Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Social Safety Theory: Understanding social stress, disease risk, resilience, and behavior during the COVID-19 pandemic and beyond

George M. Slavich

Abstract

Many of life's most impactful experiences involve either social safety (e.g., acceptance, affiliation, belonging, inclusion) or social threat (e.g., conflict, isolation, rejection, exclusion). According to Social Safety Theory, these experiences greatly impact human health and behavior because a fundamental goal of the brain and immune system is to keep the body biologically safe. To achieve this crucial goal, social threats likely gained the ability to activate anticipatory neural-immune responses that would have historically benefited reproduction and survival; the presence of social safety, in turn, likely dampened these responses. Viewing positive and negative social experiences through this lens affords a biologically based evolutionary account for why certain stressors are particularly impactful. It also provides an integrated, multi-level framework for investigating the biopsychosocial roots of psychopathology, health disparities, aging, longevity, and interpersonal cognition and behavior. Ultimately, this work has the potential to inform new strategies for reducing disease risk and promoting resilience.

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Belonging, Rejection, Evolution, Neural, Brain, Immune system, Inflammation, Health, Aging, Disease, Resilience.

Introduction

Few people have gone unaffected by the social, racial, and public health events of the past few years. What began as a divisive political climate that disparaged many turned into angry protests that culminated into a shocking insurgency on the U.S. Capitol that left five people dead [1]. Lurking in the background was another type of threat: SARS-CoV-2, a highly contagious coronavirus that causes COVID-19, which some experts believe will soon be endemic [2].

These social, physical, and microbial threats have led to substantial social isolation, loss, and human suffering [3–5]. These threats also have greatly disrupted peoples' daily lives and routines: whereas abhorrent displays of police brutality and racism have brought people to the streets to fight social injustice and inequality [6], the widespread danger of contracting COVID-19 forced people to avoid loved ones, friends, and coworkers, even as they passed away [7]. Although very different, each of these threats can be viewed through the lens of how they have degraded social safety, belonging, connection, and inclusion—resilience factors that are critical for promoting human health and wellbeing.

The goal of this article is to describe how seemingly different social, physical, and microbial threats like these can activate and influence the activity of common biological pathways that increase individuals' risk for inflammation-related diseases that promote aging as well as viral infections such as the common cold and, possibly, SARS-CoV-2. To accomplish this goal, I first introduce Social Safety Theory, a biologically based evolutionary perspective on life stress, health, and behavior [8]. Second, I review three bodies of evidence supporting this theory. Finally, I summarize several avenues for future inquiry on this topic.

Social Safety Theory

Central to Social Safety Theory is the fact that the human brain and immune system are principally designed to keep the body biologically safe. To accomplish this crucial goal, the immune system continually

monitors the internal biological environment and responds quickly when microbial infection or tissue damage are detected [9]. Depending on the specific type of threat present, either the innate or adaptive immune system becomes engaged [10,11].

When the apparent threat is a microbial infection, the evolutionarily older innate immune system uses invariant receptors on immune cells to recognize conserved features of microbes called *pathogen-associated molecular patterns*, which include lipopolysaccharide (i.e., endotoxin), bacterial and viral genomes, and double-stranded RNA viruses (e.g., rotaviruses) [12]. In contrast, cellular stress or death caused by tissue damage, bodily trauma, and ischemia lead to the release of *damage-associated molecular patterns* that regulate immune system function in the absence of a pathogenic infection [13]. When these immunologic defenses are insufficient, the body engages the evolutionarily younger adaptive immune system, which releases microbial-specific lymphocytes that neutralize or eliminate microbes based on their memory of having confronted similar threats in the past. Together, these immunologic responses provide critical protection from viruses, bacteria, and tissue damage that could cause severe infection, illness, or death if left unaddressed [14].

Cellular soldiers awaiting deployment

One of the most fascinating features of the immune system is that it does not simply wait for danger to occur before preparing its response. Rather, the immune system is a dynamic learning system that uses Bayesian forecasting to predict and prepare for threats that are *most likely to occur* based on past and current pathogen exposure statistics [15]. This ongoing education and calibration of the immune system over the lifetime refines the functional dynamics, capacity, and regulation of each individual's immunologic response. In doing so, the system can anticipate and guard against the specific threats most likely to be present in the surrounding environment in order to ensure the greatest survival advantage possible [16].

