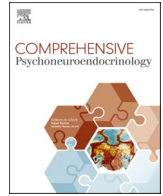


Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

# Comprehensive Psychoneuroendocrinology

journal homepage: [www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology](http://www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology)

## Caring about the family caregiver: A mentored journey building on the legacy of Janice Kiecolt-Glaser's pioneering research on caregivers' immune health

Kathi L. Heffner

*Elaine Hubbard Center for Nursing Research on Aging, School of Nursing, Department of Psychiatry, Division of Geriatrics & Aging, Department of Medicine, School of Medicine and Dentistry, University of Rochester Medical Center, United States*

### ABSTRACT

Dr. Janice Kiecolt-Glaser has had enormous impact on understanding immune and health risks for stressed and burdened caregivers of a family member living with Alzheimer's disease or related dementia (ADRD). Her scientific and educational influence continues through the generativity to which she was committed during her career, mentoring multiple graduate and postdoctoral mentees over many years. This celebratory essay serves to underscore the pearls of wisdom offered by Dr. Kiecolt-Glaser that influenced this former mentees' scientific and career choices. The purpose is two-fold. First, to pass along "pearls of wisdom" imparted by Dr. Kiecolt-Glaser that may be useful to burgeoning scientists, especially those in psychoneuro-immunology or -endocrinology, who have not been exposed to these pearls. Second, to provide mentors, who may be uncertain about their own generative influence, with an exemplar of the power and endurance of wise advice.

~ A festschrift essay of gratitude ~

In 2020, more than a quarter of individuals living in the United States – more than 16 million people – reported caring for at least one family member with Alzheimer's disease or related dementia [1]. These family caregivers provide over 18 billion hours of care, and 27 h per month more than individuals who provide care for a family member with non-ADRD chronic conditions [1]. It is expected that, without medical breakthroughs in ADRD prevention or cure, the number of people living with ADRD over the age of 65 will grow from 6.7 million to almost 14 million in the next 35 years [2]. This is concerning from a public health perspective, as we know caregiving takes a toll on health. More than 1 in 5 of caregivers surveyed rate their health as "poor" to "fair" [1]. These survey findings echo decades of research underscoring the health risks of caring for a family member with dementia [3–6], including higher prevalence of depression [7], increased cardiovascular disease risk [8], slower wound healing [9], and frailty risk [10].

Several behavioral mechanisms are known to indirectly contribute to poor caregiver health, including engagement in fewer health behaviors [5,11] such as exercise and maintaining a healthy diet, poor sleep, and excessive alcohol use. The pioneering psychoneuroimmunological research by Dr. Janice Kiecolt-Glaser was pivotal in bringing to light the direct and pernicious effects of caregiver stress on caregivers' immune function (e.g. Refs. [12–16]), including multiple aspects of immunocompetence and immunosenescence that could plausibly explain the

increased risks of caregiving stress for poor physical and mental health. Of course, the contributions of her research generalize well beyond stressed caregivers to understanding more broadly how it is that chronic stress impacts the immune system. Caregiving for a family member with dementia can be an unfortunate human model of chronic stress.

### 1. A legacy's foundation

Dr. Janice Kiecolt-Glaser published in 1987 the first evidence for a role of caregiving stress in parameters that signal immunocompetence [14]. She and her colleagues found that compared to sociodemographically-matched non-caregivers, caregivers of a family member with Alzheimer's disease were more distressed and had lower T lymphocyte counts and elevated Epstein-Barr antibody titers. Over almost four decades following those findings, she and others substantially expanded the caregiver stress research in psychoneuroimmunology, with key evidence pointing to caregiving effects on adaptive immunity and antibody responses to vaccine [13], accelerated increases in aging-related inflammation [16], and immune-mediators of wound healing [9].

Along with the immune consequences of caregiving for a family member with Alzheimer's disease, numerous studies have revealed potential pathways through which caregiving stress may weaken immune competence, increase low-grade chronic inflammation, and exacerbate poor health. These mechanisms include altered physiological stress

E-mail address: [kathi\\_heffner@urmc.rochester.edu](mailto:kathi_heffner@urmc.rochester.edu).

<https://doi.org/10.1016/j.cpnec.2024.100259>

Received 14 May 2024; Received in revised form 29 July 2024; Accepted 2 August 2024

Available online 5 August 2024

2666-4976/© 2024 The Author. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

system regulation – observed in the autonomic nervous system and hypothalamic-pituitary adrenal axis – and accelerated biological and molecular aging [6].

