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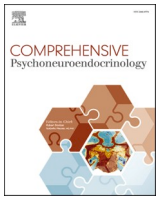

You can't spell distress without stress: Expanding our perspective of the intersection between mental and physical health in cancer survivors

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ABSTRACT

Although many breast cancer survivors adjust to cancer treatment and survivorship, a sizable subgroup of women do not do so, resulting in psychological distress. Over time, this psychological distress can contribute to immune dysfunction and accompanying worsened physical symptoms as women navigate survivorship. Dr. Kiecolt-Glaser's work and mentorship has been integral to our understanding of breast cancer survivors' immune risks, and how behavioral factors may enhance these risks. As a postdoctoral fellow in the Stress and Health Lab, under Dr. Kiecolt-Glaser's mentorship, my research focused on understanding how distress is associated with immune functioning and physical health in breast cancer survivors. In this paper, we highlight Dr. Kiecolt-Glaser's influence on our careers as a strong female research and mentor, the work completed under her mentorship, and how the field of psychoneuroimmunology can continue to expand her research to better understand how distress in the cancer context confers long-term health risks.

As past trainees of Dr. Kiecolt-Glaser, one of the titans in the field of psychoneuroimmunology (PNI) who retired after an illustrious 44-year career at The Ohio State University in 2022, this paper highlights our path towards working under her mentorship, the influence she has had on our careers, and the work completed during our time in the lab. By weaving together personal anecdotes about our experience being mentored by a strong female

Investigator with a review of our work focused on understanding distress' health impact on cancer survivors, this article provides perspectives of both the work and culture associated with Dr. Kiecolt-Glaser's lab and mentorship style. We further highlight how the field of PNI can continue to expand Dr. Kiecolt-Glaser's research to better understand how distress in the cancer context confers long-term health risks and how our work with her continues to influence our approach to teaching and mentorship with our own trainees.

1. My path to working with Dr. Kiecolt-Glaser

As a graduate student in a dual health and clinical psychology program, I[1] came to graduate school interested in the clinical psychology "side" of my training program and far less invested in the "health" side of my training. I entered a laboratory that used behavioral, self-reported, and psychophysiological (e.g., heart rate variability) indices to understand emotion regulation in people suffering from anxiety and depressive disorders. While I was interested in the physiological side, I was new to health psychology and conceptualized the physiological arousal associated with emotion regulation to be a proxy for emotional responding. It was not until my Health Psychology course with Dr. Tracey Revenson during my first year of graduate school where I received an introduction to the worlds of psychoneuroimmunology, health psychology theory, and the idea that *the emotions we were experiencing could confer long-term health risks*. As the capstone assignment in the course, I wrote an encyclopedia chapter that focused on depression and anxiety throughout the cancer trajectory. At the time, I had no idea that the beginnings of this course assignment would become a central focus of my research program a decade later.

It was this pivotal experience early in my graduate training that made me extend beyond traditionally used psychophysiological methods such as heart rate variability and skin conductance to start learning the associations between inflammation, anxiety, and emotion regulation. Knowing the integral role that inflammation had in many chronic illnesses, I sought out every conference talk, paper, and research

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[1] Throughout this paper, the first-person references regard experiences of the first author (Megan Renna), while 'we' and 'our' refers to both the first and second (M. Rosie Shrout) author.

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group I could to better understand how emotions affected inflammation and vice versa. My enthusiasm dampened, but motivation increased, when I learned that there had, at the time, been little work on these relationships. PNI research was very heavily focused on depression and mood disorders, but little on anxiety. This gap in the literature yielded my first publication in the world of PNI: a meta-analysis comparing basal inflammation levels in adults with versus without anxiety, obsessive-compulsive, and traumatic-stress related disorders. I also developed and executed an experimental manipulation of worry for my dissertation to assess inflammatory change. These projects were exciting, invigorating, and highly rewarding. I began learning the ins and outs of studying basal inflammation as well as inflammatory reactivity and recovery. Now with more than seven years of added training under my belt, I would have made some changes to the design, but they were my own, and I was so proud of them.