An even cooler feature of the immune system is that it mobilizes not just in response to *microbial threats* but also in response to *social threats* that historically indicated a heightened possibility of physical conflict or injury, both of which can lead to pathogen exposure and infection [8]. Stressors possessing this potential include social conflict, aggression, devaluation, discrimination, isolation, rejection, and exclusion. To detect such social-environmental threats, the immune system relies on the brain, which continually monitors the extent to which the individual is in a socially safe versus threatening environment. Four neural networks support this capacity: the amygdala network, mentalizing network, empathy network, and mirror network [17,18]. As shown in Figure 1, when a threat is detected, the brain can signal the immune system, and vice versa, via four pathways: the sympathetic nervous system, hypothalamic-pituitary-adrenal axis, vagus nerve, and meningeal lymphatic vessels [8,10].

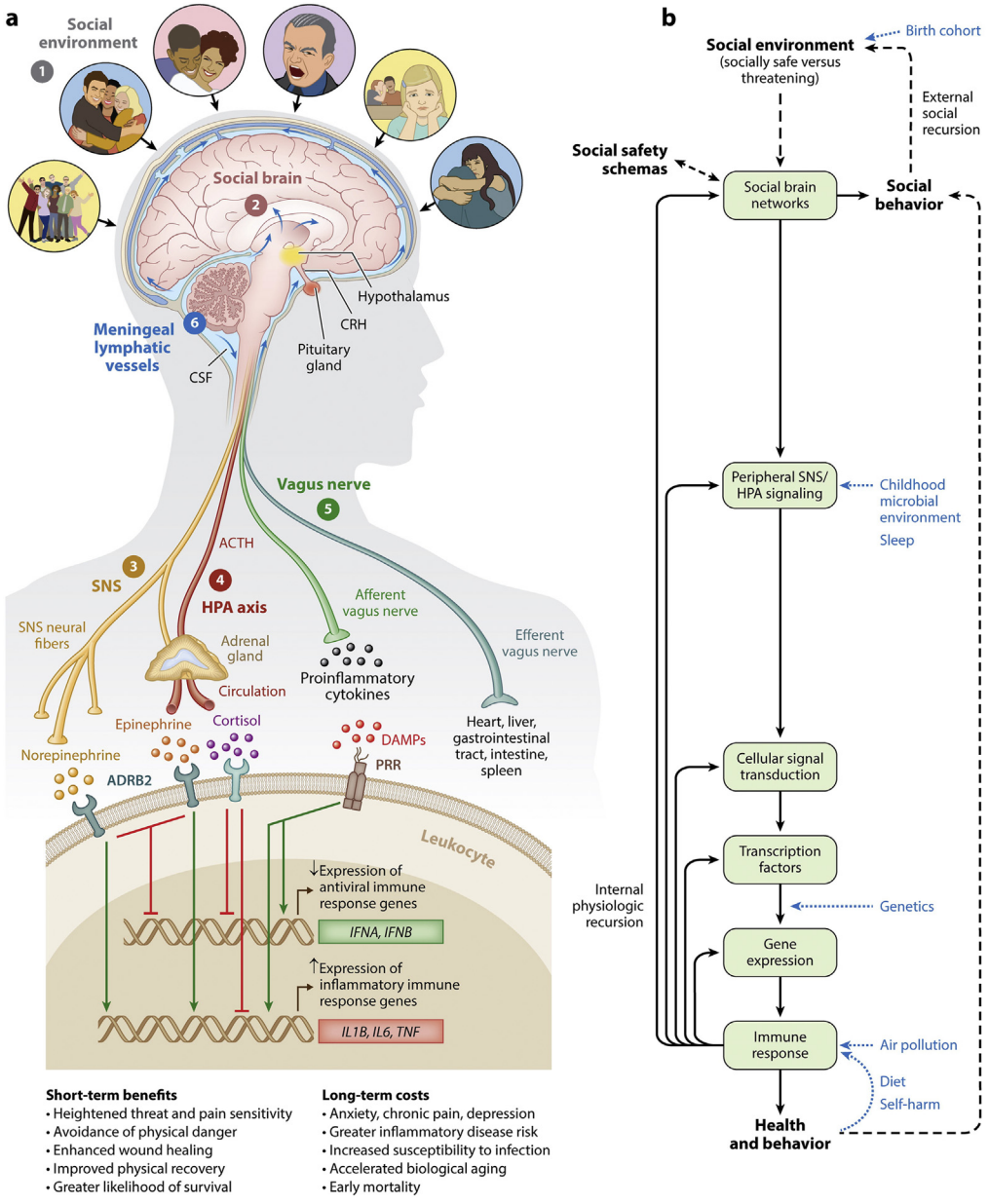
Implications of bidirectional neural-immune communication

