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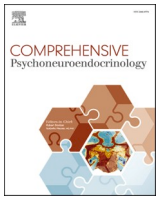

Is age more than a number? Accounting for adult development and aging in the study of psychoneuroimmunology, stress, and health

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ABSTRACT

Traditional stress-and-health models link stressors to their health consequences through a well-characterized cascade. Most of the research assumes that the stress-health sequence unfolds in the same way across adulthood, whether a person is 25 years old or 80. Taking a "developmental" or "lifespan" approach has been synonymous with studying the lasting health impacts of early life experiences. However, theories and evidence from adult development and geroscience suggest that stress-health dynamics evolve in important ways over the adult lifespan—from the stressors that we encounter, to the emotion regulation strategies that we use to confront challenges, to the psychosocial resources at our disposal, to the cellular milieu, and thus to the magnitude of stressors' biological and functional consequences. This critical review synthesizes theoretical perspectives and selected empirical literature on the social-emotional and biological dimensions of aging to promote an Integrative Model of Aging, Stress, and Health. Through this integration, the model illustrates how an interdisciplinary, developmental perspective can enrich our understanding of stress's consequences for health across adulthood. It also seeks to guide a new generation of research questions that confront aging with a multidimensional approach. The piece concludes with personal reflections on the foundational legacy of the author's mentor, Dr. Janice Kiecolt-Glaser.

1. Introduction

Traditional stress-and-health models link stressors to their health consequences through a well-characterized cascade. When stressors threaten our sense of safety and demands outweigh our perceived resources, the central nervous system triggers a coordinated response through the sympathetic-adrenal-medullary (SAM) axis—heightening blood pressure, heart rate, and inflammation—along with cortisol rises from the hypothalamic-pituitary-adrenal (HPA) axis [1]. In tandem, healthy behaviors derail: heightened arousal disrupts sleep, and alterations to appetite hormones trigger hunger and cravings [2,3], contributing to poorer food choices [4]. Triglycerides escalate further in response to high-fat foods under conditions of stress [5,6]. Nevertheless, isolated, acute stressors are thought to be benign; in some contexts, minor (nontoxic) stressors may even promote rejuvenation and cell repair in a process called hormesis [7]. Indeed, according to reactivity-focused theories and allostasis [8,9], stressors contribute to disease only when toxic patterns repeat or stretch out over long periods of time, contributing to the development of glucocorticoid resistance, insulin resistance, hypertension, and other chronic problems.

Despite the critical distinction between acute and chronic processes, our understanding of how this transition emerges *over time* remains imprecise. Further, we typically account for developmental time by controlling for chronological age. Taking a "developmental" or "lifespan" approach has been synonymous with studying the lasting health impacts of early life experiences [10]—itself an example of developmental continuity, not developmental change [11]. Indeed, we largely assume that the stress-health cascade unfolds in an age-agnostic way—the same at age 25 as age 80. However, theories and evidence from adult development and geroscience suggest that the process may evolve in important ways over the adult lifespan—from the stressors that we encounter, to the emotion regulation strategies that we use to confront challenges, to the psychosocial resources at our disposal, to the cellular milieu, and thus to the magnitude of stressors' biological and functional consequences. This critical review synthesizes theoretical perspectives and selected empirical literature on the social-emotional and biological dimensions of aging to illustrate how an interdisciplinary, developmental perspective can enrich our understanding of stress's consequences for health across adulthood. It also aims to encourage a new generation of research questions that consider aging with a

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multidimensional approach. Fig. 1 provides an overview of the proposed Integrative Model of Aging, Stress, and Health.

2. Aging as an outcome of stress (Path A, Fig. 1)

Among the many ways to account for aging, treating aging as an outcome is a fast-growing trend in health psychology. The aging-as-outcome perspective sees aging as a new way to conceptualize the state and fate of our health. This line of work has focused on testing associations with an evolving landscape of aging biomarkers, to quantify how the 'exposome'— stress and other psychosocial exposures—may accelerate or decelerate aging. In one of two biological aging measurement approaches, strong aging biomarker candidates show large age-related changes and correlate with age, thus differentiating slow from fast agers. Telomere length, insulin-like growth factor (IGF)-1, $p16^{ink4a}$, forkhead box protein O (FOXO) and klotho transcription factors, the senescence associated secretory phenotype (SASP), and GDF-15 index various aspects of the aging process (i.e., the pillars or hallmarks of aging) and have all been treated as aging-related biomarkers [12–18]. Age-graded differences in glycomics and gut microbiota have attracted attention as well [19]. Many of these markers, in addition to markers of immunosenescence, show associations with psychosocial stress [12–18, 20].

