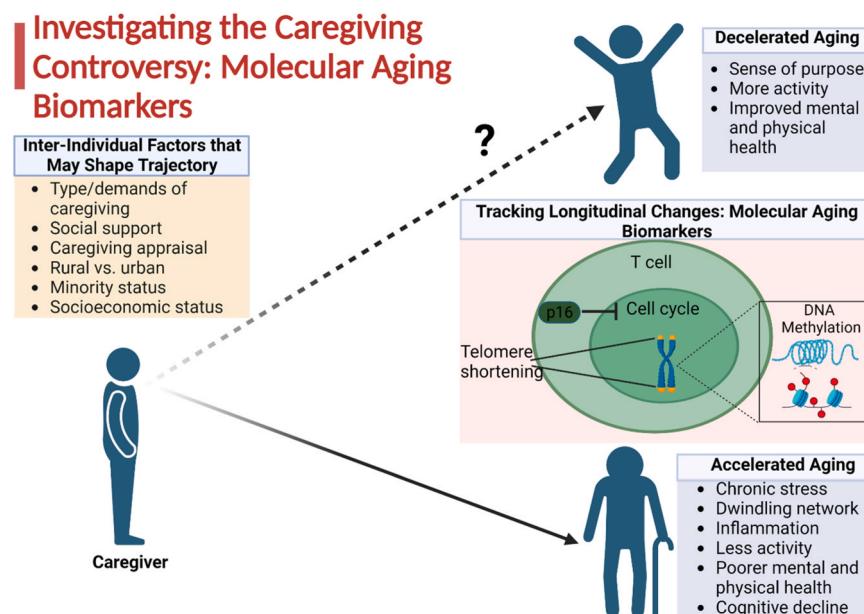


Fig. 1. Investigating the Caregiving Controversy: Molecular Aging Biomarkers. When one becomes a caregiver, many pre-existing factors can help to shape caregiving's psychological and biological impact, such as socioeconomic status. There is substantial longitudinal evidence that caregiving-related demands can accelerate the aging process, leading to faster mental and physical decline. There is also mounting epidemiological evidence that caregiving may have psychological and physical benefits, such as bolstering meaning and purpose. The use of molecular aging biomarkers, such as $p16^{INK4a}$, telomere length, and epigenetic clocks (e.g., in peripheral T cells), can help to shed light on whether, for whom, and under what conditions caregiving can accelerate the aging process. *Created using Biorender.com.*

3.1. T cell telomere length

Caregiving's inflammatory correlates have important implications for T cell telomere length. Telomere length is regulated in part by exposure to proinflammatory cytokines and oxidative stress (Damjanovic et al., 2007; Carrero et al., 2008; Aviv, 2006). Inflammation triggers T cell proliferation, one known cause of telomere shortening (Gardner et al., 2005; Carrero et al., 2008; Aviv, 2004). Oxidative stress promotes telomere erosion during cellular replication (Aviv, 2006). Oxidative stress can also stimulate the synthesis of proinflammatory cytokines such as TNF- α and IL-6 (Lipsey et al., 2008), and thus T cell telomere changes reflect the joint burden of inflammation and oxidative stress (Aviv, 2008).

Shorter telomeres predict age-associated physiologic decline, diseases of aging, and premature mortality (Cawthon et al., 2003; Brouillette et al., 2003; Demissie et al., 2006; Carrero et al., 2008; Epel, 2012; Honig et al., 2012; Ehrlenbach et al., 2009; Farzaneh-Far et al., 2008; Jeanclos et al., 2000; Nawrot et al., 2004; Benetos et al., 2001; von Zglinicki et al., 2000; Samani et al., 2001; Njajou et al., 2009; Kimura et al., 2008; Valdes et al., 2005; Hoen et al., 2011; Simon et al., 2006; Wolkowitz et al., 2010). Telomere length predicts mortality independent of chronological age; for example, in a sample of people who were 60 or older, the mortality rate from infectious disease was more than eightfold higher among those with shorter telomeres than those with longer telomeres, and heart disease deaths occurred more than three times as often in the former than the latter group (Cawthon et al., 2003). Shortened telomeres have been associated with an enhanced risk for infectious disease, hypertension, insulin resistance, cardiovascular disease mortality, rheumatoid arthritis, and diabetes (Epel et al., 2009; Cohen et al., 2013; Brouillette et al., 2003; Demissie et al., 2006; Gardner et al., 2005; Weng, 2012; Steer et al., 2007).