The implications of this bidirectional neural-immune communication are profound. First, it means that neurocognitive appraisals of the surrounding social environment as being socially safe versus threatening can influence immune system dynamics and, consequently, disease risk, aging, longevity, and behavior [19,20]. It also means that memories and social safety schemas that people have about the self, social world, and the future can affect the immune system, even in the absence of current threat [21] (See Box 1). Second, this bidirectional communication gives immunologic memory and activity resulting from (for example) lifetime pathogen and air pollution exposure, vaccination history, and childhood microbial environment the ability to affect immune system function, and thus bias and reinforce social safety schemas and their cognitive products (i.e., thoughts, attitudes, beliefs), over the lifespan [22]. Third, it gives behaviors that impact the immune system—things like consuming a pro-inflammatory diet, getting inadequate exercise or sleep, and engaging in nonsuicidal self-injury—the ability to influence neural networks that in turn affect perceptions of social safety and threat [8]. Finally, it

Box 1. Social Safety Schemas

Social safety schemas are hypothesized to develop during childhood and adolescence based on a person's perceptions of the self, social world, and future. Such perceptions are shaped by the actual situations that people encounter (e.g., abuse, bullying, social exclusion) and by the meaning and messages that individuals and their caregivers attribute to socially salient events (e.g., "You can't handle it," "Other people can't be trusted," "You're going to be alone"). These schemas in turn play critical roles in structuring attitudes, expectations, beliefs, and behaviors across the lifespan. Most relevant for Social Safety Theory are individuals' beliefs regarding whether other people generally are friendly versus hostile, predictable versus unreliable, supportive versus critical, helpful versus hurtful, and sincere versus manipulative (i.e., social world schemas). Beliefs regarding one's own ability to cope with threats (i.e., self schemas) are also important, as are people's expectations regarding their likelihood of experiencing future social isolation, failure, and danger (i.e., future schemas). Together, these beliefs shape not just occasional thoughts and emotions but also how individuals navigate their social worlds, the types of relationships people develop, and how their brains and immune systems respond to positive, negative, and ambiguous social circumstances. Republished from Slavich (2020) [8], with permission from Annual Reviews.