The extent of immune outcomes that are known to be disturbed in caregivers is remarkable. Yet, there remains much to learn about how to target and ameliorate caregiver stress to protect caregivers' immune systems and health. The research legacy of Dr. Kiecolt-Glaser or, for short and as her lab staff fondly referred to her – “Dr. K-G” – continues to be borne out in the ongoing calls for advancing interventions that foster caregiver health. Next, I describe the mentoring and guidance by Dr. K-G during my postdoctoral fellowship with her, more than 20 years ago, that influenced and influences my own scientific choices and mentoring. I also provide a description of scientific development that demonstrated how, in full circle, her foundational work on the accelerated immunosenescence evidenced by stressed and burdened ADRD caregivers came to shape current research in my lab, caring about the family caregiver. The purpose is to provide – especially for student and postdoc mentors who may be uncertain about their influence – an exemplar of the power and endurance of wise advice and influential science.

## 2. Building on the legacy: A mentored journey guided by pearls

Dr. K-G committed to helping shape her mentees' behavior in ways that would promote successful professional development in academic science. She was, after all, an astute clinical psychologist. Below are 3 pearls of K-G wisdom and examples of the ways they shaped this investigator's research and career path.

### 3. Pearl #1: Stay focused on your ‘P’ expertise in PNI

The postdoctoral fellowship period is an exquisite time of research training, void of the administrative service and teaching responsibilities that come with a future faculty position (this is acutely salient to me as I write this *festschrift* contribution on my sabbatical). As a doctorally-prepared social psychophysiology beginning this transitional postdoc phase to academic adulthood, I was eager to expand my understanding of the immune system, stress, and health frameworks, and, excitedly, PNI laboratory methodology. This latter goal prompted K-G to voice some trepidation: psychologists need not become laboratory technicians, it would be an incredible time-sink to be doing assays, and, instead, plan in the future to collaborate with expert immunologists (who have technicians). She ultimately supported me spending time in Dr. William Malarkey's endocrinology lab to learn ELISA assays, all-the-while reminding me to stay focused on furthering the ‘P’ in PNI.

The opportunity for ELISA assay training allowed me to hit the ground running in my first faculty post in a Psychology department, where there existed a wet lab and I could do ELISA assays for my own studies. Performing the assays no doubt gave me an in-depth understanding of my data and the meaning behind it. Nevertheless, spending hours in the wet lab and having a surface-level understanding of the assay methods, which meant difficulties problem-solving when things went wrong, diminished any experienced reward that could come from duplicate samples showing a <10 % coefficient of variance (although, honestly, that part was still very gratifying). When an opportunity arose to join a psychoneuroimmunology faculty research group at my current institution, the resident immunology expertise, accompanied by in-house laboratory technician support, were crucial carrots that clinched my decision to move. If anyone deserves to say, “I told you so,” it is my postdoc mentor – who told me so.

That said, it bears repeating that having the opportunity to become closely acquainted with ELISA methods has afforded a richer understanding of the data now provided to me by skilled laboratory technicians. There is great value to experiential learning of the ‘NI’ whilst nurturing the ‘P’, but it requires thoughtful balance. Psychology doctoral students interested in including immune and inflammatory biomarkers in their research indeed have more years to integrate that

learning into their training and should. I also suggest that development plans for psychology-trained postdocs engaged in PNI research training, although resting on a shorter training timeframe, should include structured exposure to PNI lab methods. In both cases, trainees will benefit immensely and will develop into savvy psychology collaborators on multidisciplinary PNI research teams that include endocrinologists and immunologists. Bringing the ‘P’ expertise to such teams can accelerate the translation of basic PNI research. Psychology expertise is critical to identify the unique human biobehavioral and neurocognitive factors underlying stress-mediated immune effects observed in animal and cellular research. People are more complex than the cells and hormones inside a Petri dish.

I have a strong appreciation now for the caution K-G voiced all-the-while supporting my interest in lab training. This pearl is principled on focus, balance, depth and breadth, hallmarks of a successful research and academic career.

### 4. Pearl #2: It is not a good idea to start your career conducting clinical trials

This pearl of wisdom stems from the years it often takes to secure funding for and complete a clinical trial, and, importantly, publish the findings. That reality does not readily align with tenure-granting institutions' timelines or tenure criteria, where in 5 years faculty candidates ideally demonstrate significant, external grant funding to be promoted and tenured; if in the U.S. and doing health-related research, this is typically independent NIH funding as a Principal Investigator.

