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# The Epigenetics of Post-Traumatic Stress Disorder in Women and PTSD in Women Veterans: Implications for Health Policy

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## Abstract

Women have long served in the military during war whether recognized or unrecognized, whether praised or unpraised, whether there by choice or not there by choice. Men and women both feel the wounds of war. So many times those wounds are very hard to ignore, and often those wounds are not so visible yet take their toll. Post-traumatic stress disorder (PTSD) is commonly associated with combat, with war, and with being a veteran (Fischer, 2014). Our understanding of women formally deployed as soldiers into combat and the consequences for these women is less well defined. Through a meta-synthesis of published studies we find that both war trauma and sexual trauma contribute to PTSD among female service members. We find the experience of war is different for women but this has changed from the experience of previous wars to the present. We have made gains in understanding PTSD in women, and in how epigenetics modulates the genetic expression of in-born tendencies and traits. We have seen evidence that epigenetic changes may even be passed on to future generations, either for good or for bad (Yehuda, Bell, Bierer, & Schmeidler, 2008). These pieces of information, and information gleaned in additional research that is needed must be synthesized into a new understanding that can be brought to defining intervention and health policy for our female soldiers who will need care based on the best of what we know for today, and tomorrow's generations



## Keywords

post traumatic stress disorder, PTSD, female veterans, women veterans, epigenetics

# Post-Traumatic Stress Disorder in Women Veterans and Health Policy Implications

Epigenetics, the mechanism of organizing and managing the genome through gene activation or inactivation, environmental influences and the resulting human health consequences, is relatively new to medicine. Altered structures, through chemical modification called methylation, which organize and manage DNA are implicated in disease (Bird, 2013, January). Epigenetic science is evolving rapidly with major findings in the last decade. Medical application research is advancing in many areas. Adrian Bird (2013) describes the work of colleagues that has the potential to reverse symptoms of Rett Syndrome through epigenomic manipulation. This type of gene therapy may have therapeutic value in various human disorders. Latham, Sapienza, and Engel (2013) emphasize that stress effects gene function by turning genes on or off through epigenetic processes and introduce us to the idea of transgenerational effects. Scientists and providers have begun to think about posttraumatic stress disorder (PTSD) within the context of genetic variations and epigenetics (Raabe & Spengler, 2013; Skelton, Ressler, Norrholm, Jovanovic, & Bradley-Davino, 2013). Yehuda and Bierer (2009) emphasize that current work in epigenetics supports an understanding of PTSD as a disordered stress response, and is helping to establish the biological mechanisms and subtypes of the disorder.

## Background

Until the second Iraq war, Desert Storm resulted in the largest war theater deployment of women in the history of the United States (U.S.) (Clift, 2014). Women currently make up over 14% of U.S. Department of Defense military forces and about 6% of its veterans (Clift, 2014; CNN Staff, 2013). The specific numbers may vary among men and women, but there has long been an association between military service in combat and an incidence of PTSD (Fischer, 2014). While a literature database search in Pubmed for “PTSD” and “combat veteran” may

yield over 40,000 articles and relevant studies, add the term "female" or "woman" or "women" and that yield drops to zero. Miranda Olff (2012) cites several authors regarding the increased likelihood of women over men to develop PTSD following trauma. This increase in risk is unrelated to exposure to traumatic events by men and women in general, though there are early life events that are connected to the presence or absence of resilience (Olff, 2012). The work of Yehuda, Bell, Bierer, and Schmeidler (2008) with PTSD in the offspring of Holocaust survivors pointed out the potential for intergenerational transmission of trauma. Epigenetic influences play a much larger role in the intergenerational transmission of genetic states than previously thought. A synthesis of what is known about the epigenetics of PTSD in women is needed. Additionally, an exploration of PTSD in the female veteran population is required. In light of a growing understanding of the role and transgenerational nature of epigenetics in PTSD, this is of particular importance. Environment changes rapidly and epigenetic management of the genome in response to those changes allows adjustment in the expression of our genes without changing the actual DNA sequence (Zucchi, Yao, & Metz, 2012). Epigenetic memory, while concerning because it may represent transgenerational origins of disease, may also hold the key to diagnosis and treatment since epigenetic changes can be undone (Zucchi, Yao, & Metz, 2012).

