Society for Women's Health Research

Illuminating the Disease Burden of Chronic Forms of Depression in Women

A Call to Action from the Society for Women's Health Research

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BACKGROUND

Depressive disorders are a group of mood disorders characterized by significant impairments in an individual's ability to perform daily tasks, driven by a persistently sad or irritable mood [1]. While there are several sub-diagnosis categories, the term "depressive disorders" typically refers to major depressive disorder (MDD) and persistent depressive disorder (PDD). These two disorders share similar features, such as depressed mood for most of the day. However, MDD requires at least five additional defining symptoms and a minimum duration of two weeks, whereas PDD requires two additional defining symptoms and must persist for at least two years [1]. An individual may be diagnosed with MDD, PDD, or both, depending on their symptom pattern.

In 2021, depressive disorders were the sixth leading cause for disability-adjusted life years (DALYs) in women globally, with an average 1,019 DALYs lost per 100,000 women (age-adjusted) [2]. In contrast, depressive disorders did not rank among the top ten causes of DALYs in men. This disease burden is particularly pronounced among younger women in the United States, ranking among the three leading causes of DALYs for women between the ages of 15 and 39, accounting for 10,246 DALYs per 100,000 women across this age group [3].

Sex Differences in Depression

The disparity in depressive disorder prevalence between sexes has been consistently documented over the years. In the latest 2023 Behavioral Risk Factor Surveillance System (BRFSS) survey, 27% of women and 15% of men indicated a current or past diagnosis of a depressive disorder, amounting in an overall lifetime prevalence of 21% in the U.S. population [4]. Over their lifetime, women experience depressive disorders at approximately twice the rate of men, with the gap emerging and being

most prevalent during adolescence [1, 5]. Sex and gender differences have also been noted in variations in symptom presentation and comorbidities. Women are more likely to exhibit atypical and somatic symptoms of depression (i.e., a combination of emotional symptoms and physical manifestations) [6]. For example, women with depression tend to experience insomnia or hypersomnia, changes in appetite, and persistent fatigue [7]. Women also tend to experience greater symptom severity than men, contributing to a higher overall disease burden [6]. While women are more likely to have higher rates of comorbid anxiety disorders, men have higher rates of comorbid substance use disorders [1, 6].

Despite documented sex and gender disparities in depressive disorders, there remain persistent gaps in our knowledge and approaches to mitigating the burden of these diseases for women. This call-to-action report aims to highlight and address gaps regarding the inconsistent use of PDD's definition, limited understanding of sex differences in PDD, and pathophysiology correlations to clinical outcomes.

GAPS & OPPORTUNITIES TO ADDRESS DEPRESSIVE DISORDER DISPARITIES FOR WOMEN

1 DEFINITION OF PERSISTENT DEPRESSIVE DISORDER

Inconsistent use of definitions and characterizations of major depressive disorder and persistent depressive disorder in literature across time confuse the evidence base, as well as future research and data reporting.

In the Unites States, the Diagnostic and Statistical Manual of Mental Disorders (DSM) is the gold standard for mental illness diagnostic guidelines. In 2013, the DSM-5 update introduced significant changes to diagnostic criteria, including the establishment of PDD as a new depressive disorder diagnosis. PDD consolidated two previously separate entities due to their similarities in disease course, development, and family history: dysthymia, a mild yet persistent form of depression, and chronic major depressive disorder, a severe form of MDD defined as an extremely prolonged major depressive episode [1]. Then in 2022, the American Psychiatric Association released the DSM-5-TR, which fortified the status of PDD as an umbrella diagnosis for both dysthymia and chronic major depressive disorder and also highlighted the importance of dual diagnosis of MDD and PDD in patients meeting criteria for both [8].

Since the 2013 guidelines, there appears to be a lack of consistency in the way PDD is referred to in current literature. The terms dysthymia, chronic depression, and episodic. and recurrent depression are often used interchangeably or grouped together, hindering efforts in building a foundation of knowledge to better understand the actual disease burden and potential treatments [9].

Evidence suggests that chronic forms of depression like PDD lead to poorer overall functional outcomes, higher rates of attempted suicides, and greater health care burden [10, 11]. When PDD is equated to dysthymia – which is largely viewed as a milder form of depression – and fails to recognize that PDD also encompasses a severe illness such as chronic MDD, misguided conceptions of PDD on personal well-being can lead to missed opportunities for interventions for hundreds of thousands of women who are disproportionately affected by PDD.