Equipped with theoretical and methodological grounding in social psychology and cardiovascular psychophysiology from my PhD program, and with postdoctoral training in psychoneuroimmunology, I was now ready to build my research program, NOT conducting clinical trials. My initial research questions revolved around understanding behavioral and psychosocial mechanisms underlying older adults' physiological stress regulation and inflammation. Nevertheless, as you will see, my research would head into and be immersed in clinical trials. I fully understand and appreciate, and find myself dispensing, this mentoring advice. For trainees itching to conduct clinical trials, I can attest to how an initial focus on experimental and observational work can move a career along most efficiently, while also paving the way for later clinical trials.

That said (sound familiar?), over the time since I started my career, systematic approaches to developing and testing behavioral interventions along the translational continuum have been articulated (e.g., Ref. [17]). These approaches underscore the critical role of developmental activities, such as community stakeholder engagement in early stages of development, feasibility studies, pilot studies, and the like, that are now more widely accepted as fundable and publishable work. For instance, there are more funding opportunities at NIH that allow for earlier stages of intervention development in preparation for a larger scale trial, all within the same funding mechanism. This evolution is allowing burgeoning clinical trialists – from psychology, public health, nursing, and other disciplines – to gain traction in their research programs and demonstrate a record of productivity that can support an independent research record and, thus, academic promotion and tenure. Likewise, NIH career development and fellowship awards more explicitly support predoctoral and postdoctoral trainees' involvement in mentors' clinical trials to provide foundational training in these research designs. For later stage postdoctoral trainees, career development awards can include an independent, pilot clinical trial. With this greater opportunity for training in clinical trials, as well as external funding and publications in intervention development, there is an opportunity for accelerating a clinical trial research trajectory. In all, I might revise this pearl of wisdom: *Have a thoughtful and strongly mentored plan if you want to start your career conducting clinical trials.*

### 5. Pearl #3: Gather as much data as you can reasonably gather

Opportunities to direct K-G studies gave her postdocs exposure to a battery of measures that were especially timely, always reflecting the multitude of potentially confounding factors that peer reviewers (that pesky reviewer 2!) loved to raise about findings from stress studies. “Is it stress or is it really depression?” “Poor sleep may be a key driver of these outcomes.” “Did you look at personality?” Having the ability to be super responsive with data analysis to these types of reviews is even better than the “noted as a limitation” response and allows one the satisfaction of saying that none of it made a difference, because, you have measured it. Apart from this tongue-in-cheek rationale, strategic and reasonable expansion of measures in a single study can accelerate progress in any area. With so many potential psychosocial moderators and mechanisms involved in whatever you study in behavioral science, stand on the shoulders of psychometric giants and assess, assess, assess.

There are also other ways that well-selected measures beyond the study’s specific aims foster impactful science. Recruiting and enrolling participants, particularly from the community, is no easy or inexpensive feat. Most importantly, study participants’ time is a gift and we owe it to our study populations to make the most of their time through impactful research. At the same time, older adults in our studies often state that research participation is highly rewarding, and they are motivated to contribute to science and the greater good. Databases rich with psychometric assessments afford undergraduate and graduate students and postdocs opportunities to generate hypotheses, test novel psychoneuroimmunological relationships, and advance knowledge in ways that, as PIs, we may have not have even considered (or we did consider but do not have the time to pursue because of, again, committee meetings). There is, however, constraint to be had with assessments, reaping rewards of unanticipated scientific discovery all-the-while being mindful of participant burden. Selection should be informed by advances in conceptual frameworks relevant to the questions at hand. For instance, K-G leveraged the content expertise of her postdocs to ensure the latest understanding of important constructs, such as from dyadic relationships research, would be included in her ongoing studies of marital stress. Likewise, there are expert resources to guide investigators on the biobehavioral factors that should be considered in data collection and study designs (e.g. Ref. [18]).

In all, it is a delicate balance between data collection and participant burden, but well worth the effort to promote accelerated science and the fostering of our study populations’ health and well-being.

### 6. Applying these pearls: Caring about the family caregiver

It has been over 20 years since Dr. K-G shared these and many other pearls of wisdom during my postdoctoral fellowship. When I reflect today on my own research program development, it is clear to me that I was continually influenced by her pearls.