## Literature Review

For the first research question, "What is known about the epigenetics of PTSD in women?" seven relevant studies currently reviewed are quantitative. One is a longitudinal study finding that older adults experiencing the most distressing traumatic event(s) in childhood also experienced more severe PTSD symptoms, were less happy, felt less social support, and less coping ability (Ogle, Rubin, & Siegler, 2013). The traumatic events were "enduring" with long-term consequences. This study did not distinguish between genders regarding findings.

A case-control study of U.S. military service members analyzed epigenetic change elements that might be measured in serum, which is more easily measured, and PTSD. Measures were taken pre- and post-deployment and patterns of altered structures were noted (Rusiecki, et al., 2012). The results may suggest factors related to resilience or vulnerability. This study did not distinguish between genders regarding findings.

The next is a prospective-cohort study that investigated the risk of PTSD diagnosis related to trauma history during pregnancy and postpartum (Seng, et al., 2013). PTSD was associated with postpartum depression and impaired bonding, and pregnancy was identified as an opportunity to interrupt the "intergenerational transmission of abuse and psychiatric vulnerability" (Seng, et al., 2013, p.1).

Another study of epigenetic biomarkers in combat veterans with PTSD following psychotherapy compared a prolonged exposure psychotherapy group to a minimal attention condition group (Yehuda, et al., 2013). Specific gene methylation structures consistent with early environmental experience were noted to be present, and stable as a mark associated with childhood experience. Treatment response was demonstrated with epigenetic structural changes, in other words response to treatment could be measured physiologically as well as psychologically (Yehuda, et al., 2013). This study did not distinguish between genders regarding findings.

The study evaluating risk for PTSD in offspring of Holocaust survivors found that maternal PTSD and PTSD in adult offspring were specifically associated, with or without paternal PTSD (Yehuda, Bell, Bierer, & Schmeidler, 2008). In paternal PTSD increased risk for PTSD was greater for female offspring, particularly if maternal PTSD was also present.

A study exploring socioeconomic position and risk of mental illness inclusive of risk for PTSD compared to epigenetic markers found associated changes in the presence of low socioeconomic position (Uddin, et al., 2013). Such evidence of epigenetic profiles may provide insights to observed health disparities among those in lower socioeconomic positions, marginalized groups, and ethnic minorities, as well as the potential to reverse the effects of such disparity. This study did not however, distinguish between genders in the findings.

A final study examines epigenetic patterns associated with immune dysregulation and psychosocial distress. Immune dysregulation observed in women newly diagnosed with breast cancer was consistent with psychosocial distress (Matthews, et al., 2011). There were some associations among the epigenetic patterns related to immune function, but not at the level of the individual cell.

For the second research question, "What is known about the incidence of PTSD in female war or combat veterans?" the oldest study found dates to 1997. This and other studies utilized the National Vietnam Veterans Readjustment Study (NVVRS) database. The role of both sexual and war traumas in the etiology of PTSD among women veterans is explored. War trauma and sexual trauma were found to have made roughly equal contributions to the likelihood of developing PTSD (Fontana, Schwartz, & Rosenheck, 1997).

Another study, also using the NVVRS database, investigated both men and women concerning family history, trauma experiences, utilized the Mississippi Scale for Combat-Related PTSD (M-PTSD) that has been validated among both men and women. Deprivation, dilemmas of war-zone health care, unit cohesion (or lack of), and a sense of purposelessness were most associated with chronic war-related distress, while personal threat and exposure to wounded and dead were less contributory. This study found that emotional support in the presence of intimate

others and of a larger and utilized support network was associated with resilience to PTSD symptoms (McTeague, McNally, & Litz, 2004).

Another cross-sectional study in 2007 of family adjustment and PTSD symptom severity among female Vietnam veterans, also utilized the NVVRS database, and survey data (Gold, et al., 2007). Symptom severity of PTSD in female veterans was associated with negative family adjustment, psychological abuse, and child behavior problems. A study that also suggested lower diagnostic thresholds for women for PTSD looked at the sensitivity and specificity of the PTSD Checklist for determining PTSD in female veterans in primary care (Lang, Laffaye, Satz, & Dresselhous, 2003).

