# INFLAMMATION, CARDIOVASCULAR DISEASE, AND METABOLIC SYNDROME AS SEQUELAE OF VIOLENCE AGAINST WOMEN

## The Role of Depression, Hostility, and Sleep Disturbance

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*Women who experience violence are significantly more likely to have serious health problems above and beyond any injuries they might incur. The intriguing question is why this is so. In this article, the author describes how three sequelae of violence against women—depression, hostility, and sleep disturbance—can increase the risk of disease. One possible mechanism by which these sequelae increase risk is by elevating levels of pro-inflammatory cytokines. These cytokines have an adaptive function in fighting infection and repairing injured tissues. However, chronically high levels of pro-inflammatory cytokines have been implicated in a wide range of diseases. The author focuses on two illnesses that have not received much attention in the violence against women (VAW) literature: cardiovascular disease and metabolic syndrome, the precursor to type 2 diabetes. Preliminary studies also suggest that treatments that can lower inflammation may be promising adjuncts for survivors of VAW.*

**Key words:** *abuse; inflammation; depression; hostility; sleep disorders*

ABUSE SURVIVORS ARE significantly more likely to have a number of serious illnesses and to die prematurely than their nonabused counterparts (Felitti et al., 2001). For example, adult survivors of childhood abuse have increased risk of chronic pain syndromes, use more health care services, and have higher health care costs than their nonabused counterparts (Kendall-Tackett, 2003). Abuse survivors are also at increased risk for cardiovascular disease, diabetes, and metabolic syndrome, the precursor to type 2 diabetes (Batten, Aslan, Maciejewski, & Mazure, 2004; Felitti et al., 2001; Kendall-Tackett & Marshall, 1999). The intriguing question is why.

Recent studies have revealed one possible mechanism: These conditions may be caused by chronic inflammation—specifically, increased levels of pro-inflammatory cytokines. Cytokines are proteins that regulate immune response. There are two broad classes of cytokines: pro-inflammatory, which increase inflammation,

TRAUMA, VIOLENCE, & ABUSE, Vol. 8, No. 2, April 2007 117-126
DOI: 10.1177/1524838007301161

## KEY POINTS OF THE RESEARCH REVIEW

- Depression, hostility, and sleep disruptions are all common sequelae of violence against women.
- Each of these increases the risk of illness.
- This risk of health problems often continues long after the abuse has ended.
- These risk factors can and do result in premature mortality.

and anti-inflammatory, which restrain it (Robles, Glaser, & Kiecolt-Glaser, 2005). Pro-inflammatory cytokines cause inflammation and help the body fight infection. When they are chronically elevated, however, they can cause disease. As two recent studies have shown, women may be more susceptible to the deleterious effects of chronically elevated pro-inflammatory cytokines manifesting as cardiovascular disease or metabolic syndrome (Batten et al., 2004; Suarez, 2006).

In this article, I review recent studies from the field of psychoneuroimmunlogy (PNI) that examine the link between inflammation and disease. Although this line of research is generally not applied to trauma survivors, it is relevant because it describes a plausible way in which sequelae of abuse can increase the risk of disease by chronically increasing inflammation. In this review, I describe the health effects of three common sequelae—depression, hostility, and sleep disturbances. The three sequelae I review tend to co-occur in abuse survivors. For example, people who are depressed can also have a hostile worldview and disturbed sleep. However, recent studies, especially on sleep disturbances in trauma survivors, have argued that these sequelae are comorbid disorders and should be examined separately (Krakow et al., 2000; Roberts, Shema, Kaplan, & Strawbridge, 2000). Depression, hostility, and sleep disturbances can negatively impact women's health in currently abusive relationships, above and beyond any injuries they incur and for many years after the abuse has ended (Woods et al., 2005).

## DEPRESSION

Depression is one of the most common of all mood disorders, and it is one of the most commonly occurring sequelae of abuse and violence (Campbell & Kendall-Tackett, 2005; Kendall-Tackett, 2003). In the trauma field, we view depression as an outcome—an endpoint that we measure in trauma survivors in the wake of traumatic events. However, researchers have now documented that depression also often leads to poor health (Frasure-Smith & Lesperance, 2005). One possible way is through its impact on the immune system.

### *Immune Dysfunction in Depression*

For several years, researchers noted that depression appeared to suppress the immune system. Depressed people have lower lymphocyte counts and decreased effectiveness of the natural killer cells, making them more susceptible to infection (Kop & Gottdiener, 2005; Robles et al., 2005). More recent studies, however, indicate that depression causes an immune dysfunction, meaning that some aspects are suppressed, while other aspects are elevated (Kiecolt-Glaser & Glaser, 2002; Kop & Gottdiener, 2005). Inflammation may be increased, which includes high levels of pro-inflammatory cytokines and acute-phase proteins, such as C-reactive protein (CRP; Kop & Gottdiener, 2005; Robles et al., 2005). The cytokines that have been identified so far that are likely to be elevated in depressed people are interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α; Robles et al., 2005).

Interestingly, cortisol levels can be elevated in depression, particularly in more severe depression. This is surprising because cortisol is generally in a feedback loop with the pro-inflammatory cytokines, and when the levels of cytokines get too high, cortisol serves to dampen these (Robles et al., 2005). So it is curious that both cortisol and pro-inflammatory cytokines could be high at the same time as they can be in depression. The answer to this apparent paradox becomes apparent when we consider the impact of allostatic load: the wear and tear that takes place when different systems respond to stressors when the organism is distressed (Dhabhar & McEwen, 2001). When the system is overloaded, as in severe stress

and depression, the normal feedback loop breaks down and fails to restrain the inflammatory response (Dhabhar & McEwen, 2001; Robles et al., 2005). This also happens in posttraumatic stress disorder (PTSD), when the cortisol response is attenuated and fails to keep immune activity in check (Delahanty, Dougall, & Baum, 2001). When this happens, the glucocorticoids may act synergistically with cytokines to enhance their activity (Connor & Leonard, 1998; Dhabhar & McEwen, 2001; Leonard, 2001).