My first faculty position started in Fall 2003. In early laboratory work and with National Institute on Aging funding for a small pilot study, I, my collaborators, and graduate and undergraduate students collected data on older adults’ cortisol, cardiovascular, and inflammatory markers, at rest and in response to acute stressors, including memory tasks. Pearl #3: *Gather as much data as you can*. This single pilot study resulted in multiple contributions to understanding psychophysiological pathways in older adults’ health and well-being, including identifying the roles of: older adults’ sleep quality in inflammatory responses to acute stress [19]; insulin-like growth factor (IGF)-1 in associations between depressive symptoms and memory deficits [20]; and poor emotion regulation capacity that may be concomitant with worse subjective memory [21]. My postdoctoral fellow is currently working on a manuscript reporting, from analyses of these same pilot study data, the role of executive function in older adults’ heart rate variability and emotion regulation to acute laboratory stress. Numerous conference presentations and posters have also supported graduate students’

research education. We jokingly call this “the dataset that will never die.” It is a treasure trove of discovery.

By founding my lab on human experimental research, I was unintentionally following Pearl #2: *It is not a good idea to start your career conducting clinical trials*. As a new faculty member in an experimental health psychology area in a psychology department, I was returning to my experimental research underpinnings of my doctoral training. Making the aforementioned move to a medical center a handful of years later, I found myself collaborating with expert clinical psychology interventionists with common interests that I had developed in my first faculty post. These collaborations with clinical scientists afforded the opportunity to use evidence-based, targeted interventions (e.g., the highly efficacious cognitive-behavioral therapy for insomnia) as manipulations to test mechanisms of healthy aging (e.g., does sleep improvement reduce chronic knee pain?). That meant conducting clinical trials, but, in line with K-G’s pearl, only after initial grant funding and publications set me up for continued scientific contributions, supported by further funding and the breathing room afforded by academic promotion to wait years to complete these clinical trials.

A most valuable contribution of these data was the opportunity to provide proof-of-concept for central hypotheses ultimately tested in randomized controlled trials. In a trial funded by the National Institute on Aging in 2016, we are analyzing data (finally – thank you, COVID-19 pandemic) to test a central hypothesis that cognitive decline will accelerate immunosenescence in older adults exposed to chronic stressors, insofar as such decline reflects an overall reduction in “adaptive capacity,” or the ability to respond flexibly and adaptively to environmental challenges. In full circle, a most valuable contribution to framing the significance of this trial was the decades-long research by Dr. Kiecolt-Glaser underscoring how the chronic stress of caregiving for a family member with dementia can accelerate immune aging. To test this central hypothesis, we attempt to strengthen adaptive capacity in stressed and burdened family ADRD caregivers with a highly effective cognitive (processing speed) training and observe concomitant effects on emotion regulation (manuscript in prep), in the hopes of slowing immunosenescence (data analysis underway). In another trial resting on K-G’s foundational work, we are examining the role of mindfulness training as a means to bolster caregivers’ influenza vaccine antibody responses; with eventual center grant funding, we have fostered development of interventions for lonely caregivers [22] – and now flash forward to 2024 after engaging hundreds of stressed and burdened family caregivers in research to promote caregiver well-being, I have become fully committed to caring for the family caregiver, and return time-and-again to Dr. K-G’s findings when we consider mechanisms and outcomes in emerging work around caregiver stress and well-being, asking, “what did K-G learn about that?” Because she usually had learned something about “that” (Pearl #3 *Gather as much data as you can within a single study.*).

*Stay focused on your ‘P’ expertise in PNI (Pearl #1)*. I return to this pearl because it is one that has supported my capacity to stay focused on the role of psychosocial stressors in older adults’ health and aging. Working in multidisciplinary research teams, particularly when you have an interest in stress and immune function, it is easy to become captivated by collaborators’ basic physiology and immunology research. Questions about basic biological stress mechanisms underlying health outcomes start attracting one’s attention and a lure of working with cells and petri dishes in squeaky clean, controlled environments can be tantalizing. It just seems so much “easier” than human subjects protocol reviews, clinical trials regulatory requirements, and the complexities of recruiting and managing human beings in research. To all those “P” researchers in PNI, we must hang in there and we must keep trainees excited about their role. We “Ps” are needed to contribute to understanding the human complexities – the integrated psychosocial, biological, and behavioral complexities – that underlie stress responses, stress adaptation, and healthy aging.

## In gratitude

Dr. Kiecolt-Glaser committed herself to that “P” in PNI, substantially growing the study of human stress effects on the immune system by investing in her numerous graduate student and postdoc trainees who continue fostering the research. This generativity ensures her legacy and her continued influence in the field. I am honored and grateful to be a part of that academic family tree, and thank you, Jan, for your commitment to fostering the next generations of scientists, especially women scientists. I hope that this celebratory writing stands as an exemplar of Dr. Janice Kiecolt-Glaser’s impact – in science and in mentorship.