Some data show that dementia family caregivers have shorter telomeres in T cells and monocytes than noncaregivers (Damjanovic et al., 2007). However, the large Nurses' Health Study showed no associations between long-term patterns of caregiver burden and leukocyte telomere length in older women who were caring for an ill or disabled relative (Chang et al., 2018). Findings in T cell proliferation between caregivers

and controls have also been mixed (Damjanovic et al., 2007). Leukocytes include T cells, B cells, and monocytes, and telomeres in these cell types shorten at different rates (Lin et al., 2016, 2015); thus the absence of an association could reflect blood samples with different compositions of cell types (Barger and Cribbet, 2016) – a limitation when measuring telomeres. Data focused on telomere length in CD8 +CD28- T-cells would be ideal for resolving these discrepancies, due to this cell type's central importance in aging (Chen et al., 2018).

A related consideration is that psychological distress drives replication of herpesviruses including cytomegalovirus (CMV) and Epstein-Barr virus (EBV) by impairing the ability of the cellular immune response to control viral latency (Glaser and Kiecolt-Glaser, 1994; Jaremka et al., 2013; Fagundes et al., 2013b, 2012a; Bennett et al., 2012). The enhanced replication of memory CD8 + T-cells induced by CMV proteins (and perhaps EBV) can exhaust virus-specific CD8 + T-cells. The periodic reactivation of these latent viruses provides a source of viral proteins that stimulate a cellular immune response to the viral proteins. Chronic exposure to high CMV and EBV antigens can promote progressive telomere shortening in antigen-specific CD8 +T-cells. Moreover, sustained stimulation of cell division in virus-specific T-cells has been associated with reductions in telomere length and telomerase activity in CD8 + T cells among even healthy people (Pawelec et al., 2009; van Baarle et al., 2008).

3.2. Cellular senescence: $p16^{INK4a}$

The expression of $p16^{INK4a}$ in peripheral blood T cells provides a noteworthy human aging biomarker. Elevated $p16^{INK4a}$ expression is a biomarker of cellular senescence, a state in which cells no longer respond to proliferative cues. Senescent cells accumulate throughout the body with age and are associated with reduced regenerative capacity and the onset of age-related disease. In mouse models, the synthetic deletion of $p16^{INK4a}$ positive cells attenuates numerous age-related pathologies (Martin et al., 2014), (Baker et al., 2016; Childs et al., 2016; Moiseeva et al., 2023; Patil et al., 2019) many of which may be mediated by $p16^{INK4a}$ positive immune cells. For example, when old splenocytes were transplanted into young mice, senescent cell numbers increased

throughout the body, leading to early mortality (Yousefzadeh et al., 2021). These findings suggest that elevated levels of $p16^{INK4a}$, particularly in immune cells, could significantly impact caregiver health.

There are several advantages to using $p16^{INK4a}$ as an aging biomarker. Levels of $p16^{INK4a}$ in human peripheral blood T cells increase more than 10-fold over 60 years (Liu et al., 2009). By contrast, telomere length decreases less than two-fold over the same period (Liu et al., 2009). The larger dynamic range of $p16^{INK4a}$ allows for more precise measurement, facilitating tracking of changes over shorter timeframes. Unlike first-generation epigenetic clocks, chronological age explains only 40–42% of the variance in $p16^{INK4a}$ expression (Teyssier et al., 2012; Liu et al., 2009). It is hypothesized that $p16^{INK4a}$ expression closely reflects physiological age due to this property. Examples of age-related conditions associated with $p16^{INK4a}$ include osteoarthritis, diabetes, Alzheimer's Disease, insomnia, heart failure, atherosclerosis, frailty, and fibrosis (Smitherman et al., 2020; Rosko et al., 2019; Carroll et al., 2023; Reed and Miwa, 2023; Melk et al., 2004; Meyer et al., 2016; Aversa et al., 2023).