The Veterans Health Administration (VHA) evaluated use of care as it relates to gender in 2007, compared socio-demographic health characteristics of men and women (Frayne, et al., 2007). Female veterans tended to be younger, used more outpatient services overall than inpatient. Female veterans also utilized more non-VHA services than male veterans.

A 2008 study was conducted examining direct and indirect links between childhood maltreatment, PTSD, and women's health in female Veteran's Affairs (VA) primary care patients. A positive association was found between childhood maltreatment, adult sexual assault and PTSD (Lang, et al., 2008). Both childhood maltreatment and PTSD were associated with poorer health functioning.

The only randomized controlled trial encountered is the "Exploration of Gender Differences in How Quality of Life Relates to Posttraumatic Stress Disorder in Male and Female Veterans" study that found similar poor quality of life in both male and female veterans with PTSD (Schnurr & Lunney, 2008). A comparative study of Iraq and Afghanistan female veterans with male and female war zone veterans of previous eras found some important changes. A

reduction in reported sexual assault in female veterans of Iraq and Afghanistan when compared to female veterans of the Persian Gulf War and Vietnam was noted. Contributing factors for this reduction included changes in policies regarding the handling of reported sexual assault. The study noted lower disability ratings for psychiatric disorders as well (Fontana, Rosenheck, & Desai, 2010).

Finally, a qualitative case report gives the experience of a retired combat nurse diagnosed with chronic PTSD, from pre-deployment through her journey toward recovery and re-engagement in life (Feczer & Bjorklund, 2009). Experiences of both resiliency and vulnerability are probed. The evidence gained from the other quantitative studies is reflected at a deeper, more reflective level, yielding insights.

## Literature Review Conclusion Analysis

The epigenetic studies demonstrate that there are measurable chemical altered structures, called DNA methylation, associated with PTSD. Some of these chemically altered structures are inherited from one generation to another. There is also evidence of reversals in these altered structures in response to certain types of therapeutic interventions. Further study is needed to determine what measures are the best identifiers for specific epigenetic changes associated with certain diseases or disorders. Further study is needed to determine what therapeutic interventions have the greatest measurable impact both physiologically and psychologically. Further study is needed to explore if there are gender differences and what these differences might be.

The studies of PTSD in female veterans cover a greater span of time. Change has occurred between the Vietnam/Persian Gulf War and the Irag/Afghanistan wars. Of note is the unique oncidence of sexual trauma to PTSD in female veterans (Fontana, Rosenheck, & Desai, 2010; Fontana, Schwartz, & Rosenheck, 1997; Lang, et al., 2008; McTeague, McNally, & Litz,

2004). Deprivation, a lack of unit cohesion, and a sense of purposelessness all contribute to PTSD in women, while unit cohesion, emotional support and a support network are important to resiliance (McTeague, McNally, & Litz, 2004). A common theme with the epigenetic studies is the impact on the family and future generations with evidence of negative family adjustment and child behavior problems.

## Policy Analysis

It is important that women serving in the military and our female veterans be provided care based on evidence (Resnick, Mallampalli, & Carter, 2012). The total incident PTSD cases newly diagnosed between 2000 to January, 2014 among Operation Iraqi Freedom, Operation New Dawn, and Operation Enduring Freedom deployed troops numbered 118,829 (Fischer, 2014), but these numbers are not broken out by gender. The incidence of PTSD in women after traumatic events is reported in the literature to be higher than in men (Olff, 2012), however we currently have no corroborating or refuting evidence in a combat situation. We do have evidence of epigenetic changes as important in gender differences in PTSD. Rachel Yehuda and Linda Bierer (2009) discuss the relevance of epigenetic findings and their implications for the diagnostic definitions for PTSD. They emphasize the importance of trauma exposure as an etiologic factor, and the utility that epigenetic methods may provide to the future of PTSD diagnosis and treatment (Yehuda & Bierer, 2009).