Figure 1



Social Safety Theory is grounded in the understanding that the primary purpose of the human brain and immune system is to keep the body biologically and physically safe. To accomplish this challenging task, humans developed a fundamental drive to create and maintain friendly social bonds and to mount anticipatory biobehavioral responses to social, physical, and microbial threats that increased risk for physical injury and infection over the course of evolution. (**a**) Accordingly, the brain continually monitors the (1) social environment, interprets social signals and behaviors, and judges the extent to which its surroundings are socially safe versus threatening. These appraisals are subserved by the (2) amygdala network, mentalizing network, empathy network, and mirror neuron system (i.e., the social brain). When a potential social threat is perceived, the brain activates a multilevel response that is mediated by several social signal transduction pathways—namely, the (3) SNS, (4) HPA axis, (5) vagus nerve, and (6) meningeal lymphatic vessels. These pathways enable the brain to communicate with the peripheral immune system and vice versa. Whereas the main end products of the SNS (i.e., epinephrine and norepinephrine) suppress transcription of antiviral type I interferon genes (e.g., *IFNA*, *IFNB*) and upregulate transcription of proinflammatory immune response genes (e.g., *IL1B*, *IL6*, *TNF*), the main end product of the HPA axis (i.e., cortisol) generally reduces both antiviral and inflammatory gene expression but also can lead to increased inflammatory gene expression under certain physiologic circumstances (e.g., glucocorticoid insensitivity/resistance). The vagus nerve in turn plays a putative role in suppressing inflammatory activity, whereas meningeal lymphatic vessels enable immune mediators originating in the CNS to traffic to the periphery, where they can exert systemic effects. (**b**) This multilevel "Biobehavioral Response to Social Threat" is critical for promoting well-being and survival. However, it can also increase risk for negative health and behavioral outcomes when it is sustained by internal physiologic or external social recursion. As described in Slavich (2020) [8], several factors can also moderate these effects, including birth cohort, childhood microbial environment, sleep, genetics, air pollution, diet, and self-harm behavior. A person's developmentally derived social safety schemas play a particularly important role in this multilevel process as they shape how social-environmental circumstances are appraised. Social safety schemas thus influence neurocognitive dynamics that initiate the full range of downstream biological interactions that ultimately structure disease risk and human behavior. Abbreviations: ACTH, adrenocorticotropin hormone; ADRB2, β2-adrenergic receptor; CNS, central nervous system; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; DAMPs, damage-associated molecular patterns; HPA, hypothalamic–pituitary–adrenal; PRR, pattern recognition receptor; SNS, sympathetic nervous system. Republished from Slavich (2020) [8], with permission from Annual Reviews.

provides a multi-level, mechanistic explanation for how the brain and immune system realize the evolutionally adaptive, crucial goal of avoiding social threats and developing and maintaining friendly social bonds, making this drive a central organizing principle of human psychology and behavior [23–25].

Evidence supporting Social Safety Theory

As reviewed in Slavich (2020) [8], these principles of how social-environmental processes affect the human brain and immune system, and vice versa, translate into three main tenets of Social Safety Theory, which are that: (1) Humans evolved to foster social safety, (2) Social safety is beneficial for human health and behavior, and (3) Social threat is harmful for human health and behavior. Evidence supporting these tenets, which is summarized below, comes from a variety of fields, including anthropology, psychology, sociology, epidemiology, and public health.

Tenet 1: Humans evolved to foster social safety

Replaying the social, racial, and public health events of the past few years could easily give the impression that humans evolved to behave antisocially. However, the consensus is that *Homo sapiens* demonstrate a strong affinity for others who are similar and a tendency to exhibit hostility toward strangers [26]. These preferences are consistent with the goal of keeping the body biologically safe, and they historically increased the likelihood of both reproductive success and survival [27].

As a wealth of comparative, developmental, and paleoanthropological research has shown, natural selection for prosociality was first evident about 2.6 million years ago in the Paleolithic, and it enabled humans to live, hunt, and gather together in groups [28–30]. These behaviors gave rise to more sophisticated mechanisms supporting interpersonal communication and coordination, including the ability to mentalize, experience others' distress, exhibit compassion and empathy for others, tolerate and manage social conflict, and control urges to behave aggressively [29,31]. As a result, humans nowadays demonstrate a strong, evolutionarily driven desire to foster friendly relationships [28], and they tend to prefer others who are kind, emotionally warm, and socially safe [29]. The ultimate benefits of this highly evolved motivational drive are unmistakable, as everyday life now take place in buildings, cities, and systems that required exceptional in-group cooperation and communication to create [27,32].

Tenet 2: Social safety is beneficial for human health and behavior

The upside of developing and maintaining social safety goes beyond day-to-day living and includes substantial benefits for lifelong health and behavior [33]. As compared to individuals experiencing low social integration, for example, those who are socially well-integrated exhibit less systemic inflammatory activity [34] and, partly as a consequence, tend to live much longer [35]. These beneficial effects are evident in the general population but also in a variety of specific clinical contexts including upper respiratory illness [36], acute myocardial infarction [37], HIV/AIDS [38], stroke [39], heart disease [40], and cancer [41]. Notably, these benefits of social safety for wellbeing and mortality are comparable to or exceed those conferred by other well-established risk factors, including smoking, obesity, and physical inactivity [42].