In a second class of biological aging measures, the machine-learning-based clock approach has produced increasingly sensitive algorithms using age- and health-graded CpG patterns of DNA methylation. First-generation epigenetic clocks trained models on chronological age, and later generations improved prediction of clinical outcomes by training models on dimensions of health and mortality [21]. The newest clocks achieve even more promising results by estimating organ or system-specific ages, given that organs age at different rates [22,23]. Social hallmarks of aging—which track closely with the social determinants of health—are associated with accelerated epigenetic clock aging [21,24,25].

It is not surprising that people who experience toxic psychosocial stress [7] also exhibit signs of advanced biological aging. Many of the stress-reactive outcomes researchers have studied for decades, such as inflammation, reflect aging processes or the consequences of aging processes. For instance, biologists have theorized that inflammaging, wherein chronic, systemic inflammation rises with age, results from sustained triggering of macrophages and other aspects of the innate immune system by a variety of stressors (not only psychological, but also bacterial, viral, thermal, chemical, etc.) [26]. Thus, the robust evolutionary advantage of a strong innate immune response becomes a disadvantage, decades beyond the reproductive years. For this reason, inflammation is one of seven pillars of biological aging that are thought to contribute to age-related diseases, e.g., Alzheimer's disease, osteoarthritis, cancer, etc. [27]. This means that the mountains of previous research on stress' ties to inflammation shed light on how stress relates to dimensions of biological aging. However, the routine practice of controlling for age in stress-health studies partials *out* variance in inflammation tied to aging (or, between-person age differences) and frames these associations as age-invariant—the same, regardless of age. To explicitly incorporate aging into our models of stress and health, and thus to examine aging-related inflammation (i.e., inflamm-aging), for instance, age is best treated as a moderator (Path C, Fig. 1).

Although aging clocks distill information about biological age, there is currently no singular clock or aging biomarker that can capture the full landscape of aging processes. Indeed, with differential rates of system aging [23] and an array of hallmarks [28] and pillars [27] of aging— including adaptation to stress, epigenetic changes, inflammation (i.e. altered intercellular communication), macromolecular damage, metabolic alterations, loss of proteostasis, stem cell exhaustion, cellular senescence, mitochondrial dysfunction, and telomere attrition—the landscape of biological aging measurement is likely to remain complex.

Both measurement approaches have important roles in the next generation of stress-and-aging research. Epigenetic and other algorithmic biological clocks provide summative snapshots of aging that will be necessary to gauge the efficacy of anti-aging treatments and interventions, as well as to hone our understanding of the most pernicious sources of psychosocial stress. Examining singular aging biomarkers and markers of immunosenescence will clarify the roles of specific mechanisms. Latent factors that include multiple hallmarks or pillars of aging seem like a promising way to study aging at a higher level while making it possible to examine single mechanisms, although these models require large sample sizes. Moreover, according to the hierarchical model of aging metrics [29], accelerated biological aging translates to subclinical phenotypic changes (e.g., in gait speed, grip strength), and then to functional decline over time. These phenotypic and functional factors provide additional rich information about the aging process and have also been linked to various forms of psychosocial stress [30,31], consistent with the larger model. Using longitudinal studies to understand the timescale of these transitions remains a critical next step. Beyond the focus on any particular aging-related outcome, adopting open-science practices, such as pre-registering hypotheses, transparently reporting all outcomes, and also evaluating publishability based on the rigor of the design and measurement rather than the statistical significance of the results, will be instrumental in advancing the science of stress and healthy aging.