Among individuals with dementia with major depressive disorder (MDD), $p16^{INK4a}$ expression levels were almost double that of the matched controls (Teyssier et al., 2012). In addition, higher anxiety scores were strongly correlated with greater $p16^{INK4a}$ expression in the depressed group. Caregivers' higher rates of clinical depression compared to non-caregivers (Dura et al., 1990, 1991; Vitaliano et al., 1997; Schulz et al., 1990; Light and Lebowitz, 1989; Gallagher et al., 1989) suggest that caregivers would have higher $p16^{INK4a}$ levels. Compared to non-caregivers, dementia caregivers have poorer diets and they exercise less (von Kanel et al., 2011b; Vitaliano et al., 2003; Rullier et al., 2014; Torres et al., 2010; Burton et al., 1997; Fredman et al., 2006). Diet and exercise show reliable relationships with depression as well as healthy aging, and they also affect $p16^{INK4a}$ expression (Liu et al., 2009; Schafer et al., 2016). Thus, $p16^{INK4a}$, as one of the best aging biomarkers, provides a promising avenue for understanding the health effects of caregiving.

3.3. DNA methylation and epigenetic age

Mounting evidence suggests that social and behavioral factors influence somatic DNA methylation (DNAm) patterns (Needham et al., 2015). For instance, the DNAm patterns of identical twins diverge with age in a process known as "epigenetic drift" (Bocklandt et al., 2011). Such changes in DNAm can alter gene expression, providing a molecular mechanism by which social and behavioral factors impact biological fitness and health outcomes (Needham et al., 2015). Epigenetic clocks take advantage of these changes in DNAm to try and predict mortality and age-related morbidity more accurately than chronological age alone and provide new tools to investigate the impact of social and behavioral factors on healthspan (Hannum et al., 2013; Horvath, 2013).

Epigenetic clocks are regression models that use DNA methylation ratios to predict age-related variables like chronologic age, morbidity, mortality, and other health parameters. Typically, each clock is built using methylation data from over 800,000 genomic sites in thousands of individuals. The first epigenetic clocks used elastic net regression to identify DNA methylation patterns associated with chronological age in peripheral blood (Hannum) or multiple tissue types (Horvath) (Hannum et al., 2013; Horvath, 2013). Second-generation clocks aimed to improve upon their predecessors by more accurately approximating healthspan. These clocks factored blood-based clinical measures associated with morbidity and mortality (PhenoAge), time-to-death, or surrogates of health like smoking packyears, serum adrenomedullin, and C-reactive protein (GrimAge, GrimAge2) into their regression models (Lu et al., 2022).

Finally, more recent third-generation models (e.g., DunedinPACE (Belsky et al., 2022) have taken a slightly different approach to biological age prediction. Unlike other DNAm algorithms, the DunedinPACE (i.e., Dunedin (P)ace of (A)ging (C)alculated from the (E)

pigenome) was developed to capture the *pace* of aging, trained on 20-year trajectories of physiological and biomarker changes in a single-year birth cohort (Belsky et al., 2022). The unique single-age design of the training data eliminates the confound of cohort differences, and the life stage of the cohort (ages 26–45) prevents the conflation of chronic disease incidence with normative aging processes, in contrast to the other clocks that were trained on studies of older adults. Within the Dunedin cohort, DunedinPACE scores predicted functional measures of aging (balance, walking speed, grip strength, functional limitations), cognition (perceptual reasoning, working memory, processing speed), and aged appearance as rated by outside observers. Participants whose DunedinPACE scores indicated an accelerated pace of aging had higher risks for chronic disease onset and earlier mortality in the VA Normative Aging Study and Framingham Offspring Study. Effect sizes were similar to those of GrimAge and larger than those of the other clocks (i.e., PhenoAge, Hannum, Horvath). In the Framingham Study, the links between DunedinPACE and cardiovascular disease incidence, disability, and mortality remained statistically significant after accounting for the other metrics, despite small to moderate correlations with these clocks (Belsky et al., 2022).