Social safety also benefits behavior. For example, in addition to predicting more positive health behaviors across the lifespan [43], social safety is associated with greater perseverance, productivity, and achievement at work and school [44,45], in addition to more volunteering and fewer sick days [46]. Fostering and maintaining social safety thus confers several notable benefits to human health, wellbeing, longevity, and behavior.

Tenet 3: Social threat is harmful for human health and behavior

In addition, a sizeable literature exists documenting the varied ways in which social threats such as interpersonal conflict, isolation, rejection, and exclusion negatively impact lifelong health and behavior. Consistent with Social Safety Theory, for example, targeted rejection has

Box 2. Social Safety and Psychopathology

Social Safety Theory hypothesizes that maximizing social safety and minimizing social threat made humans exquisitely sensitive to social information and created a deep motivation to foster, maintain, and restore social safety whenever possible. Positive social safety schemas provide individuals with a favorable sense of the self, social world, and future that promotes a stable feeling of social connection, affiliation, inclusion, and belonging. In contrast, negative social safety schemas give rise to thoughts and feelings about the self, social world, and future that can oscillate or change in response to varying social feedback and circumstances. Whereas positive social safety schemas enable normative psychosocial development and the formation of healthy interpersonal relationships, negative social safety schemas promote pathological thoughts and attempts to maintain social safety and relevance and are a core social-cognitive characteristic of many forms of severe psychopathology—whether it be an individual with borderline personality disorder who seeks excessive reassurance from others, a person with narcissistic personality disorder who continually exaggerates their import, or someone experiencing delusions who places him or herself at the center of a never-ending conspiracy theory or investigation. Indeed, disturbances in one's social safety schemas may be key to understanding abnormal cognitive, emotional, and behavioral patterns that are central to a variety of different psychiatric disorders. Republished from Slavich (2020) [8], with permission from Annual Reviews.

been found to hasten the onset of depression [47,48], promote suicidal ideation [49], upregulate molecular signaling pathways that increase systemic inflammation [50], and downregulate molecular signaling pathways that reduce systemic inflammation [51]. Likewise, being exposed to verbal attacks, social exclusion, devaluation, and aggression heightens inflammatory reactivity to social stress [52], promotes an increased pro-inflammatory/reduced antiviral skewing of the leukocyte basal transcriptome [53], and accelerates biological aging as indexed by telomere length [54]. As described in Box 2, these effects can foster the development of a variety of affective and personality disorders. They also translate into a significant increase in mortality risk that equals 26% for low socioeconomic status, 26% for perceived loneliness, 29% for social isolation, and 32% for living alone [55,56].

Like social safety, social threat also greatly affects behavior. Beyond reducing engagement in prosocial behaviors such as helping, donating, and cooperating [57], exposure to social threat can promote anger, procrastination, aggression, and withdrawal, as well as numerous externalizing behaviors such as fighting, cursing,

Box 3. Issues for Future Research on Social Safety Theory

(a) **Fundamental nature, conceptualization, and measurement of social safety and social threat**
- Many types of experiences can help promote social safety, including social acceptance, affiliation, cohesion, belonging, interaction, inclusion, and connection. Which of these are most beneficial for social safety and why? What is the hierarchical organization of these and other salutatory social experiences?
- Conversely, many types of experiences can be considered social threats, including social conflict, aggression, devaluation, discrimination, isolation, rejection, and exclusion. Which of these are most detrimental for social safety and why? What is the hierarchical organization of these and other related forms of social adversity?
- What are the best instruments, methods, and approaches for measuring social safety and social threat on both the individual and collective level? Does the best approach differ across the life course, such as for young children (who cannot easily self-report) versus older adults?
- What are normative levels of social safety and social threat across people of different backgrounds, age groups, genders, cultures, and nations?

(b) **Development and impact of social safety and social threat over the lifespan**
- What impact do prenatal programming processes have on experiences of social safety and social threat over the life course?
- How do social safety schemas develop during childhood and adolescence? When do they solidify? What social relationships and experiences are most impactful in this regard? Are there sensitive or critical periods during which time social safety schemas are particularly malleable or sensitive to positive or negative social-environmental input?
- Relatedly, are there sensitive or critical periods during which time experiences of social safety or social threat exert particularly strong effects on human health, wellbeing, longevity, or behavior? How persistent are these effects, and how and when can they be changed?
- How are experiences of social safety and social threat affected by birth cohort, culture, religion, and other macro factors, collective processes, and belief systems?
- What social, cultural, environmental, and biological processes underlie the intergenerational transmission of the propensity to view others and the world as a socially safe versus threatening place? What is the relative contribution of individual versus collective processes in the persistence of social safety and threat over time?