3. Age as a predictor of stress (Path B)

To complicate the picture further, it may not only be that stress accelerates biological aging and functional decline, but also that social-emotional development across adulthood changes how we experience and manage stress itself. For the last 30–40 years, two major theories of social-emotional aging (among other theories [32]) have spurred

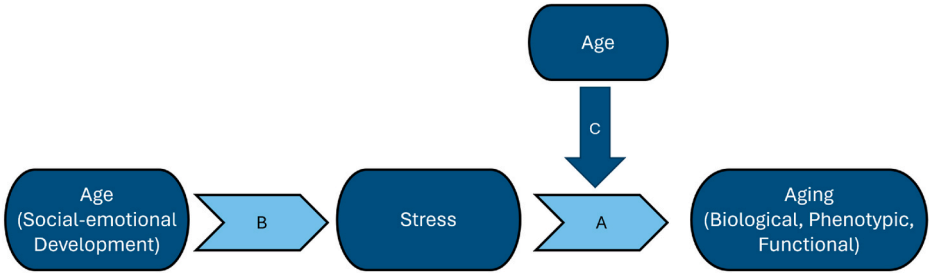

Fig. 1. Integrative Model of Aging, Stress, and Health.
Note. This figure provides an overview of the paths presented. Path A describes aging as an outcome of psychological stress. Drawing from Lazarus's transactional model [103], this conceptualization of stress includes the occurrence of stressors, stressor appraisals, and perceived stress. Path B connects social-emotional aging to adults' experience of psychological stress. Path C highlights that the consequences of stress for accelerated aging may grow with older age. Scientific evidence for Path C has most often treated chronological age as the moderator, which serves as a proxy for the loss of physiological resilience with advanced biological aging.

scientific advancement and stoked lively intellectual debate. In an effort to explain epidemiological trends showing that older adults had greater positive affect than younger counterparts, the first theory—socioemotional selectivity theory (SST) [33]—suggests that with older age and less time to live, adults increasingly shift their focus from instrumental goals to social-emotional goals, drawing near to loved ones and maximizing emotional well-being. This leads to a positivity bias in preferentially attending to and remembering positive over negative information, as well as disengaging from distress-inducing stimuli.

Extending SST, the Strength and Vulnerability Integration (SAVI) model [34,35] further posits that, with advancing age, individuals benefit from their increased experience with managing stressors and challenges. In particular, this manifests in proactive coping, which can shape stressor appraisals. For example, a few studies have documented that older adults, compared to younger counterparts, report lower perceived stress in reaction to the Trier Social Stress Test (TSST), and thus exhibit smaller heart rate (HR) and cortisol responses in parallel [36,37]. This makes sense in the context of shifting motivations and greater experience: according to the theories, with diminishing time horizons, older adults are less attached to achievement-oriented goals, and thus may take their performance on the Trier less seriously than younger counterparts, for whom the high-pressure, evaluative nature of the task is highly relevant.

In addition, according to the discrete emotion theory of affective aging [38], the value and likelihood of individual emotions can evolve over the course of adulthood. On average, the degree to which individuals feel anger decreases across the adult lifespan, whereas sadness remains constant over adulthood and increases in advanced older age [39]. Indeed, compared to younger adults, older adults become less angry in response to anger-inducing experimental stimuli, and equally sad or sadder in response to sadness-inducing stimuli [38]. Moreover, one study reported evidence that anger shares stronger associations with chronic illness and inflammation for the oldest old than does sadness, suggesting greater maladaptive consequences [40]. In this respect, usual experimental stimuli that intend to trigger perceived stress and evoke negative emotions may have divergent effects not only between age groups, but within age groups across tasks. In addition, some tasks may elicit relatively stronger emotional responses in older adults. For example, scenarios and tasks involving loved ones and health may carry more emotional weight than tasks centered squarely around achievement without personally relevant themes [41,42]. Beyond this, standard cognitive batteries may inadvertently trigger aging-related stereotypes, causing participants to worry about their own performance to the point of *interfering* with their performance, which can be further exacerbated by fears of decline and of losing independence [43]. Taken together, we must consider how the social-emotional developmental context impacts validated tasks and measures when designing experimental procedures.

In addition to possible age differences in how experimental tasks are received, there may also be a larger divergence between patterns seen in the laboratory and in daily life among older adults compared to younger counterparts. SST and SAVI predict that older adults readily prune away problematic weak ties and proactively avoid stressors when possible. Indeed, older adults report experiencing fewer stressors in daily life, in part because they tend to sidestep hassles like interpersonal conflict [44]. This raises questions about whether stressful tasks administered in the lab accurately reflect older adults' experience in daily life and, thus, whether physiological and emotional responses to such tasks have less relevance for long-term health in older age.