DSM-5-TR reports that prevalence of PDD is approximately two-fold higher in women compared to men, with an overall 12-month prevalence of 0.5% and 1.5% of the adult U.S. population for dysthymia and chronic MDD, respectively [12]. However, this data is based on a study published in 2010, with more recent estimates of the national PDD prevalence being difficult to find.

CALL TO ACTION

Promote research focused on the prevalence and burden of disease of PDD in the United States, using updated DSM definitions. One of the most important sources of global burden of disease data is hosted by the World Health Organization, yet the latest report relies on the DSM-IV definition that categorizes depressive disorders into MDD and dysthymia. Omitting chronic MDD in the DSM-5 reclassification umbrella of PDD potentially underestimates the burden of chronic forms of depression [13]. Additionally, since the DSM provides clear diagnostic criteria and codes that can be reconstructed over time, efforts should be made to align previously collected data with current definitions, allowing for a more accurate assessment of PDD's true burden.

As the DSM definitions are aligned throughout literature, attention should also be paid to ensure congruency with the International Classification of Diseases (ICD) guidelines – a system of medical coding typically utilized in the U.S. for health data collection and insurance billing.

2 SEX DIFFERENCES IN PERSISTENT DEPRESSIVE DISORDER

Limited understanding of sex differences in persistent depressive disorder disease progression and treatment outcomes hinder progress in developing effective screening tools and interventions.

While the disparity in depressive disorder prevalence between men and women has a solid foundation of evidence to support it, sex differences in the course and outcomes of these disorders, particularly PDD, are not as well-established. A 2017 study from Switzerland found that the prevalence of lifetime PDD was 22.9% among women compared to 12.5% among men, and the majority of PDD patients had chronic major depressive disorder (lifetime prevalence: 19.6% in women and 10.2% in men) [14]. These patients also suffered the highest disease severity, compared to patients with pure dysthymia, single-episode MDD, or other forms of depression.

However, research on PDD is sparse, and sex-based analyses are not routinely conducted when examining factors that influence the progression of depression [9, 15]. Moreover, the lack of sex-specific analysis in other aspects of PDD – such as severity measures and associated comorbidities – leaves additional gaps in our understanding of the disorder.

The notable gender gap in depression prevalence emerges during adolescence [5]. Some researchers suggest that the activation of sex hormones during puberty influences future stress responses in adolescent girls, increasing their susceptibility to stress-related mood disorders, such as depression [15]. Evidence also indicates that persistent depressive disorder, when it begins in adolescence, carries significant long-term health burdens, and is associated with poor adult mental health and occupational outcomes [16-18]. In females, persistent depression is linked to increased use of both inpatient and outpatient care in adulthood, as well as higher overall health care expenditures.

Depression can also impact physical health. A 2018 study showed an inverse association between persistent depression and cognitive scores in middle-aged women, but not in men (19). Another study found an association between increased HBA1C levels (a biomarker for diabetes) and recurrent MDD in women with a BMI of 30 or higher (categorized as obesity) compared to their counterparts without MDD. No such association was observed in men [20]. Although not statistically significant, a more recent study suggested higher hazard ratios for all-cause, cardiovascular disease, and ischemic heart disease mortalities in women with depression compared to men [21]. These findings highlight the importance of further research on the effects of PDD on women's health.

CALL TO ACTION

Promote sex analysis framework in future research exploring PDD. Despite budding evidence of the effects of long-term depression on overall health outcomes, with unique impacts on women, research on PDD in women remains underdeveloped. Studies often fail to incorporate sex-based analyses, limiting our understanding of how biological, social, and environmental factors shape the course and outcomes of PDD. A recent Cochrane review of maintenance treatment for PDD identified only 10 eligible studies, with the most recent being published in 2004 [22]. While each study included a sufficient number of women, the reviews did not perform sex-based analyses of therapy outcomes. This oversight, whether due to insufficient source data or research design, represents a missed opportunity to gain critical insights into diagnostic differences, treatment responses, and potential outcomes for women, an all-too-common failing in disease research [23]. Without this perspective, gaps in knowledge persist and potential effective interventions are hindered. Promoting a standardized sex analysis framework in PDD research can help drive more effective, evidence-based approaches to diagnosing, treating, and preventing PDD in diverse populations.