(c) **Biopsychosocial mechanisms linking experiences of social safety and threat with health, wellbeing, aging, and mortality**
- What social, psychological, neural, physiologic, immunologic, molecular, genetic, and genomic mechanisms give experiences of social safety and social threat the ability to affect human health, wellbeing, and behavior?
- How are experiences of social safety and social threat affected by factors that impact inflammatory activity, such as diet, sleep, exercise, nonsuicidal self-injury, health behaviors, childhood microbial environment, air pollution, vaccination history, bisphenol A and phthalates (e.g., from water bottles and food storage containers), pesticides (e.g., from crop protection and food preservation), heavy metals (e.g., cadmium, lead), electromagnetic fields (e.g., from mobile phones and Wi-Fi networks), pollen (e.g., from grass and trees), and excessive noise (e.g., from construction and vehicle traffic)? What role do these factors play in regulating the social signal transduction pathways that shape experiences of social safety and social threat?
- Conversely, how do changes in the activity of social signal transduction pathways affect experiences of social safety and social threat over time?
- How do social threat-related changes in neural-immune communication affect disease risk, aging, and mortality risk?
- How do experiences of social safety and threat spread across social networks? Can these network dynamics help explain why certain complex phenotypes or diseases cluster in particular areas, groups, or populations?
- How can Social Safety Theory be useful for better understanding health disparities experienced by (for example) racial and ethnic minority populations, sexually and gender-diverse individuals, persons of low objective or perceived social status, or those exposed to sexism, racism, ableism, or ageism?

(d) **Identification of individual and collective treatment targets and interventions for reducing social threat and enhancing social safety**
- Which social, psychological, or biological mechanisms that mediate experiences of social safety or social threat are modifiable and thus candidates for becoming potential treatment targets?
- Which individual and collective interventions are most effective for reducing experiences of social threat, promoting experiences of social safety, and enhancing individual and collective psychosocial resilience and wellbeing?
- How permanent are treatment-related changes in social safety and social threat? Are there particular developmental periods during which time interventions for reducing social threat or enhancing social safety are particularly impactful or effective?
- What mechanisms underlie positive treatment effects?
- What issues need to be taken into account to develop culturally sensitive interventions for reducing social threat and promoting social safety?

cheating, rule-breaking, and stealing [58]. The benefits and costs of these experiences are thus difficult to overestimate: whereas social safety dampens systemic inflammation, reduces viral and inflammation-related disease risk, extends the lifespan, and promotes healthy behaviors, experiencing social threat can upregulate inflammation, increase pro-inflammatory and reduce antiviral gene expression, accelerate biological aging, and increase individuals' risk for early mortality.

Future directions

Looking forward, there are several avenues of scientific inquiry that would help to address key questions and predictions derived from Social Safety Theory. Broadly speaking, these issues pertain to the (a) fundamental nature, conceptualization, and measurement of social safety and social threat; (b) development and impact of social safety and social threat over the lifespan; (c) biopsychosocial mechanisms linking experiences of social safety and social threat with health, wellbeing, aging, and mortality; and (d) identification of individual and collective treatment targets and interventions for reducing social threat and enhancing social safety. Specific issues concerning these four topics are described in Box 3.

Conclusion

In conclusion, divisive politics, interpersonal conflict, and COVID-19 have the ability to degrade the social fabric that makes humans resilient and keeps us alive and well. However, we need not let it be so [59,60]. The drive to socially cooperate and connect is deeply embedded in the human brain and immune system, and the more we learn about these fascinating dynamics, the more we will ultimately understand human life, wellbeing, and longevity.

Author contributions

The article was conceptualized, written, and … wait for it … submitted for publication by G.M.S.

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Conflict of interest statement

Nothing declared.

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