Throughout my graduate training, I was the inflammation expert in my lab. In typical imposter syndrome fashion, I was positive that I was not an expert in anything, never mind PNI-related methods and research. For my postdoctoral training, I wanted to learn from an expert—actually, *the* PNI expert, Dr. Kiecolt-Glaser. My first email to her introduced myself and I attached a copy of my CV. Dr. Kiecolt-Glaser's response took me aback for its plain, but kind language. She simply said, "Megan, very nice CV …", along with some details about opportunities that she had available (her response to Dr. Shrout's postdoc application—the second author of the current paper—had the same direct yet complimentary tone: "Rosie, I am impressed by your materials …" followed by potential dates for a phone interview). I never had anybody talk so plainly but in a way that made me feel so complimented. We would soon learn that this was indeed Dr. Kiecolt-Glaser's trademark style: not a lot of fuss and tells you like it is, good or bad.

We were post-doctoral fellows in the Stress and Health Lab under the mentorship of Dr. Kiecolt-Glaser for two years, overlapping the entire time except for Dr. Shrout's first and my last month. In part, we co-authored this paper together because, while we each have personal and professional relationships with Dr. Kiecolt-Glaser, our training, mentorship, and work with her are tightly intertwined. I started in August 2019 and ended in July 2021. Through funding from a National Cancer Institute T32, my work shifted to focus on breast cancer survivors. Leveraging my expertise in clinical psychology (yes, I actually developed enough confidence to admit to myself that I had expertise in the areas of psychodiagnostics and emotion regulation), I began generating hypotheses based on more than 15 years of cancer-related data that others had not yet really explored in the worlds of PNI or cancer. I was interested in understanding how common psychological experiences of survivors were associated with heightened inflammation, self-rated health, and other commonly assessed immune markers. Complementing my focus, Dr. Shrout was interested in how survivors' satisfying romantic relationships offered protection against such emotional, physical, and immunological threats.

Working with Dr. Kiecolt-Glaser was more than just working with a titan in the field of PNI. It was also the first time that I had a female research mentor. Despite attending an all-women's undergraduate institution and being involved in research for more than a decade, as a postdoc in Dr. Kiecolt-Glaser's lab, I was finally, for the first time, able to sit in a room with all women talking about science. My time in the Stress and Health Lab, working with an all-women research team is what helped, in part, inspire my burgeoning research on the unique health threats to women like breast cancer survivors. Our research together has now spanned almost half a decade of work focusing on understanding the unique health threats that breast cancer survivors who experience psychological distress face as they navigate different points along the cancer trajectory. Going back to that final assignment in my Health Psychology course during that first year of graduate school, I was inspired to do research that filled in the black boxes of how psychological distress influenced physical health among these women, with inflammation and related biological processes being a central focus.

2. A brief overview of mental and physical health risks to breast cancer survivors

The inspiration I gained to study how distress influences physical health in cancer survivors led me to a thorough review of the available literature when I started my postdoctoral fellowship under Dr. Kiecolt-Glaser's mentorship. There are many findings supporting the idea that stress and its associated psychological impacts heighten inflammation and the physical symptoms (e.g., pain, fatigue) associated with cancer treatment and survivorship. Epidemiological data suggest that cancer survivors have twice the likelihood of poor health and disability as individuals without a cancer history [1]. Many stressors emerge throughout the cancer trajectory including diagnosis, treatment, physical side effects, medical decision-making, and changes in role functioning. When people experience a variety of or prolonged stressors, distress is a typical result. While experiencing stress may be expected or typical as the result of lifestyle changes, treatments, and the uncertainty associated with a cancer diagnosis, distress results when well-being becomes impacted, leading to lasting discomfort, tension, and psychological implications such as diagnoses of anxiety or depressive disorders. Cancer-related distress can prime physiological dysfunction and high symptom burden among breast cancer survivors. Fueling this distress, cancer treatment and survivorship present several uncertainties: fears of the disease progression, recurrence, side effects, changes in physical functioning, and early mortality. Each of these uncertainties can contribute to anxiety and depression. A recent meta-analysis found higher rates of anxiety and depression among breast cancer survivors compared to women with no cancer history [2]. The stressors that survivors experience promote immune dysregulation and reduce quality of life among survivors [3–5].