CALL TO ACTION

Develop guidelines to screen for PDD in adolescents and in women. Current screening guidelines for depression focus on assessing MDD starting at age 12 and do not address chronic forms of depression [24-26]. Due to its chronic nature, PDD takes longer to diagnose than other forms of depression, as symptoms must persist for at least two years. Many individuals with early-onset PDD struggle to distinguish their symptoms from their sense of self, and health care providers often focus on immediate mood changes rather than the broader chronic course of the disorder [9]. Early recognition of depression improves disease trajectory and increases remission rates [25]. Moreover, research on the efficacy of screening for PDD in women is crucial, as women are disproportionally affected by the disorder. Broadening awareness among diverse health care providers, including OB/GYN and primary care physicians, and other women's health practitioners, would help establish a more robust opportunity for recognizing and documenting PDD patterns over time in female patients. This approach would account for women's unique life stages and experiences, potentially leading to earlier diagnoses, more effective, gender-specific interventions, and improved patient outcomes.

3 PDD PATHOPHYSIOLOGY CORRELATION TO CLINICAL OUTCOMES

Establishing a link between physiological profiles of persistent depressive disorder and clinical outcomes is pertinent for the identification of clinically relevant therapeutic targets.

With advancements in genetic sequencing tools, recent years have seen significant progress in understanding the physiological, genetic, and epigenetic profiles of depression. Studies have identified unique biological footprints in depression associated with each sex [6]. One study, using animal models and postmortem human subjects, found differences between females and males in brain-expressed transcriptional patterns of genetic hubs that function as stress-susceptibility mediators [27]. Importantly, research has identified genetic markers potentially associated with an increased risk of depressive disorders in women. Additionally, findings suggest that the genetic burden in men with depressive disorder is higher than in women, indicating a potential alternative mechanism underlying women's susceptibility to the condition [28].

There is some evidence that sheds light on the potential variations in disease course between men and women. In addition to transcriptional differences, studies have proposed distinctions in anatomical brain abnormalities between men and women with depression [6]. These anatomical differences may overlap with the distinct comorbid profiles commonly associated with each sex, such as higher rates of anxiety in women and substance use disorders in men. A genome-wide study in the United Kingdom found sex-specific markers for depression and strong

correlations between broad MDD and metabolic-related genetic variants in women only [29].

To note, these and other studies primarily focus on MDD, and most examine physiological factors that contribute to susceptibility rather than to differences in clinical presentation between men and women.

For example, insights into sex-based differences in antidepressant metabolism have yet to translate into improved clinical efficacy [30]. Selective serotonin reuptake inhibitors (SSRIs) – a class of antidepressants – are more effective in premenopausal women than in men or postmenopausal women, indicating a potential role of sex hormones in treatment response. Additionally, some evidence suggests that estradiol may alleviate depressive symptoms in women, while testosterone has similar effects in hypogonadal men [6]. This underscores the importance of further research into the physiological profiles of depression to refine treatment strategies and improve patient outcomes.

Mental health illnesses are often stigmatized, and to the untrained eye, the line between emotional well-being and clinical depression may seem blurred. The misconception that individuals can control their condition leads to those with depression being unfairly labeled as lazy, unmotivated, or incapable. This may be even more pronounced in PDD, where the depressive symptoms persist over extended periods. Establishing a clear physiological profile of depression could help combat these biases by providing concrete evidence of the biological changes associated with PDD. Beyond reducing stigma, understanding the physiological underpinnings of PDD is important for improving disease characterization and identifying additional targets for therapeutic interventions.

CALL TO ACTION

Examine clinical differences in the course of disease, centering sex-based physiological profiles in PDD patients. As more sex-specific biological patterns emerge in characterizing PDD, the need to translate these findings into actionable clinical insights grows. However, many discoveries related to genetic, transcriptional, and neurobiological differences remain unreplicated, limiting their clinical application [28]. Research has largely focused on MDD and susceptibility rather than the course of disease in PDD. As the burden of PDD on women's health is explored, establishing a strong foundation for characterizing its sex-specific biological profile is essential. A deeper understanding of how sex-specific factors influence antidepressant efficacy, comorbidities, and disease trajectory will also enable more personalized treatment approaches, ultimately improving outcomes for both women and men.