It is worth noting that, apart from Horvath's original algorithm, most epigenetic clocks derive from the methylation patterns of peripheral blood cells in healthy volunteers (Hannum et al., 2013; Horvath, 2013; Lu et al., 2022; Belsky et al., 2022). Therefore, the predictive ability of each epigenetic clock may vary based on the sample type and cohort studied.

Increasing evidence links epigenetic age acceleration (EAA) to a greater risk of morbidity and mortality. EAA is the difference between an individual's epigenetic age and the average epigenetic age of people with the same chronological age. Therefore, an EAA greater than zero indicates accelerated aging. The ability of EAA to predict clinical phenotypes varies between epigenetic clocks due to differences in the health parameters, populations, and sample types used to train each algorithm. For example, in a study of almost 7000 volunteers from five independent cohorts (FHS, InChianti, JHS, WHI BA23, and WHI EMPC) (Lu et al., 2019), GrimAge EAA predicted time-to-death and cancer onset with greater accuracy than PhenoAge EAA or any of the first-generation clocks. Relationships between EAA and age-associated morbidities also vary based on the epigenetic clock and cohort employed. However, meta-analyses reveal consistent associations between the epigenetic clocks and smoking, body mass index, reduced physical activity, alcohol use, cancer, and cardiovascular disease (Oblak et al., 2021). Socioeconomic factors are also consistently associated with age acceleration (Oblak et al., 2021), with greater GrimAge EAA and PACE values noted among socioeconomically disadvantaged adults from the MESA (Multi-Ethnic Study of Atherosclerosis) and Health and Retirement Study (HRS) cohorts (Schmitz et al., 2022). Together, these observations support the potential of epigenetic clocks to inform studies on the impact of environmental and societal parameters on health and aging.

The use of epigenetic clocks to study the health-related impacts of chronic stressors is still in its infancy. However, it is clear that stress can provoke persistent changes in DNA methylation (Houtepen et al., 2016; Vinkers et al., 2015). For example, cumulative lifetime stress predicted accelerated epigenetic aging in an urban, African American cohort (Zannas et al., 2015). In a longitudinal study of military personnel deployed to Afghanistan, traumatic stress was associated with accelerated epigenetic aging within a six-month period (Boks et al., 2015). In other work, lifetime PTSD severity was associated with accelerated epigenetic age estimates as compared to chronological age (Wolf et al., 2016). Demonstrating the role of psychological wellbeing, patients with major depression have a higher DNAm age than controls, with a dose-response relationship: increased symptom severity predicts greater DNAm aging (Han et al., 2018, 2021; Protsenko et al., 2021). Of particular interest is its acceleration in major depressive disorder patients who had a median of two years of excess cellular aging even after controlling for sex, current smoking status, and body mass index (Lu

et al., 2019; Protsenko et al., 2021). In summary, although caregivers' DNA aging has not been studied, associations of stress and depression with accelerated DNA aging provides a basis for expecting aging-related consequences of caregiving-related stress.

4. Consideration of moderating factors

4.1. Gender differences: depression, inflammation, and caregiving

Female caregivers report higher levels of anxiety and depressive symptoms than males, as well as greater burden (Vitaliano et al., 2003; Schulz and Martire, 2004; Pinquart and Sorensen, 2006). Based on depression's close ties to inflammation (Kiecolt-Glaser et al., 2015), women's responses to caregiving may be particularly relevant for several reasons. First, inflammation-induced mood and behavior changes appear to be more prominent among women than men (Derry et al., 2015). For example, women respond to transient elevations in inflammation with stronger feelings of loneliness and social disconnection than men, a characteristic that likely contributes to the 2:1 ratio of women to men in depressive disorders (Moieni et al., 2015). Additionally, prior depression, somatic symptomatology, interpersonal stressors, childhood adversity, obesity, and physical inactivity are all factors that elevate inflammation (Kiecolt-Glaser et al., 2015), and women have disproportionately higher representation than men in each of these domains (Derry et al., 2015). Relationship-related distress has stronger ties to inflammation among women than men (Derry et al., 2015), and the association between depression and marital quality is stronger among women than men (Whisman, 2001). Accordingly, these gender differences in depression and inflammation can lead to greater caregiving-related health risks for women than for men.

