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Sex Differences in Disorders of the Brain and Heart-A Global Crisis of Multimorbidity and Novel Opportunity

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The corona virus disease 2019 (COVID-19) crisis has led to an increasing recognition of the critical associations of sex (eg, immunity differences) and gender (eg, health care utilization differences) with disease outcomes and lack of data reported by sex. While this is commendable, the issues are not new. There is no better example than the global crisis of sex/gender differences in the cooccurrence (or multimorbidity) of the 3 major chronic diseases of our time (major depressive disorder [MDD], cardiovascular disease [CVD], and Alzheimer disease [AD]), interconnected disorders of the brain and heart, that are critical preexisting conditions into which the COVID-19 infectious crisis has interacted. Over a century, medical progress markedly extended longevity by approximately 30 years. However, this resulted in a high prevalence of these chronic diseases creating substantial adverse effects on health care and economic systems globally.

Cardiovascular disease and MDD are the leading causes of disability worldwide, and their co-occurrence was slated to be number one in 2020.[1] Both are significant risk factors for AD, which left unabated will likely affect 152 million people by 2050.[2] Women are at the epicenter of this crisis,[3] facing a higher risk for multimorbidity of brain and heart disorders for which we have no effective therapeutics. Women have twice the risk for MDD as men[4] and twice the rate of its co-occurrence with CVD,[4] which is associated with 3 to 5 times greater risk for CVD death. Women also represent more than two-thirds of patients with AD worldwide, and this is not only because of longevity.[2]

Targeting research on sex differences in shared causes of disorders of the brain and heart from early development through aging presents a unique opportunity for medicine to think

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out of its departmental silos and accelerate development of more efficacious therapeutic and prevention strategies to combat multimorbidity. A life span approach will identify common early origins for MDD, CVD, and AD that reveal themselves in the same individual over time. Given that MDD and sex differences therein emerge just postpuberty, psychiatry could lead the way in therapeutic development at the neural-cardiac interface that is sex-dependent and used early for prevention of CVD and AD later in life.

The multimorbidity crisis is also one of the most pressing economic threats of our time, including medical and societal costs.[3] In 2015, MDD in the US cost more than $210.5 billion inflation-adjusted dollars. Annual global CVD costs will likely rise to more than $1 trillion in 2030,[5] with AD at $2 trillion by 2030. Costs are highest for patients with multimorbidities, accounting for more than 90% of Medicare spending.

The economic threat is especially severe for women, who are an increasingly powerful element of the global economy and comprise the majority of unpaid caregivers. In high-income countries, women have achieved important economic progress, and in low- and middle-income countries, female education and service-sector employment increased over 20 years.[6] However, the growing burden of brain and heart disorders threatens to slow or undo progress, especially in low- and middle-income countries attempting simultaneously to navigate pre-epidemiologic transitions, the rise of noncommunicable diseases, and shifting demographics.[6]

Chronic conditions generate substantial costs by increasing caregiving needs, primarily provided by women. High caregiving demands occur during early midlife when women are often most professionally and economically successful, as US family caregivers are approximately age 49 years.[2] This typically encompasses the menopausal transition, representing another peak period for MDD female risk. Women account for two-thirds of dementia caregivers, providing, in 2018, 18.5 billion unpaid care hours (or approximately $234 billion).[2,5] For CVD, the US costs of caregiving will likely more than double from $61 billion in 2015 to $128 billion in 2035.[5] Globally, women's underpaid and unpaid health/mental health care work represents an invisible subsidy to health systems estimated at more than $1 trillion annually.[6] Once again, these needs and costs are highest for multimorbid conditions. Thus, addressing this health and economic crisis through research, practice, and policies that account for sex/gender across the life span targeted to multimorbidity of brain and heart disorders offers an opportunity to solve an ever-worsening health and economic crisis for which psychiatry could lead the way.

