

The Increasingly Recognized Association of Depression and Heart Disease: Are there Gender-Specific Risks?

Approximately 20 percent of patients with various forms of cardiovascular illness also suffer from diagnosed depression.

Moreover, cardiovascular disease and depression not only can accompany one another, but scientists investigating the interplay between psychological factors and physical conditions have known for some time that depression is a *risk factor* for cardiovascular disease for both women and men. Furthermore, both in community studies and among clinical samples of those with cardiovascular disease, depression is a much more potent risk factor for mortality from heart disease than other psychosocial factors.

In terms of gender difference, emerging evidence indicates that the percent of women with depression post-heart attack is higher than it is for men, and that the risk for cardiac disease conferred by an existing depression is particularly high for young women, compared either to older women or men who suffer from this clinical syndrome, according to Dr. Viola Vaccarino.

Vaccarino, one of *Women's Health Research at Yale's* earliest investigators and now Professor and Chair of Epidemiology at Emory University's Rollins School of Public Health, returned to Yale in May to give a grand rounds lecture on the relationship between depression and cardiovascular disease, and the gender-specific risks that are beginning to be revealed.

Each year, in collaboration with our Program, the Department of Psychiatry's Women's Behavioral Health Division invites a researcher to lecture on a topic of mutual interest. This year, we invited Vaccarino because of her contributions to the understanding of how women differ from men in experiencing cardiovascular disease. Through research supported by *Women's Health Research at Yale*, she was

one of the first investigators to show that significantly fewer women than men had chest pain as the chief symptom of heart attack, and to establish that women, particularly young women, fared worse than men after cardiac bypass surgery.

More recently, Vaccarino's evolving research has focused on the association between two highly prevalent health conditions - depression and cardiovascular disease - with an emphasis on underlying factors linked to both conditions.

Vaccarino studies the effects of several kinds of factors that may explain the association between depression and cardiovascular disease. These include unhealthy lifestyle (smoking, poor diet and lack of exercise), inherited genetic traits and/or family history, and, perhaps a critically important, particularly in women, yet less explored factor - the effects of severe stress early in life, such as maltreatment during childhood and adolescence.

Vaccarino said she believes that all these factors are contributory, yet the effects of stress have garnered less attention until relatively recently. She maintains that various types of early severe stress, especially abuse in childhood, have a lasting psychological *and biological effect*, and alongside current lifestyle vulnerabilities and genetic susceptibilities, play an important role in the heightened risk of cardiovascular disease.

"The hypothesis is that women experience more of these early severe stressful events, and that this kind of exposure, even if it goes away, remains as a



Viola Vaccarino, M.D., Ph.D.



psychological scar that also affects biology,” Vaccarino said in a recent interview. “As a consequence, the body’s hormonal stress-response systems, which are known to affect cardiac function, do not develop the way they should, and there can be enduring effects on the cardiovascular system.”

She points to some reports that have begun to suggest such a link:

- A study published in 2007 in the Proceedings of the National Academy of Sciences found an association between maltreatment during childhood and clinically significant indicators of cellular inflammation (an early sign of cardiovascular disease) in adulthood. This study followed a population of more than 1,000 New Zealanders from birth to age 32.
- A 2004 survey of information from more than 17,000 adult members of a health maintenance organization in California, reported in the journal *Circulation*, found an association between childhood maltreatment and ischemic heart disease, a condition characterized by reduced blood supply in the heart muscle due to coronary artery disease (plaque buildup in the arteries).

Although neither of these studies analyzed the outcomes by gender, another study, which *did* include an analysis by gender, suggests that this relationship may be localized more powerfully in women. This study, by Mazure and colleagues published in the *Journal of Clinical Psychiatry* in February 2004, found an association between childhood maltreatment and cardiovascular disorders in a nationally representative sample of more than 5,000 adults, about half women and half men, diagnosed with depression at age 18 or older.