To consider a specific example, dyadic studies of married couples have produced equivocal evidence for developmental trends. On the one hand, a longitudinal study of marital behavior observed in the laboratory showed consistent declines in hostility over 13 years [45]. Indeed, assuming partners are in the same life stage and thus share similar time horizons, both partners may be motivated to avoid conflict to maintain harmony and well-being [41]. On the other hand, cross-sectional age differences in relationship satisfaction and marital behavior are inconsistent [46,47]; one study found that older couples treated each other with *greater* hostility than younger couples [48]. In addition, a daily diary study of interpersonal stressors among a sample of partnered individuals found that older adults had fewer interpersonal tensions with people other than the spouse, but daily marital discord was no less frequent among older adults compared to younger counterparts [49]. Thus, the fact that older adults may structure their social lives to maximize emotional well-being and closeness with loved ones suggests that lab paradigms—those inducing conflict or involving study confederates—may not emulate daily life. Moreover, reactions to marital stressors may vary with the emotional context. For instance, the physical or emotional suffering of a close social partner brings aging-related social and emotional motivations into conflict, which may result 1) in a breakdown of protective avoidance strategies, risking a person's own emotional well-being, or 2) in social disengagement, which may harm the relationship [50]. In early evidence, a laboratory-based study of marital behavior found larger inflammatory responses to a partner's suffering than to marital conflict [50]. Even so, many questions remain about how social interactions change with adult development, given the complexity of dyadic and partner influences.

Unlike the aging-as-outcome approach, the aging-as-predictor literature has not placed much emphasis on the measurement of social-emotional aging itself, even though researchers acknowledge that chronological age is only a rough index for the underlying psychological processes. The Future Time Perspective scale [51] was developed to capture perceived time horizons, an important feature theorized to drive changing motivations over adulthood. However, it is not as widely used as chronological age, which itself is nearly ubiquitous across studies. Further, associations between future time perspective and hypothesized outcomes are sometimes mixed [52]. One explanation for the mixed findings is that the underlying dimensions of social-emotional aging are complex and multidimensional. Time horizons and shifting motivations contribute to developmental changes alongside the strengths gained with life experience and learned adaptation to loss [35]. At the same time, drawing on evidence that older adults do *not* use unique emotion regulation strategies, Isaacowitz and English [53] point to possible differences in decisions *whether* to regulate emotions as well as goal setting and striving.

In addition, the neurobiological basis for the positivity bias itself remains a mystery; many theories have been put forth, including the aging brain hypothesis, the cognitive control model, and most recently, the autonomic compensation model [54]. Moreover, longitudinal studies have complicated the established narrative that emotional well-being increases with age. For instance, using data from the Midlife in the United States (MIDUS) study, Charles and colleagues [55] found that while older adults had higher levels of well-being on average compared to younger age groups, younger and middle-aged individuals actually showed within-person declines in negative affect. Among the oldest old, daily and monthly negative affect increased. Indeed, any increases in positivity are likely nonlinear, leveling off and reversing at some point in older age. These contrasting patterns in cross-sectional age differences compared to longitudinal changes highlight the fact that cross-sectional data cannot be used to surmise developmental patterns, given their confounding by cohort and period effects [56,57]. The complexity of social-emotional patterns across tasks and domains only reaffirms the need for longitudinal data to definitively resolve cohort-confounded discrepancies. These considerations should be taken into account when designing studies that target stress in middle-aged and older populations.

4. Age as a moderator (Path C)

According to SAVI, when older adults are unable to proactively avoid or reframe stressors, the strengths of social-emotional development break down, resulting in emotional distress. For example, in the MIDUS study, on days when older adults engaged in an argument, their negative

affect reactivity was no different from younger adults—in contrast to the affective benefits older adults experienced when they avoided an argument [44]. Longitudinal evidence shows that a sense of control declines over time [58], suggesting that this unfavorable scenario may increase in older age. In addition, as the SAVI model and others have highlighted, the physiological consequences of stressors may be altered by the vulnerabilities associated with biological aging. Indeed, the 'hallmarks' and 'pillars' of biological aging reflect, and result in, degrading resilience over time [27,28].