4.2. Addressing health inequities

Individual differences among caregivers in psychiatric history, race and ethnicity, sexual minority status, comorbidities, socioeconomic status (SES), geographic location (rural/urban), and social support may moderate health risks (Vitaliano et al., 2003). There are consistent findings, summarized in a recent meta-analysis, that Black dementia caregivers have better psychological well-being than White caregivers ($d=-.22$), perhaps due to larger support networks (Liu et al., 2021). Less consistent findings indicate that Hispanic/Latino dementia caregivers may have lower levels of physical well-being than their White counterparts ($d=.12$) (Liu et al., 2021). Also, care recipients with lower SES receive their dementia diagnosis at more advanced stages than their more affluent peers (Petersen et al., 2021), which may translate to months and years of undiagnosed and troublesome symptoms, as well as little support from the healthcare system. Meta-analytic evidence indicates that caregivers with lower SES have poorer health outcomes (Pinquart and Sorensen, 2007). However, molecular aging biomarkers would certainly add to this literature.

More research is needed about other potential moderators. For example, although geographic disparities for dementia care recipients are well-established, in that rural care recipients have higher mortality rates and are more likely to be in a nursing home than those in urban areas (Arsenault-Lapierre et al., 2023), less is known about geographic disparities in caregiver outcomes. In one study among urban and rural dementia caregivers in Sweden, caregiving was associated with a greater financial impact among rural caregivers than urban caregivers, yet rural caregivers reported more familial support (Ehrlich et al., 2015). This financial impact may result from greater difficulty accessing routine healthcare, leading to more frequent hospitalizations (Arsenault-Lapierre et al., 2023). Geographic disparities in dementia caregiving will soon become a more central issue, as the global burden of dementia is expected to increase from 57.4 million cases in 2019–152.8 million cases in 2050 – largely due to population growth and aging in developing countries (Nichols et al., 2022). Also, little is

known about health disparities of dementia caregivers who are sexual and gender minorities (SGM). One recent cross-sectional study found that 78% of SGM dementia caregivers were above the clinical cut score for probable depression, and depression scores were higher for Black SGM caregivers than White SGM caregivers (Anderson et al., 2021). Another cross-sectional study showed that although SGM dementia caregivers reported higher family quality of life scores than their heterosexual counterparts, they also reported more financial difficulties and were more likely to be employed than those who identified as heterosexual. The lens of intersectionality (e.g., racial/ethnic minorities living in rural areas) combined with use of molecular aging biomarkers to index change at the subcellular level would help to advance the field.

5. Moving the field forward

The longitudinal examination of dementia spousal caregiving and molecular aging would be consequential for several reasons. First, the molecular aging measures have clinical significance for health. A growing literature has linked each of the three aforementioned molecular biomarkers to adverse health behaviors, aging, age-related diseases, and mortality (Cawthon et al., 2003; Epel et al., 2009; Cohen et al., 2013; Brouillette et al., 2003; Demissie et al., 2006; Gardner et al., 2005; Weng, 2012; Steer et al., 2007; Marioni et al., 2015; Breitling et al., 2016; Epel et al., 2010; Hannum et al., 2013; Teyssier et al., 2012)—but only telomere length has been related to caregiving. Assessing other novel molecular aging markers that index cellular senescence (p16^{INK4a}) and epigenetic age repeatedly over time would show how spousal dementia caregiving dynamics relate to lifespan and health span, thereby resolving current inconsistencies in the caregiving literature. The new frontier for caregiving research is to uncover relationships between behavior and molecular aging.