Both acute and chronic stress increase inflammation [6,7]. At the biological level, chronic inflammation in adults without a cancer diagnosis increases morbidity and disability [8,9]. A proinflammatory environment promotes tumor initiation, growth, and metastases, contributing to poorer prognoses, risk for recurrence, and reduced survival among cancer survivors [10–12]. Inflammation also contributes to distressing physical side effects associated with cancer treatment and survivorship, including fatigue and pain [13]. Further, heightened inflammation increases the risks of comorbid disease development including cardiovascular disease, osteoporosis, diabetes, and others among cancer survivors [11,14,15]. These conditions pose additional threats to survivors' long-term health and physical functioning.

Breast cancer survivors experience many troubling symptoms during and after cancer treatment. Nearly 30 % of breast cancer survivors suffer from chronic pain five years after treatment [16]. Advanced cancer survivors also often endure pain and fatigue simultaneously [17]. Fatigue may also persist for years after cancer treatment [18] and can worsen self-reported physical symptoms above and beyond oncological treatment [19]. These unpleasant physical symptoms increase depression and/or anxiety [20,21] and thus reduce participation in everyday pleasant activities and negatively impact quality of life [22]. In addition to the somatic symptoms experienced, many survivors also report cognitive difficulties throughout survivorship. For example, breast cancer survivors had poorer executive function, working memory, and general cognitive function than women without a history of cancer [23, 24]. Across studies, research highlights that several aspects of cognitive function including memory, focus, and processing speed are impaired following chemotherapy and hormone-related therapies in breast cancer survivors [25]. Further, up to 67 % of breast cancer survivors reported focus and/or memory problems after treatment completion [26–30]. Self-reported cognitive problems predict distress, fatigue, and poorer quality of life [31–34].

This brief synopsis of findings highlights the psychological, cognitive, biological, and somatic effects of breast cancer diagnosis, treatment, and survivorship. Although many women adapt both physically and psychologically following diagnosis and treatment, there remains a

sizable subgroup who experience distress resulting from their cancer experience. Those women experiencing high and varied levels of distress was exactly the group that we were most interested in understanding during our postdoctoral fellowships.

3. Our cancer research under Dr. Kiecolt-Glaser's mentorship

As a postdoctoral fellow in the Stress and Health Lab, under Dr. Kiecolt-Glaser's mentorship, I published eight first authored publications. Four of these focused on the association between psychological distress and physical health in breast cancer survivors. I also helped to coordinate an NCI-funded R01 study that examined inflammatory reactivity to a vaccine challenge among breast cancer survivors. I also co-authored seven of Dr. Shrout's papers, including three of her cancer-related publications, and Dr. Shrout co-authored all of the publications described below. Our work together examined how breast cancer survivors' emotional, psychological, and physical health changed across early survivorship. While Dr. Shrout's work focused on the health benefits of romantic relationships [3,35,36], my papers focused on how cancer-related distress and distress disorder diagnoses (e.g., generalized anxiety disorder, major depressive disorder, post-traumatic stress disorder) impact health and emotion regulation abilities, including maladaptive regulation and its association with objective and subjective symptom ratings. The papers I led are summarized below.

At the symptom level, this work showed that cancer-related distress can indirectly impact the relationship between perseveration and fatigue, sleep problems, pain, and self-rated health in breast cancer survivors [37]. We then expanded on this work to examine how distress among breast cancer survivors could contribute to dysregulation at the biological level. In a 2020 paper, we examined how within-person fluctuations in cancer-related distress corresponded to higher inflammation in breast cancer survivors across three distinct timepoints: after diagnosis, 6 months post adjuvant treatment, and 18 months post adjuvant treatment [38]. At each visit, women completed the Impact of Events Scale which was modified from its original version to assess cancer-related distress, and a blood sample was collected to measure inflammation. We assessed how within-person increases in cancer-related distress, as well as how average distress levels, related to fluctuations in inflammation across visits. Findings revealed that at the within-person level, when a woman's own cancer-related distress was higher than usual, her inflammation was also higher. Thus, at visits where women had higher cancer-related distress than they typically did throughout the study, they also had higher inflammation. Interestingly, cancer-related distress was not linked to inflammation at the between-person level. That is, changes in women's own distress levels, but not average changes between survivors' cancer-related distress, were associated with inflammation. Testing within-person processes helped us to understand how a survivor's own distress changes before and after treatment in addition to how these changes relate to inflammation across visits, rather than how distress and inflammation compare to other women. These findings highlight the importance of a within-person approach to survivorship.