With declining resilience, recovery from stressors becomes increasingly difficult and drawn out [7,59]. For instance, in an experimental study, when older adults were instructed to ruminate, their systolic blood pressure (SBP) remained higher during the recovery period compared to younger adults' and older adults' in the control condition [60]. This aligns with findings from a 31-study meta-analysis that showed older adults' larger SBP reactivity to laboratory stressors than younger counterparts' [61]. These changes are attributable to arterial stiffening and decreased sensitivity to beta-adrenergic receptors, baroreceptors, and chemoreceptors with age [61,62]. In addition, among 45 studies that administered a pharmacological challenge or psychosocial laboratory stressor, older adults exhibited larger cortisol responses than younger adults [63]. Mirroring this trend, in a diary study, only older adults showed significant associations between daily negative affect and higher nighttime cortisol [64]. These findings align with the glucocorticoid cascade hypothesis [63,65], which suggests a vicious, self-reinforcing cycle initiated by aging: loss of glucocorticoid receptors on the hippocampus leads to decreased inhibition of cortisol, which in turn further damages the hippocampus. On the other hand, older adults have lower heart rate (HR) reactivity to stressors than their younger counterparts [61], thought to be driven by decreased maximal HR, itself a result of aging-related changes in the myocardium and a decline in atrial pacemaker cells [61,62].

A meta-analysis of acute inflammatory responses to psychosocial stressors did not find age differences [66], although for many of the inflammatory markers, there were too few studies to test age as a moderator. At the same time, it is possible that age-related differences in behavioral and emotional responses to laboratory stressors contributed to heterogeneity, with variation across tasks and stimuli [53]. Moreover, heightened inflammation associated with inflamm-aging results in higher baseline levels. Indeed, circulating inflammation creates DNA damage and accelerates cell senescence; aged cells, in turn, secrete more cytokines, known as the senescence-associated secretory phenotype (SASP) [67]. SASP can lead to senescence in normal cells and result in an inability to clear senescent cells and inflammation, a self-fueling cycle. In this way, it is possible that psychosocial stressors lead to outsized inflammatory consequences with older age. For example, among couples, older adults showed a stronger association between a history of intimate partner violence and inflammation compared to younger counterparts [68]. Likewise, in two separate studies, the effect sizes of older couples' immune reactivity to conflict were medium to large [69], whereas effects in younger couples were small to medium [70]. In turn, larger stress-related inflammatory responses predict heightened blood pressure and arterial stiffness over time [71,72], and emotion reactivity to minor daily hassles is linked to both higher inflammation [73] and increased 10-year risk for chronic conditions [74]. In addition, repetitive inflammatory responses to stressors may not only resolve more slowly in older age, but also may have greater potential to induce phenotypic and functional changes, resulting in clearer clinical consequences. For instance, prolonged elevation of proinflammatory cytokines after surgery is associated with poorer survival among older patients [75]. Stronger negative affect reactivity to daily stressors preceded greater allostatic load over time, but only among older adults, not younger [76]. Using data from the German Socio-economic Panel, researchers documented a similar pattern between stressful work and more frequent sick days that trended stronger for older adults, although the interactions were not significant [77].

This potential for greater physiological and phenotypic consequences among older adults may also reflect a more general dependency on the quality of the psychosocial environment, which can create an opportunity for meaningful benefits in addition to risks. For instance, among couples ages 22 to 77 who engaged in a support discussion, older adults' inflammatory dynamics were most strongly tied to the quality of the discussion: happily married older adults who received high-quality support had the smallest TNF-α responses of all groups, and unhappily married older adults who received poor-quality support had the largest increases in TNF-α across the day [78]. Among couples who received a punch biopsy wound and discussed a problem in their marriage, those who reflected on the discussion with more positive language in their private thought-listings had lower subsequent cortisol, but only older adults showed a subsequent association with faster wound healing [48]. In addition, older couples show stronger within-couple correlations in their fasting glucose and baseline blood pressure compared to younger adults [79]. This may reflect greater sensitivity to the social environment (i.e., the partner's health behaviors, emotions, etc.), convergence between partners over time [80], or the concentrated influence that partners have in older age given smaller social networks (SST) [33].

