From discrimination and dis-ease to aging and disease-an epigenetic connection

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The three pillars of an effective, safe, and successful society are equity, diversity, and inclusion (EDI). Equity denotes fair access to and the provision of opportunities to everyone. Diversity reflects and celebrates the rich and unique range of human differences, and inclusion signifies the importance of valuing, respecting, and empowering everyone across all societies and cultures.

Although global EDI efforts are expanding, discrimination is still a challenge for large groups in our society, such as women, immigrants, elderly people, racial minorities, lower-income persons, people with disabilities, sexual and gender minorities, and people experiencing addiction and mental health challenges.[1,2]

Discrimination is a multifaceted issue that affects individuals' health in many ways. It limits access to healthcare resources, lowering overall quality of life, and is a stressor and social determinant of health that causes adverse effects through the direct physiologic impact of stress that may later manifest as disease. Although analyses of discrimination and its health outcomes are still emerging, the research accumulated over the past few decades suggests that discrimination is a powerful stressor.[1–3]

While short-term physiologic reactions to acute stress are often adaptive, persistent chronic stress causes deleterious outcomes. Discrimination is a chronic, ongoing, and unpredictable stressor that activates numerous cascades of stress-related emotional, physiological, and behavioral changes. Mechanistically, the hypothalamic-pituitary-adrenal (HPA) axis is associated with, governs, and responds to stress. Physiologically, constant and aberrant activation of the HPA axis due to chronic stress affects metabolism and is implicated in the inflammatory responses of many general and mental health issues. For example, elevated HPA axis activity has been associated with race-, sex-, and weight-related discrimination.[4] Furthermore, individuals facing discrimination often exhibit trauma-related hypervigilance, heightened responsiveness, and a constant need to protect themselves against additional stress and trauma, further amplifying and perpetuating stress.[3–6]

A chronic stressor causing severe trauma, discrimination leads to numerous metabolic and inflammation responses, referred to as the "allostatic load," that overburden organisms and cause significant wear and tear.[7] A recent systematic review and meta-analysis found that experiences of everyday discrimination were associated with depression, anxiety, psychological distress, and mental illness, indicating a clear cumulative dose-response relationship between discrimination and mental health outcomes.[3] Discrimination is associated with cardiovascular disease and hypertension disparities in African Americans, especially women.[7] Furthermore, discrimination is an important contributor to preterm birth, prenatal inflammation, asthma, and the occurrence and exacerbation of autoimmune diseases.[3,7] Daily discrimination causes high-impact health and mental health effects in children and adolescents.[3]

Several studies have suggested a link between discrimination, premature aging, and decreased life expectancy. The allostatic load from discrimination may cause inferior health and early physiologic aging in African Americans and Indigenous peoples.[3,8] Among older adults, experiencing discrimination has been associated with a risk of death.[9] A recent pioneering study by McKenna and colleagues showed that race-related lifetime stress exposure and discrimination elicit internalized anger and cause detrimental epigenetic alterations that may elevate the risk of adverse health outcomes and promote aging. This is the first study to provide mechanistic evidence that discrimination may lead to accelerated aging, calling for more studies to discern the link between discrimination, epigenetics, and aging.[10] Furthermore, health outcomes associated with discrimination, including cardiovascular disease, hypertension, asthma, and autoimmune conditions, are age-related diseases with important epigenetic underpinnings.

The magnitude of discrimination in the modern world (experienced by 18–45% of individuals in

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vulnerable groups[2]) may be a key contributor to the vulnerable populations accelerated biological and psychological aging. Nevertheless, the potential mechanistic role of discrimination in aging, both biological and subjective/psychological, remains overlooked. Because epigenetic changes are pliable and reversible, timely intervention and the prevention of discrimination may mitigate the potential severe health consequences in victims of discrimination.

The COVID-19 pandemic has re-exposed severe issues of systemic discrimination in care access. Many long-COVID manifestations (especially psychological-related long-COVID manifestations) resemble stress and trauma responses and, if compounded by extant discrimination stress and trauma, may culminate in severe outcomes. Hence, individuals who experience discrimination may be at a high risk of severe long COVID-19 and are, at the same time, disproportionally affected by COVID-19. Moreover, COVID-19 may facilitate already accelerated aging in individuals experiencing discrimination.

We predict that the stress and trauma of discrimination lead to accelerated biological and psychological aging in affected individuals. Additionally, COVID-19 may further disproportionally exacerbate aging in individuals experiencing discrimination. Hence, along with accelerating our efforts to end discrimination, it is paramount to address key unanswered questions to delineate the health effects of discrimination in the context of disease and aging. Developing proper health measures to combat these issues is crucial.

Contributors

All authors contributed to creating this commentary. Anna Fiselier and Olga Kovalchuk conceptualized the article and delineated the key arguments. Anna Fiselier wrote the first draft. All authors discussed, provided comments, data and suggestions, and edited several versions of the manuscript. All authors approved the final version.

Declaration of interests

The authors declared no conflicts of interest associated to this work and no financial interests or commercial benefits associated with the current work. A.F. declares patent applications outside the current work, and leadership in PlantBiosys, Swysh and HumaniThé — biotech start-up companies outside the current work. J.R. declares the CIHR grant "Transgender Youth in Clinical Care: A Pan-Canadian Cohort Study of Medical, Social and Family Outcomes". J.R. declares stock options in Gilead Sciences outside the current work. R.T. declares speaking fees, Master Clinician Alliance on opioid crisis outside of the current work. R.T. declares unpaid leadership — President (2019-2021) and current board member of the Alberta Pain Society, and past board member of Canadian Society of Addiction Medicine. R.T is a Co-Founder and Chief Medical Officer, The Newly Institute; there is no commercial benefit from this publication. T.J. declares Speaker's Bureau, Advisory Board Honoraria from several companies, all outside the current work. O.K. declares grant from the CIHR "Understanding the sex-specificity of cancer-associated cognitive impairment: from molecular mechanisms to behavioural outcomes" outside the current work. O.K. declares patent applications outside the current work, and leadership in PathwayRx, PlantBiosys, Swysh and HumaniThé — biotech start-up companies outside the current work.

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