In shifting the focus from distress to psychological disorders characterized by elevated levels of distress, a 2022 paper using Stress and Health Lab data examined distress disorder histories and physical symptoms in breast cancer survivors across two samples. Women from the first sample were breast cancer survivors recruited following cancer surgery but before they began adjuvant treatment such as chemotherapy or radiation. The second sample of women were recruited 1–9 years following their chemotherapy or radiation treatments. This study tested whether having a history of a distress disorder, such as generalized anxiety disorder or major depression, influenced self-reported pain, fatigue, self-rated health, and sleep quality. Women who had a distress disorder had more pain and fatigue, lower sleep quality, and poorer self-rated health compared to those without a disorder, regardless of where they were in the cancer trajectory [39]. When examining other physiological markers of health, we tested changes in heart rate variability (HRV) before, during, and after an experimentally induced social stressor (The Trier Social Stress Test [TSST]) in breast cancer survivors. Specifically, we compared rates of HRV changes across the TSST between survivors with distress disorder histories compared to those without. What we found was striking: women with histories of a distress disorder had blunted HRV before, during, and after the TSST. These findings show distress disorder histories as unique risk factors associated with reduced cardiovascular function via diminished HRV among breast cancer survivors. Given that cardiovascular disease is the leading cause of death among Stage I breast cancer survivors [40], these findings highlight an important intervention point in promoting longevity among survivors: promoting psychological health among women who have histories of distress-related disorders, not just those experiencing current distress.

Psychological distress among both breast cancer survivors and physically healthy people can be either heightened or dampened because of the emotion regulation skills they use. Expanding on my prior work, we tested if two specific emotion regulation skills – worry and mindfulness – differentially predicted trajectories of pain, fatigue, and cognitive functioning across the day in breast cancer survivors. While these trajectories were based on subjective reporting of symptoms, we also looked at a hot/cold plate task to measure pain and examined survivors' performance on the Hopkins memory test. Findings showed that survivors who worried more and were less mindful experienced more self-reported memory problems, focus problems, and cold pain sensitivity [41]. Lower mindfulness also corresponded to higher self-reported fatigue and hot pain sensitivity and objective ratings [41]. These findings suggest that negative emotions, which are often rooted in psychological distress, and an inability to effectively regulate them, can influence a woman's experience during cancer survivorship and worsen their overall psychological and physical health. In contrast, mindfulness, an adaptive way to help regulation negative emotions, offers benefits and highlights the potential for these adaptive emotion regulation skills to serve as a protective factor for women throughout survivorship.

4. Learning from and expanding on Dr. Kiecolt-Glaser's work

Dr. Kiecolt-Glaser's influence can be seen throughout each of the studies presented above. Each paper used Dr. Kiecolt-Glaser's Stress and Health Lab grant-funded breast cancer data, many of which were R01-level projects. One of the excellent aspects of Dr. Kiecolt-Glaser's projects is that she looks beyond the central aims to think about other variables of interest, thus presenting opportunities for secondary analyses by her trainees and collaborators. Dr. Kiecolt-Glaser's trainees, many of whom are also featured within this special issue, have had a prolific track recording of publishing high-quality, high-impact secondary analyses from these projects. One of the challenges of being a trainee of Dr. Kiecolt-Glaser's is coming into the Stress and Health Lab and matching the caliber of ideas and analysis of the trainees that came before you. We each found ways to distinguish ourselves—Dr. Shrout with romantic relationships in breast cancer survivors, along with dyadic health effects—and a clear pathway that I found for myself was through studying distress, a construct that had not been widely explored by herself or her past trainees. Through our long discussions on PNI research and theory, biological assessment, and data analysis, we not only learned invaluable expertise from each other, but we also published multidisciplinary research that shaped our career trajectories.