On the other hand, in a meta-analysis examining the ties of loneliness and social isolation to mortality, Holt-Lunstad and colleagues [81] documented an opposing effect of age, wherein samples of participants with average ages younger than 65 had larger associated mortality risks than those with older samples. Although the authors excluded suicide as an outcome from the meta-analytic sample, middle-aged individuals may have experienced more deaths of despair, induced by substance use and other maladaptive coping strategies, which may share a more direct association with loneliness and isolation. In addition, older adults die for many other reasons at higher rates, and this heterogeneity may shrink the signal-to-noise ratio for the link between social disconnection and mortality, particularly among the oldest old. Moreover, social disconnection is quite common in older age, and thus, reduced variation in loneliness and isolation may shrink the effect on mortality. Beyond these considerations, many confounding factors may explain these age differences or further moderate the associations, including psychosocial resources (social support, optimism, conscientiousness), fastidiousness in health behaviors and preventive medication use, and biological sources of resilience (genetic and epigenetic)—all critical sources of reserve capacity. It may be that greater temporal distance between the predictor and outcome invites more opportunities for additional moderators to complicate expected effects. Even so, taken together, this work underscores the importance of considering how age may moderate the effect of psychosocial factors on health, while taking into account other sources of influence.

5. The many roles of cognition in stress, health, and aging

As a core feature of adult development and functioning, cognition plays a role in all aspects of the stress-aging process. Within Path A (i.e., the effects of stress on aging, Fig. 1), psychosocial stress elevates neuroinflammation by upregulating central catecholamines, which in turn prompt microglia to release IL-1β [82]. In turn, this triggers a cascade of microglial activation and monocyte trafficking to the brain. In parallel with this mechanistic data, meta-analytic evidence links heightened perceived stress—particularly chronic stress—with elevated dementia risks [83,84]. By contrast, the functional impacts of acute stressors on cognitive performance seem to vary across dimensions of cognition, as well as contexts and groups. In a 12-study meta-analysis, acute laboratory stressors had negative effects on episodic memory and verbal fluency, no impact on executive functioning, and—specifically among older adults—a positive effect on working memory [85]. However, in a daily diary study [86], response times to a working memory task were slower on days with higher stress compared to days with lower stress, regardless of age. Taken together, toxic stress [7] appears to contribute to cognitive risks in part through inflammatory processes, but effects on

cognitive performance may not be seen with acute stressors and in healthy populations.

Cognition is also at the center of associations between social-emotional development and stress (Path B). In her dynamic integration model, Labouvie-Vief [32] argued that cognitive resources enable individuals to process negative emotions, which are comparatively more demanding than positive emotions. Moreover, she posited, cognitive decline—not dwindling time horizons—accounts for older adults' decreased negative affect. Aligned with this idea, one study found that fluid cognition supports emotion regulation efforts: adults with higher fluid cognition had less negative emotional reactivity to daily stressors than did their counterparts with lower fluid cognition [87]. Similarly, social withdrawal and emotional disturbance may serve as prodromal symptoms that forewarn the development of dementia [88–90].

Given its implications for emotion regulation, cognitive decline may also amplify the effect of stress on healthy aging (Path C). According to a study comparing individuals with mild cognitive impairment (MCI) to cognitively healthy older adults, daily stressors elicited stronger negative affect reactivity among individuals with MCI than among their non-MCI counterparts [91]. In this vein, those experiencing cognitive decline may stand to benefit from interventions that target emotion regulation as a mechanism, in tandem with other treatments. Indeed, systematic reviews and meta-analyses that have synthesized the early work on mindfulness- and meditation-based interventions in the context of MCI and dementia show promising preliminary results for quality of life and perceived stress, as well as cognitive functioning and underlying changes in brain morphology [92,93].

6. The challenges of taking aging into account

Considering adult development and aging in the study of stress and health requires confronting many practical and conceptual challenges. Historically, older adults have been inadvertently excluded from health research due to their health conditions and medications, or they have been overtly excluded due to presumptions about their health problems. According to a landmark analysis of NIH trials, one third of phase III clinical trials had arbitrary upper age limits, and two thirds of the studies had fewer older adults than would be expected for the prevalence rates in the given disease or condition of interest [94]. Of course, scientists have an interest in maximizing the signal-to-noise ratio by limiting variation in comorbidities and medications, which have important consequences. This means that the older adults who are enrolled into health-focused studies typically do not represent the older population at large. However, eliminating such exclusions would not only require larger sample sizes and thus larger budgets and longer recruitment periods, but also may require exceedingly complex models to account for these multiple interacting contributors. Even beyond the effects of comorbidities and medications, aging itself is characterized by increasing heterogeneity across adulthood [95,96]. Thus, addressing these problems may require high-dimensional data and models designed to accommodate the complexity.