While there has been important progress since the passage of the National Institutes of Health Revitalization Act in 1993, substantial gaps and barriers continue to constrain sex- and gender-based research.[7] In neuroscience, animal studies are 5.5:1 exclusively male to female samples, including for depression, for which fewer than 45% use female animals, even given higher female incidence. Most animals in CVD research are male or unspecified.[7] Further, to our knowledge, there are few systematic clinical studies of sex differences in the brain and heart in MDD, how the body metabolizes psychoactive drugs, and the association of women's reproductive stage with MDD illness prognosis and treatment and effect on the heart.[7] In CVD mixed-sex trials, approximately 33% of

participants are women, only 25% to 33% report outcomes by sex,[7] and even fewer design studies based on sex, a fact also true for AD.[2]

Health care clinicians are slow to act on sex-or gender-based findings or clinical guidelines. While there are exceptions in psychiatry (eg, reproductive psychiatry), attention to sex and gender is inadequate. In addition, research tends to examine each disease independently (even though there is clinical attention to cardiovascular psychiatry) and at a static point in an individual's life rather than throughout life. This prevents us from understanding the shared effect of psychological, biological, social, and environmental factors across organs and tissues over a lifetime.

Thus, we are at an inflection point. To better serve communities and accomplish the vision for precision medicine, we need to develop a new cross-sector, cross-disciplinary effort to enhance investigations and translate findings on sex differences in the connections between brain and heart disorders. Given that the multimorbidity crisis is one of the most pressing economic threats in health care that has worsened with COVID-19, we suggest 4 elements of an effective partnership between academics, industry, advocacy, and policy to address this crisis now:

1. Sustained investment in time and resources for research to understand the shared causes of disorders across the brain and heart with the goal of translation into targeted sex-dependent therapeutics.
2. Financial support from National Institutes of Health (NIH) that crosses disorders, organs, and tissues, thus reaching beyond the NIH call for gender equality in clinical trials, necessitating greater federal commitment of cross-NIH and nonfederal funding for studies
3. Widespread adoption by investigators and funders of a life span approach to tackling multimorbidity of brain and heart disorders that is targeted toward sex/gender differences from prenatal development through aging and illness causes before disease manifestation. We suggest there are shared developmental risk factors for sex differences in MDD, CVD, and AD[4] and that sex/gender differences will differ depending on timing over the life span.
4. Development and adoption of policies from governmental agencies and private industries that promote lifelong wellness (ie, risk reduction and prevention) using a sex differences lens and investigating how social/psychological determinants differentially affect men and women.

Psychiatry is positioned to take a lead role in addressing the multimorbidity of MDD, CVD and AD given that MDD is the first of these disorders to emerge postpuberty. More than 90% of CVD is preventable. What if we could prevent CVD later in life by treating MDD with therapeutics that target the neural-cardiac interface in a sex-dependent way at the level of the brain, cardiac tone, and/or the vasculature? Clinical and academic partnerships across departments and disciplines can develop strategies to accomplish this.

Given the scale and speed of the crisis, we must act now to develop novel initiatives focused on sex/gender differences targeted toward multimorbidity of brain and heart disorders to

achieve precision medicine. This will not only create a healthier environment in which there is life beyond the COVID-19 crisis but will contribute to understanding and ameliorating preexisting conditions resulting in sex differences in risk, severity, and mortality. This has the potential to drive the scientific and therapeutic breakthroughs that our communities need and alleviate the economic tsunami that will occur if ignored.

Conflict of Interest Disclosures:

Dr Goldstein is on the scientific advisory board/consultant for and has equity interest in Cala Health outside of the submitted work. The authors are founder (Dr Goldstein) and leaders (Drs Goldstein, Langer, and Ms Lesser) of the Innovation Center on Sex Differences in Medicine (ICON), a collaborative effort of Massachusetts General Hospital and the Harvard T. H. Chan School of Public Health, partnering with WomenAgainstAlzheimer's. The authors' effort and time were supported by this partnership in addition to Drs Goldstein and Langer's time, in part, supported by grant ORWH-NIMH U54 MH118919 (Specialized Center for Research on Sex Differences). No other disclosures were reported.

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