## Epilogue

One last K-G pearl of wisdom: *No more than 4 prepositions in a sentence.* I really hope I nailed that one here.

## Funding source

Work described in this essay was funded by National Institute on Aging grants R03AG030029, R21AG041942, R01AG049764, R01AG052495, P30AG064103.

## CRedit authorship contribution statement

**Kathi L. Heffner:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

## Declaration of competing interest

none.

## References

- [1] AARP and National Alliance for Caregiving, Caregiving in the U.S. 2020, 2020.
- [2] 2023 Alzheimer’s disease facts and figures, *Alzheimers Dement* 19 (4) (2023) 1598–1695.
- [3] M. Pinquart, S. Sorensen, Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis, *Psychol. Aging* 18 (2) (2003) 250–267.
- [4] S. Sorensen, et al., Dementia care: mental health effects, intervention strategies, and clinical implications, *Lancet Neurol.* 5 (11) (2006) 961–973.
- [5] P.P. Vitaliano, J. Zhang, J.M. Scanlan, Is caregiving Hazardous to One’s physical health? A meta-analysis, *Psychol. Bull.* 129 (6) (2003) 946–972.
- [6] L.M. Christian, et al., Understanding the health effects of caregiving stress: new directions in molecular aging, *Ageing Res. Rev.* 92 (2023) 102096.
- [7] M. Pinquart, S. Sorensen, Associations of caregiver stressors and uplifts with subjective well-being and depressive mood: a meta-analytic comparison, *Ageing Ment. Health* 8 (5) (2004) 438–449.
- [8] R. von Kanel, et al., Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 61 (9) (2006) 963–969.
- [9] J.K. Kiecolt-Glaser, et al., Slowing of wound healing by psychological stress, *Lancet* 346 (8984) (1995) 1194–1196.
- [10] K.B. Dassel, D.C. Carr, Does dementia caregiving accelerate frailty? Findings from the health and retirement study, *Gerontol.* 56 (3) (2016) 444–450.
- [11] R. Schulz, L.M. Martire, Family caregiving of persons with dementia: prevalence, health effects, and support strategies, *Am J Geriatr Psychiatry* 12 (3) (2004) 240–249.
- [12] J.K. Kiecolt-Glaser, R. Glaser, Psychological stress and wound healing: Kiecolt-Glaser et al. (1995), *Adv. Mind Body Med.* 17 (1) (2001) 15–16.
- [13] J.K. Kiecolt-Glaser, et al., Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proceedings of the National Academy of Sciences of the United States of America* 93 (7) (1996) 3043–3047.
- [14] J.K. Kiecolt-Glaser, et al., Chronic stress and immunity in family caregivers of Alzheimer’s disease victims, *Psychosom. Med.* 49 (5) (1987) 523–535.
- [15] J.K. Kiecolt-Glaser, et al., Psychoneuroimmunology: Psychological influences on immune function and health, *Special Issue: Behavioral medicine and clinical health psychology.* 70 (3) (2002) 537–547.
- [16] J.K. Kiecolt-Glaser, et al., Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Sciences of the United States of America* 100 (15) (2003) 9090–9095.
- [17] L. Onken, Implementation science at the national Institute on aging: the principles of it, *Public Policy & Aging Report* 32 (1) (2022) 39–41.
- [18] M.F. O’Connor, et al., To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers, *Brain Behav. Immun.* 23 (7) (2009) 887–897.
- [19] K.L. Heffner, et al., Sleep disturbance and older adults’ inflammatory responses to acute stress, *Am J Geriatr Psychiatry* 20 (9) (2012) 744–752.
- [20] F. Lin, et al., Associations between depressive symptoms and memory deficits vary as a function of insulin-like growth factor (IGF-1) levels in healthy older adults, *Psychoneuroendocrinology* 42 (2014) 118–123.
- [21] K.L. Heffner, et al., Subjective memory in adults over 50 years of age: associations with affective and physiological markers of emotion regulation, *Ageing Ment. Health* 26 (5) (2022) 971–979.
- [22] K.A. Van Orden, K.L. Heffner, Promoting social connection in dementia caregivers: a call for empirical development of targeted interventions, *Gerontol.* 62 (9) (2022) 1258–1265.