Another practical limitation of taking aging into account emerges because researchers age on the same timescale as the people we study. Even though we know that studying cross-sectional age differences cannot replace tracking within-person changes over time [57], cross-sectional studies predominate given the expense, slow pace, and thus impracticality of longitudinal studies. Moreover, both types of studies must contend with cohort and period effects—historical shifts in stressors, socially acceptable emotion regulation strategies, normative configurations of social relationships, as well as pharmaceuticals' impact on aging. Indeed, the scientific discovery of vaccines and antibiotics extended the lifespan and gave opportunity for chronic conditions to develop at higher rates.

Drug development will likely continue to shape aging outcomes. For example, statins, widely used in preventive medicine, vastly reduce cardiovascular events and lower inflammation. Metformin not only reduces inflammation but is also a top candidate for the first anti-aging pharmaceutical trial in humans [97]. In addition, a recent study found that MIDUS participants taking metformin were protected from the association between depressive symptoms and inflammation [98]. However, this buffering effect did not replicate in an older sample of Mexican Americans, suggesting that systemic disparities may be at work. NIH has invested in a series of longitudinal cohort sequential studies around the world that are instrumental to efforts in understanding how the exposome alters aging across historical periods and cultural contexts [99]. Although these provide a rich resource for examining an impressive range of phenomena at a high level, these large epidemiological studies necessarily lack granularity in specific areas and at a mechanistic level. There are good opportunities to scale mechanistic research by building such studies into existing cohorts, although the procedures and prospects for doing this may be limited and vary by cohort and study team.

7. Lingering questions

Many open questions frame future directions for the study of aging, stress, and health. As mentioned before, both acute and chronic processes are well-characterized, but the timing of the transition between the two is not well understood and likely varies between individuals. With technological advancements and cost reductions, will it be feasible to chart their time courses, e.g., how stressor pileup and resource depletion may contribute to the development of glucocorticoid resistance? In terms of psychosocial dimensions, will it be feasible to develop an index of psychosocial aging similar to epigenetic age estimates? From a biological perspective, will it be possible to parse the effects of age-related diseases and medications from the effects of normative aging (a matter of philosophical debate for some)? Regarding the contours of adult development, is it possible to identify and establish sensitive periods for the course of aging? These may include landmarks such as retirement, assumption of a caregiving role, bereavement, and relocation [100]. Finally, what results from the interplay of social-emotional and biological aging? Does the acceleration of biological aging make us feel older and, in turn, behave as if we are older, i.e., by forming a positivity bias? Can anti-aging drugs change our mindset and the way we approach stressors?

8. Summary and implications

This review synthesized disparate perspectives on aging that, to date, have advanced independently. Taking an interdisciplinary view highlights the remarkable ways that aging may shape the association between stress and health. Not only can stress accelerate biological aging, but also social-emotional aging can alter the way people approach stressors, underscoring the need to critically evaluate the relevance and psychological impact of stressor paradigms. Moreover, the social-emotional strengths of aging break down under conditions of uncontrollable stress, which may result in more adverse physiological sequelae for older adults. At the same time, the increasing importance of psychosocial resources creates an opportunity for behavioral interventions to have meaningful health benefits that may translate to prolonged functioning and independence. An interdisciplinary approach to aging will enhance our understanding of stress's health consequences and shed light on how to leverage psychosocial strengths to extend the healthy years.

9. Personal reflections on Dr. Janice Kiecolt-Glaser's legacy in science and mentorship

This work serves as a tribute to the legacy of my postdoctoral mentor, Dr. Jan Kiecolt-Glaser. It integrates my graduate training in adult development and aging with training in psychoneuroimmunology (PNI), stress, and health, acquired in Jan's lab. I hope the review mirrors Jan's proclivity for uniting diverse perspectives, as together with her husband

and collaborator Dr. Ron Glaser, Jan was among the early pioneers to integrate two fields previously thought to be unrelated, psychology and immunology. Jan first inspired me as a graduate student when I read her 2001 "Marriage and Health: His and Hers" [101] and Kiecolt-Glaser et al. (2005) [102], the groundbreaking work that linked couples' interactions to inflammation and wound healing. I wondered whether the immune system was involved in the dynamics I studied at the time—everyday interactions in older couples and their effects on pain—and I dreamed of one day training in psychoneuroimmunology.