By leveraging my past experience in my graduate school lab studying distress, I was able to capitalize on questions that focused on how cancer-related distress can alter women's physical health as they navigate the cancer trajectory. My graduate school lab studied emotion regulation in distress disorders – specifically generalized anxiety disorder, major depressive disorder, and other conditions that are characterized by emotion dysregulation broadly. By taking this expertise and coupling it with classic theories and perspectives from PNI, I was able to

ask novel questions that advance PNI research in cancer survivors. Integrating Dr. Shrout's expertise in romantic relationships, we showed that survivors' satisfying relationships were associated with lower stress, fatigue, depressive symptoms, pain, gut leakiness, and inflammation [3,35,36]. This collaborative work provided evidence that the quality of survivors' relationships, rather than the relationship itself, provided the most health benefits. I also used theories from clinical psychology to better conceptualize the role of distress in women's overall physical and psychological wellbeing. Dr. Kiecolt-Glaser was also affirming of this approach to idea conceptualization. Although we spoke somewhat different languages when it came to theories and constructs of interest, we agreed on the piece of writing that Dr. Kiecolt-Glaser found most important. By integrating theories from across areas, I was able to generate novel, testable hypotheses that pushed PNI and breast cancer research forward.

5. Significance of these contributions and future directions

Decades of research from Dr. Kiecolt-Glaser and others show stress' health risks. As stress increases, so does inflammation. This creates a dangerous pathway through which psychological health can contribute to chronic illness. PNI researchers have paved the way for understanding how stress implicates biological functioning and have shown that interpersonal stress, chronic stress, and acute laboratory stressors increase inflammation. Our work with Dr. Kiecolt-Glaser highlights some important avenues for future research on cancer survivors. Our work under Dr. Kiecolt-Glaser's mentorship would suggest, however, that looking at stress alone is too simplistic. Specifically, various aspects of distress – along with a failure to effectively regulate distress – comes with notable biological risks. It is also important for PNI researchers to expand our measurement and understanding of distress as people navigate the cancer trajectory. For example, our work on distress disorder histories highlights the need to not only look at current distress, but also histories of distress and how they may affect women's health trajectories. Further, we often used a within-person approach to understand individual-level associations between distress and the immune system. For example, showing that on visits when survivors had more cancer-related distress, anxiety symptoms, and depressive symptoms than what was typical for them, women also had higher inflammation and leptin provides a more nuanced view of the relationship between mental and physical health than what has typically been explored in PNI to date [38,42].

There are several evidence-based interventions to alleviate distress for people with and without cancer. Our research under Dr. Kiecolt-Glaser's mentorship shows the health risks when distress is not regulated or treated. Not only can distress affect the quality of life for breast cancer survivors, but also their overall longevity as they navigate survivorship. Psychological services for breast cancer survivors that directly address cancer-related distress and focus on ways to reduce suffering may improve negative health effects. Although we did not specifically examine interventions targeting distress, the treatment implications are clear: survivors need screenings for psychological distress, and services need to be available for those who express these issues. Our findings underscore the need for screening for and treating distress in breast cancer survivors, in line with recommendations from the American Society of Clinical Oncology and accreditation standards for cancer facilities set forth by the American College of Surgeons Commission on Cancer [43,44]. Likewise, it is too simplistic to only consider the implications of current distress as women navigate the cancer trajectory. Instead, understanding both past and current psychological experiences can help inform health care workers and those in social work, psychiatry, and psychology of the health threats posed by these past experiences.

When considering mental health treatment, evidence-based psychological interventions are known to improve cancer-related distress. For example, evidence-based interventions such as mindfulness based stress reduction are beneficial in offsetting some of the psychological and physical symptom consequences associated with breast cancer survivorship [45,46]. However, future work should identify treatment mechanisms that enhance survivors' inflammation and overall physical health. Despite clear psychological and physical health benefits, barriers that limit cancer survivors use of these treatments include not having access to these interventions, medical appointment burden, physical health complications, and/or the affordability of specialized mental health services [47]. Striking a balance between accessibility, feasibility, and effectiveness of psychological interventions is still a work in progress within the field of psycho-oncology, with more attention needed on tailoring and adapting existing treatments to meet the distress-related needs of cancer survivors.