Further, this type of investigation would provide important causal information about the interactions between molecular aging and chronic stress. These findings could serve as the underpinnings for caregiving's impact on inflammation-related disorders including cardiovascular disease, metabolic syndrome, arthritis, diabetes, frailty, and functional decline (Kiecolt-Glaser et al., 1995; Vitaliano et al., 2005, 1996; Lee et al., 2003; von Kanel et al., 2011a, 2011b; Fredman et al., 2010a; von Kanel et al., 2008; Kolanowski et al., 2004; Dassel and Carr, 2016; Shaw et al., 1999; Grant et al., 2002; Vitaliano et al., 2002). Accordingly, these data could provide additional support and refinement for the theory of inflammaging, which connects chronic inflammation with accelerated biological aging (Franceschi et al., 2000; McElhaney et al., 2012). However, molecular aging biomarkers go far beyond inflammation to directly address the impact on longevity and health span.

Furthermore, an additional novel mechanistic pathway remains to be examined. Specifically, CMV seropositivity is associated with enhanced CD8 + T cell replication. Considerable research from our lab and others has shown that stress and depression reactivate CMV, as well as other herpes viruses (Glaser and Kiecolt-Glaser, 1994; Fagundes et al., 2013b, 2012a; Bennett et al., 2012; Applegate et al., 1999; Glaser et al., 1985a; Kiecolt-Glaser and Glaser, 1987; Cacioppo et al., 2002; Fagundes et al., 2012b, 2014; Glaser et al., 1985b, 2005, 1994, 1993, 1991; Kiecolt-Glaser et al., 1984; Waldman et al., 2008; Christian et al., 2012). Thus, a novel future direction is whether enhanced CMV and EBV replication contribute to telomere shortening in this T cell subset. In addition, recent work has linked marital distress and depression with intestinal permeability, a “leaky gut,” and heightened inflammation (Kiecolt-Glaser et al., 2018). Exploring this pathway in relation to molecular aging biomarkers is a promising direction for enhancing basic science data within the aging literature.

Most research on dementia caregivers' health has focused on comparing their health outcomes to those of non-caregivers. This approach is valuable for characterizing health disparities, where they exist, but would be enhanced by a greater focus on the mechanisms that drive these differences. Harmonizing fine-grained measures of caregiver

experiences across population-based studies and smaller, mechanistic studies would further enhance our ability to synthesize these disparate literatures. Incorporating a strengths-based perspective into the study of dementia caregivers' health would also enrich this area of research (Yu et al., 2018). Indeed, according to data from the National Health and Aging Trends Study and National Study of Caregiving, dementia family caregivers who reported higher purpose in life also felt a greater sense of reward from providing care (i.e., greater caregiving gains), compared to those with less purpose in life (Polenick et al., 2019). A balanced approach that takes into account caregivers' risk factors and seeks to identify resilience factors as well will be strongly positioned to maximize caregivers' healthy years. Current stress-reducing interventions for dementia caregivers benefit some outcomes (i.e., cognition) but fail to show meaningful change in inflammatory markers and immune function (Allen et al., 2017).

Future work in this domain must consider moderating factors, especially as they relate to health disparities among marginalized populations. Minority status itself is a chronic stressor, and dementia caregiving responsibilities in that context may be even more burdensome and detrimental. Incomplete consideration of sample characteristics and moderating factors (e.g., type of relationship with the person experiencing dementia, total caregiving burden) may help to explain apparent inconsistencies in the literature. As described, marked gender differences are observed in inflammatory responses to stress, risk for mood disorders and anxiety, as well as access to broader social support networks. In addition, limited research has examined the role of factors including having a racially minoritized identity, residing in rural versus urban areas, or socioeconomic status. It can be difficult to recruit such individuals to participate in research in the first place, but especially if they are the primary caregiver of a dementia care recipient. Future research designs should take into account the additional participation barriers that these individuals may face and attempt to address them with more flexible and less burdensome research designs. Greater attention to these and other potential moderators will bring clarity and add nuance to this literature.

In sum, incorporating state-of-the-art biomarkers into the caregiving stress paradigm will enhance understanding of the ways in which chronic stressors promote an accelerated aging phenotype. A clearer identification of both the risk-related and protective dimensions in relation to molecular aging biomarkers would provide a better foundation for designing dementia caregiver targeted intervention studies.

Declaration of Competing Interest

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