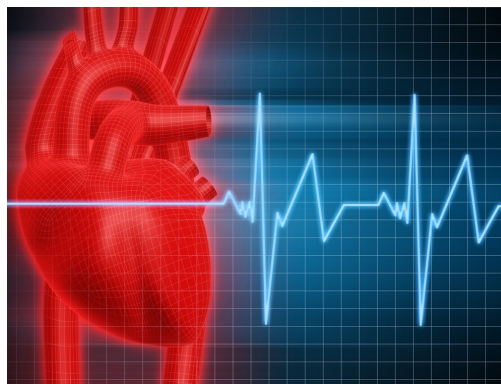
The results of this study showed that a reported history of childhood abuse or neglect was associated

with an almost nine-fold increase in cardiovascular disorders in women (but no effect in men), as well as a significant increase in the odds of lifetime depressive disorders for both women and men. Moreover, the study results suggest, childhood maltreatment may also be associated with a younger onset of cardiovascular disease in women.

Many previous studies have demonstrated that women experience depression at twice the rate for men, and that men have higher rates of cardiovascular disease than premenopausal women. However, interestingly, in this nationally representative sample of more than 5,000 women and men, these expected sex difference ratios in depression and cardiovascular disease were found *only* in those who *did not* report a history of childhood maltreatment. In those reporting childhood maltreatment, the protection against cardiovascular disease normally experienced by women was reduced as was the lower vulnerability to depression typically experienced by men.

It may turn out, according to Vaccarino, that these types of severe enduring stress result in both cardiovascular disease and depression through common pathways that damage the cardiovascular system, impair the immune system, and alter a key part of the neuroendocrine system called the HPA axis (hypothalamic-pituitary-adrenal axis) which is responsible for regulating reactions to stress as well as mood and emotions.

“To ultimately understand the link between cardiovascular conditions and depression and, importantly, prevent the development of these conditions,” Vaccarino said, “we need to look in detail at how stress affects these systems and we need to focus on sex differences.” ■



Q & A with Dr. Vaccarino **Cardiovascular Disease, Depression** **and Gender-Specific Risk**

Q: What is the one critical issue regarding women and cardiovascular disease that we need to understand in order to reduce morbidity and mortality?

A: There are many issues that need to be addressed to fully understand the pathophysiology, risk factors, diagnosis and clinical care of cardiovascular disease in women. My own perspective is that the area of mind-heart connections is a relatively neglected area that may be particularly important for women's risk, and may become very fruitful in defining women's cardiovascular risk and developing effective prevention strategies.

Q: You have stated that we need to look at the specific pathways and underlying mechanisms that may explain the link between stress early in life, particularly childhood maltreatment, and cardiovascular disease in women with depression.

Can you briefly describe the areas needing investigation?

A: One is dysregulation of neuroendocrine systems involved in the stress response, which could increase cardiovascular risk through a "wear and tear" mechanism. Another involves immune mechanisms leading to increased cellular inflammation, which is an underlying phenomenon of many chronic conditions. Others include genetic factors and metabolic factors, such as insulin resistance and metabolic syndrome, which are also influenced by stress.

Q: If you could design studies that would substantially help gain an understanding of this apparent gender-specific risk, what would those studies be?

A: A lifespan study is really needed, which has not yet been done with respect to cardiovascular risk and gender differences. Such a study would take a long time to complete and be expensive, but would be the most rigorous way to examine and answer this question. ■

About the Investigator: Viola Vaccarino, M.D., Ph.D.

Professor & Chair of Epidemiology—Rollins School of Public Health, Emory University

- M.D. from Milan University
- Came to Yale in 1989 to pursue doctoral training in epidemiology, earning her Ph.D. from Yale in 1994.

Dr. Vaccarino's interest in the interconnections between psychological and biological health, particularly as they relate to heart disease in women, was fostered during her years at Yale. Soon after *Women's Health Research at Yale* was established in 1998, Vaccarino was twice awarded pilot funds to study cardiovascular disease. Both studies revealed important gender differences, finding that:

- women fared significantly worse than men following heart bypass surgery - with women suffering more pain, infection, lower physical functioning and twice the likelihood of readmission to the hospital. These findings laid the groundwork for studying why

these differences exist, and demonstrated the importance of developing gender-specific interventions that can improve the health of women after bypass surgery.

- only 54% of women hospitalized with a heart attack had a chief complaint of chest pain, compared with 69% of men. In addition, younger women were twice as likely to have respiratory symptoms as their chief complaint when hospitalized with a heart attack than men of the same age. Clarification of gender differences in clinical presentation demonstrated the need to recognize and treat acute coronary ischemia in women more promptly. ■