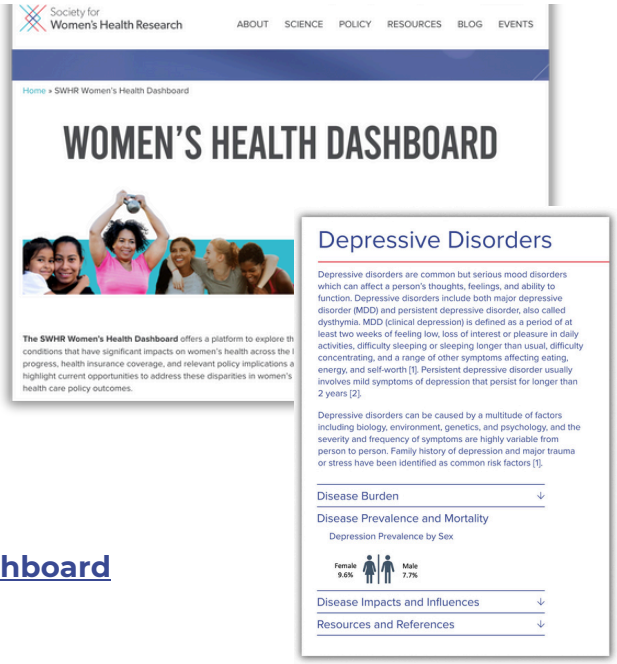
ABOUT THE SOCIETY FOR WOMEN'S HEALTH RESEARCH

The Society for Women's Health Research (SWHR) is a national nonprofit and thought leader dedicated to advancing women's health through science, policy, and education while promoting research on sex differences to optimize women's health. Founded in 1990 by a group of physicians, medical researchers, and health advocates, SWHR is making women's health mainstream by addressing unmet needs and research gaps in women's health. Thanks to SWHR's efforts, women are now routinely included in medical research studies and more scientists are considering sex as a biological variable in their research. SWHR Science & Policy Programs identify research gaps and address unmet needs in diseases and conditions that exclusively affect women or that disproportionately or differently affect women.

SWHR WOMEN'S HEALTH DASHBOARD

The SWHR Women's Health Dashboard offers a platform to explore the latest national and state data on diseases and health conditions that have significant impacts on women's health across the lifespan.

SWHR works to bring attention to these issues and highlight opportunities to address these disparities in women's health, and track progress regarding science, education, and health care policy outcomes.



The focus areas featured on the Dashboard are:

- **Chronic liver disease and cirrhosis**
- **Chronic obstructive pulmonary disease**
- **COVID-19**
- **Depressive disorders**
- **Ischemic heart disease**
- **Lung cancer**

Explore the SWHR Women's Health Dashboard:
https://swhr.org/programs/womens-health-dashboard

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. [5th ed.] American Psychiatric Association Publishing: Washington, DC; 2022.

2. Patwardhan V, Gil GF, Arrieta A, et al. Differences across the Lifespan between Females and Males in the Top 20 Causes of Disease Burden Globally: A Systematic Analysis of the Global Burden of Disease Study 2021. Lancet Public Health. 2024 May;9(5):e282-e294.

3. World Health Organization. Global Health Estimates 2021: Disease Burden by Cause, Age, Sex, by Country and by Region, 2000-2021. Geneva: 2024. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys. Accessed 18 Feb 2025.

4. Centers for Disease Control and Prevention. 2023 BRFSS Survey Data and Documentation. Available from: https://www.cdc.gov/brfss/annual_data/annual_2023.html. Accessed 03 Dec 2024.

5. Salk RH, Hyde JS, Abramson LY. Gender Differences in Depression in Representative National Samples: Meta-analyses of Diagnoses and Symptoms. Psychol Bull. 2017 Aug;143(8):783-822.

6. Eid RS, Gobinath AR, Galea LAM. Sex Differences in Depression: Insights from Clinical and Preclinical Studies. Prog Neurobiol. 2019 May;176:86-102.

7. Cavanagh A, Wilson CJ, Kavanagh DJ, Caputi P. Differences in the Expression of Symptoms in Men Versus Women with Depression: A Systematic Review and Meta-analysis. Harv Rev Psychiatry. 2017 Jan/Feb;25(1):29-38.

8. Bradley L, Noble N, Hendricks B. DSM-5-TR: Salient changes. The Family Journal. 2022;31(1):5–10.

9. Schramm E, Klein DN, Elsaesser M, Furukawa TA, Domschke K. Review of Dysthymia and Persistent Depressive Disorder: History, Correlates, and Clinical Implications. Lancet Psychiatry. 2020 Sep;7(9):801-812.

10. Klein DN, Kotov R. Course of Depression in a 10-year Prospective Study: Evidence for Qualitatively Distinct Subgroups. J Abnorm Psychol. 2016 Apr;125(3):337-348.