For months after starting the postdoctoral position, I continued to be starstruck by this visionary woman in science, whose career seemed larger than life. The more I learned about Dr. Kiecolt-Glaser, the stronger my sense of awe grew. *Over 200 publications. Studies on how stress affects a wide range of health dimensions—innate immunity, vaccine responses, allergies, wound healing, metabolism. Interventions using relaxation, aromatherapy, yoga, omega-3 supplementation. An NIH MERIT award to follow dementia caregivers longitudinally.* Funding *from 5 NIH institutes for 30+ years. Featured in a book by a New York Times bestselling author. Interviewed on Good Morning America. And she writes novels in her free time?!* This seemed to be research lore, impossible for a human to accomplish in one lifetime—beyond the 12 labors of Hercules. Part of being her mentee meant getting to watch and learn how she works, adopting and adapting these practices, and now sharing them with my own mentees.

Jan's clear vision for what is important in science and in life has served as a guide to success for so many. She has a keen talent for mastering and writing about new scientific literatures, as well as integrating research from disparate fields with the study of human stress. During my time in the lab, she added the gut microbiome and biological aging to her already-impressive repertoire. Healthy, efficient routines structured her schedule. Inspired by the work of Robert Boice, mornings always began around 8am with daily writing, frequently aided by dictation software. Meetings followed, often while pedaling at a Desk Cycle and sometimes snacking on raw sweet potato sticks. Simple systems—an index card, flair pen, and manila folders for each day of the week—kept tasks organized. Jan recruited an incredible team of people, including several staff members who spent their entire career in her lab—a clear testament to how well she treated them. She routinely left the office around 4pm for pilates, with balance and boundaries supporting her physical, mental, and spiritual well-being. Pairing talent, structure, and an excellent team with her elegant writing style and sustainable routines, Jan moved fluidly from idea, to IRB protocol, pilot study, R01 proposal, data collection, analysis, and publications, again and again—leading to a long series of exciting discoveries.

In addition to learning her recipe for success through observation, I was the direct beneficiary of Jan's generous mentorship. She provided a foundation of structure and support, protecting our weekly meeting times and delivering fast feedback on writing through audio recordings, which always conveyed a sincere, interested tone. Being embedded in a team of staff, graduate students, and undergraduate research assistants enabled me to learn the PNI protocols in a hands-on way and to practice critical skills that I have since relied on as a principal investigator—supervising staff, mentoring students, overseeing recruitment, and interfacing with collaborators—while also reserving time for analyzing data and writing.

With this support structure, I enjoyed access to 30+ years of rich data, a researcher's playground, along with a great deal of intellectual freedom in pursuing my own research questions—critical for my growth as an independent researcher. This was a formative period for my own thinking, where I integrated my background in aging and dyadic relationships with PNI approaches to consider the health implications of aging relationships in new ways. Jan was generous enough to support me in writing a K99/R00 proposal and offered an incredible opportunity to embed my task in her larger study, which has generated intriguing results and led to important follow-up questions. In addition, Jan routinely invited me to collaborate in writing papers, provided guidance on interfacing with the media, promoted me at conferences, and delivered compliments shared "behind my back" (the sincerest kind of praise). She has written endless letters of support and shared wisdom on navigating academic jobs. Indeed, beyond Jan's expertise in PNI, she is also masterful in scaffolding growth—targeting the zone of proximal development with a blend of support and autonomy.

Undoubtedly, these experiences reflect larger themes that will be echoed by all of Jan's mentees. She has made profound impressions on us not only as individuals, but also in her efforts to connect us together to form lasting support networks. Together, we will live out and pass on her legacy of collaboration, humanity, mutual support, and scientific rigor to the next generation.

CRediT authorship contribution statement

Stephanie J. Wilson: Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

I have no actual or potential conflicts of interest to report.

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