Screening recruits for exposure to trauma prior to enlistment and deployment, preventing the exposure of those who are most vulnerable to PTSD is appropriate today. It has been suggested that the symptom threshold in women needs to be lowered. This needs to be fully evaluated and analyzed and this can be done with the benefit of measuring for DNA methylation consistent with PTSD. The appropriate diagnosis and management of PTSD has the potential to

impact not only our female veteran population, but future generations in ways we are just beginning to understand (Seng, et al., 2013; Yehuda, Bell, Bierer, & Schmeidler, 2008). Tools to assist in screening for health concerns for the female veteran population are not lacking, such as the two question screen for Military Sexual Trauma (MST), or the PC-PTSD screening tool particularly when used in conjunction with the MST (Fitzgerald, 2010). With epigenetics these can be expanded in the near future. Therapeutic strategies also need to be analyzed while measuring the pre- and post-therapeutic epigenetic changes associated with PTSD. Now is the time to fund and be a part of this type of translational research and work. Barriers may exist for women to report their health concerns in the military or while a veteran that need to be removed. Resnick, Mallampalli, and Carter (2012) report increased pelvic floor disorders, urinary tract infections, bladder pain syndrome and urinary incontinence and discuss how the military settings may promote conditions placing women at higher risk. A female soldier or veteran may find only frustration for urogenital health disorders when she is treated by a Urologist or similar provider who rarely cares for female patients. In this or similar circumstances she may choose not to seek care. Being faced with being served in an environment where women's unique needs are not understood is a barrier that was not addressed in the studies. This gap in knowledge additionally must be scrutinized.

## Current Limitations

This systematic review has limitations that should be considered in any discussion of possible applicability to the populations of women who have post traumatic stress disorder and our women veterans with PTSD. Of the seven studies considered in addressing the first question regarding the epigenetics of PTSD, only one stands out as giving a glimpse of the gender differences in humans that need to be further examined (Yehuda, Bell, Bierer, & Schmeidler,

2008). The nine studies regarding PTSD in our female veterans provide an array of information, however due to the variability in how this information is measured and the data analyzed comparison is not straight forward.

## Recommendations for Future Directions

Epigenetic tags along with other markers of biological vulnerability can help to identify those who are at greatest risk of PTSD so that prevention and early intervention strategies can be put into place (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008). Currently, there is insufficient data upon which to recommend profound change yet, however the clinical experience of the review team supports the concept of intergenerational vulnerability and the need to implement prevention and intervention strategies available today.

It was clear that both war trauma and sexual trauma contributed to PTSD in women and that policies that have been implemented have begun to make a difference and decrease the incidence of sexual trauma among female service members in more recent wars. Ongoing enforcement of these policies needs to be maintained and improved upon. Ongoing research is needed as previously emphasized. Resnick, Mallampalli, and Carter (2012) point out that gender differences drew attention to a better treatment for traumatic brain injury and research regarding the gender differences in PTSD may yield similar insights.

## Conclusion

This meta-synthesis examined what the epigenetics of post traumatic stress disorder in women and found that there is evidence of transgenerational transmission of epigenetic changes particularly related to maternal PTSD. There is promise in the potential to interrupt current vulnerability and this cycle of intergenerational vulnerability by understanding that early and repeated trauma exposure results in epigenetic changes that are measurable and reversible.

Intervention and treatment guided by epigenetics must be explored. Nursing has an opportunity to utilize genomic strategies for prevention and intervention to benefit patient populations as emphasized in the DNP Essentials emphasizing scientific underpinnings for practice.

This meta-synthesis investigated PTSD in women veterans and identified both war trauma and sexual trauma as contributors to PTSD among female service members. In more recent wars female service members have experienced less severe psychopathology and less sexual trauma than in previous wars that have been studied. Women experience fewer supports, greater exposure to certain types of trauma, and different levels of pathology than male counterparts. Women experience a unique impact from PTSD in their lives and their utilization of veterans health services are different. Nurses have the opportunity to intervene in primary care settings, where many female veterans seek care outside of VHA facilities, and make a difference based on an evolving and growing body of evidence in genomics.

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