11. Hung CI, Liu CY, Yang CH. Persistent Depressive Disorder has Long-term Negative Impacts on Depression, Anxiety, and Somatic Symptoms at 10-year Follow-up among Patients with Major Depressive Disorder. J Affect Disord. 2019 Jan 15;243:255-261.

12. Blanco C, Okuda M, Markowitz JC, Liu SM, Grant BF, Hasin DS. The Epidemiology of Chronic Major Depressive Disorder and Dysthymic Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2010 Dec;71(12):1645-1656.

13. Liu J, Liu Y, Ma W, Tong Y, Zheng J. Temporal and Spatial Trend Analysis of All-cause Depression Burden Based on Global Burden of Disease (GBD) 2019 study. Sci Rep. 2024 May 29;14(1):12346.

14. Vandeleur CL, Fassassi S, Castelao E, et al. Prevalence and Correlates of DSM-5 Major Depressive and Related Disorders in the Community. Psychiatry Res. 2017 Apr;250:50-58.

15. Kuehner C. Why is Depression More Common among Women than among Men? Lancet Psychiatry. 2017 Feb;4(2):146-158.

16. Ssegonja R, Alaie I, Philipson A, et al. Depressive Disorders in Adolescence, Recurrence in Early Adulthood, and Healthcare Usage in Mid-adulthood: A Longitudinal Cost-of-illness Study. J Affect Disord. 2019 Nov 1;258:33-41.

17. Alaie I, Philipson A, Ssegonja R, et al. Uppsala Longitudinal Adolescent Depression Study (ULADS). BMJ Open. 2019 Mar 1;9(3):e024939.

18. Weavers B, Heron J, Thapar AK, et al. The Antecedents and Outcomes of Persistent and Remitting Adolescent Depressive Symptom Trajectories: A Longitudinal, Population-based English Study. Lancet Psychiatry. 2021 Dec;8(12):1053-1061.

19. Wang W, Lu K, Du Q, et al. Association between Depressive Duration and Cognitive Decline in Middle-aged and Older Adults: Evidence from the Health and Retirement Study 2010-2018. J Affect Disord. 2024 Nov 1;364:286-294.

20. Holsen LM, Huang G, Cherkerzian S, et al. Sex Differences in Hemoglobin A1c Levels Related to the Comorbidity of Obesity and Depression. J Womens Health (Larchmt). 2021 Sep;30(9):1303-1312.

21. Zhang Z, Jackson SL, Gillespie C, Merritt R, Yang Q. Depressive Symptoms and Mortality Among US Adults. JAMA Netw Open. 2023 Oct 2;6(10):e2337011.

22. Machmutow K, Meister R, Jansen A, et al. Comparative Effectiveness of Continuation and Maintenance Treatments for Persistent Depressive Disorder in Adults. Cochrane Database Syst Rev. 2019 May 20;5(5):CD012855.

23. Antequera A, Cuadrado-Conde MA, Roy-Vallejo E, et al. Lack of Sex-related Analysis and Reporting in Cochrane Reviews: A Cross-sectional Study. Syst Rev. 2022 Dec 26;11(1):281.

24. American Academy of Family Physicians. Clinical Preventive Service Recommendation: Depression. Available from: https://www.aafp.org/family-physician/patient-care/clinical-recommendations/all-clinical-recommendations/depression.html. Accessed 21 February 2025.

25. US Preventive Services Task Force; Barry MJ, Nicholson WK, et al. Screening for Depression and Suicide Risk in Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2023 Jun 20;329(23):2057-2067.

26. US Preventive Services Task Force; Mangione CM, Barry MJ, et al. Screening for Depression and Suicide Risk in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. JAMA. 2022 Oct 18;328(15):1534-1542.

27. Labonté B, Engmann O, Purushothaman I, et al. Sex-specific Transcriptional Signatures in Human Depression. Nat Med. 2017 Sep;23(9):1102-1111.

28. Kang HJ, Park Y, Yoo KH, et al. Sex Differences in the Genetic Architecture of Depression. Sci Rep. 2020 Jun 18;10(1):9927.

29. Silveira PP, Pokhvisneva I, Howard DM, Meaney MJ. A Sex-specific Genome-wide Association Study of Depression Phenotypes in UK Biobank. Mol Psychiatry. 2023 Jun;28(6):2469-2479.

30. Sramek JJ, Murphy MF, Cutler NR. Sex Differences in the Psychopharmacological Treatment of Depression. Dialogues Clin Neurosci. 2016 Dec;18(4):447-457.