Lastly, future work should identify characteristics that may enhance risk for distress among survivors. For example, cancer pa survivors vary widely based on many sociodemographic variables, including, but not limited to, race, ethnicity, sexual orientation, and age. Further, factors like socioeconomic status and geographic location can significantly affect how accessible and affordable quality care is for them. The work done by Dr. Kiecolt-Glaser has led to outstanding advancements in our understanding of stress' biological impact. The collection of participants from central Ohio, many of whom were being treated at Ohio State Wexner Medical Center for their cancer care, yielded homogeneous samples in terms of sociodemographic makeup. Preliminary findings in Annelise Madison's 2021 paper, my colleague and Dr. Kiecolt-Glaser's graduate student, found that breast cancer survivors identifying as Black or African American, compared to white survivors, reported worse psychological health throughout diagnosis and survivorship [48]. Much work still needs to be done to understand the needs of a diverse group of survivors.

On a personal level, there are many future directions that we see for ourselves, now as professors, research mentors, and early career researchers that are guided by our lessons learned from Dr. Kiecolt-Glaser. With her legacy and mentorship in mind, we have each started our own labs, began advising PhD students, and secured external funding to study stress and distress in breast cancer survivors. We have continued our interdisciplinary collaborations with each other and several others past Stress and Health Lab mentees, including Annelise Madison and Stephanie Wilson. Inspired by Dr. Kiecolt-Glaser, one of our first projects together as assistant professors examined daily associations in relationship satisfaction, stress, and physical symptoms among breast cancer survivors and their partners (Shrout et al., submitted, this special issue). We hope our collaborations are one way Dr. Kiecolt-Glaser's legacy will continue—collaborations and friendships that Dr. Kiecolt-Glaser's Stress and Health Lab made possible.

When I was negotiating for my current job, so many of our conversations focused on the anxiety of asking for what I needed to get my work done. Dr. Kiecolt-Glaser emphasized to me that a man would be more likely to ask for these things, and subsequently be more likely to get these things. She was right. I have been inspired by and deeply appreciative of my male research mentors that I had before Dr. Kiecolt-Glaser. In fact, they are still some of the first people I go to for advice and people who I consider to be extremely dear to me. However, it was the lessons learned in Dr. Kiecolt-Glaser's lab that helped me to advocate for myself, know my worth as a researcher, and pave the way for my own female mentees to be successful. Dr. Kiecolt-Glaser inspired my mentorship approach. While I used to feel so apprehensive about receiving her audio recordings of feedback on my papers and abstracts, I now find that it is an incredibly helpful way for me to communicate with my trainees and explain the *why* of the edits I am making to them. My approach to mentorship has always been that I take my work extremely seriously, but that I do not take myself very seriously, and hope to inspire this in my students. Dr. Kiecolt-Glaser showed us that taking our work seriously means not bending or stretching our research programs to chase funding opportunities, and instead advocating for what we need to do our work and telling a story in each paper or grant application.

We teach these lessons to our students; we encourage them to come with not only ideas, but to emphasize why these ideas matter, and to create a hook as if they are story telling. We talk to our graduate students, all of whom at the time of drafting this paper are women, about the lessons learned from Dr. Kiecolt-Glaser as we introduce them to her data and help them craft ideas inspired by her work. Importantly, I also talk to them how it was not until my postdoctoral fellowship that I had the privilege of sitting in a room to do research, full of and exclusively made up of, women. We are deeply aware that they are watching us and learning from not only our feedback on their writing and work, but also on how we carry ourselves as female early career academics at R1 institutions. We mentor with empathy and warmth, and I have a deep appreciation for the work my students are doing and difficulty of navigating a clinical psychology doctoral program. However, we make it a point to emphasize that this easy manner is not to be confused with a lack of care for our work, its quality, or our integrity as researchers building extremely specific, theoretically based programs of research. In my clinical work, I have been introduced to and practiced the principle of dialectics: two seemingly opposite things that can both be true. Inspired by my many different settings in which I have trained, I work to make both of these exist simultaneously in everything that I do. I can be warm, empathetic, and easy-mannered, *and* I can be firm and relentless in the quality that I expect from my research, lab, and students. The latter half of this dialectic is what I am most grateful for from Dr. Kiecolt-Glaser and her mentorship over the past five years, and something that I will strive to emulate throughout my career to make her proud and continue her outstanding legacy.

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Megan E. Renna: Writing – original draft, Project administration, Conceptualization. **M. Rosie Shrout:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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