### *How Depression Influences Health*

A number of health problems have been associated with depression, including coronary heart disease, myocardial infarction, chronic pain syndromes, premature aging, impaired immune function, impaired wound healing, and even Alzheimer's disease (Kiecolt-Glaser & Glaser, 2002; Kiecolt-Glaser et al., 2005; Simopoulos, 2002; Wilson, Finch, & Cohen, 2002). Of particular interest for our discussion is the link between depression and cardiovascular disease. Depression is a risk factor for cardiovascular disease (Frasure-Smith & Lesperance, 2005). Patients who become depressed after a myocardial infarction (MI) are 2 to 3 times more likely to have another one and are 3 to 4 times more likely to die (deJong et al., 2006; Lesperance & Frasure-Smith, 2000). The risk was not only for those suffering from major depression but also for milder forms as well.

Kop and Gottdiener (2005) hypothesize that depression in early adulthood may actually promote vascular injury and that the immune system may increase further early-stage cardiovascular disease by encouraging lipid and macrophage deposits. For people with preexisting cardiovascular disease, chronic inflammation can reduce the stability of plaque, which can lead to acute cardiac episodes.

One recent study, using data from the National Comorbidity Study, found that a history of child maltreatment (physical abuse, sexual abuse, and/or neglect) increased the risk of both cardiovascular disease and depression. Interestingly, the link between child maltreatment and cardiovascular disease was especially strong for women, with maltreated women having a nine-fold increase in cardiovascular disease compared to nonmaltreated women. The authors did not find a link between depression and cardiovascular disease, however, once child maltreatment was added to the analysis. Indeed, it was trauma history, rather than depression, that accounted for the variance in cardiovascular disease (Batten et al., 2004).

Although still preliminary, these studies suggest that depression and trauma influence cardiovascular health. In the next section, I describe a set of studies that suggest that hostility can have a similar effect.

## HOSTILITY

For women with a hostile worldview, life is not benign. As a psychological construct, hostility includes interpersonal mistrust, suspiciousness, cynicism about human nature, and a tendency to interpret the actions of others as aggressive (T. W. Smith, 1992). Several recent studies have found high rates of hostility among abuse survivors, a finding that is not surprising given their life experiences. In a sample from primary care, 52% of female sexual abuse survivors indicated that they could not trust others compared with 17% of the nonabused women (Hulme, 2000). Teegen (1999) found in her community sample that approximately half of the sexually abused women described their current views toward life, themselves, and others as very negative.

Other types of trauma were also related to hostility. In a sample of 90 women veterans (Butterfield, Forneris, Feldman, & Beckham, 2000), women who had PTSD reported significantly higher levels of hostility than women without PTSD. PTSD was related to all measures of health, with poorer outcomes for women with PTSD, even after controlling for age and education.

### *The Health Effects of Hostility*

Hostility is a reaction that may have been adaptive at one point in the survivor's life and served to protect the survivor from further danger.

However, hostility has a well-documented negative impact on health. Trait hostility increases physiological arousal because of the way hostile people interpret the world; they are more likely to perceive even neutral events as negative, responding strongly because they perceive interpersonal threat (Kiecolt-Glaser & Newton, 2001).

Hostility has garnered a great deal of attention because of its link to cardiovascular disease, which is the leading cause of death in the United States for both men and women. In their review, T. W. Smith and Ruiz (2002) noted that people who are high in trait hostility are more prone to ischemia and constriction of the coronary arteries during mental stress. Trait hostility predicted new coronary events in previously healthy people. For patients who already have coronary heart disease, hostility sped up progression of the disease.

More recently, hostility was associated with higher levels of circulating the pro-inflammatory cytokines IL-1α, IL-1β, and IL-8 in 44 healthy, nonsmoking, premenopausal women. The combination of depression and hostility increased levels of IL-1β, IL-8, and TNF-α (Suarez, Lewis, Krishnan, & Young, 2004). There was a dose-responsive effect: The more severe the depression and hostility, then the greater the production of cytokines. A study with men had similar results (Suarez, 2003). The author noted that increased levels of IL-6 predicted both future risk of cardiac events and all-cause mortality. He hypothesized that IL-6 may mediate the relationship between hostility and these health problems.

Hostility also increases the risk of metabolic syndrome. In a 3-year follow-up of 134 White and African American teens, hostility at Time 1 predicted risk factors for metabolic syndrome at Time 2 (Raikkonen, Matthews, & Salomon, 2003). These risk factors were at the 75th percentile for age, gender, and race and included BMI, insulin resistance, ratio of triglycerides to HDL cholesterol, and mean arterial blood pressure.

More recently, Suarez (2006) studied 135 healthy patients (75 men, 60 women), with no symptoms of diabetes. He found that women with higher levels of depression and hostility, along with a propensity to express anger, had higher levels of fasting insulin, glucose, and insulin resistance. These findings were not true for men, and they were independent of other risk factors for metabolic syndrome including BMI, age, fasting triglycerides, exercise regularity, or ethnicity. The author indicated that these findings were significant because prestudy glucose levels were in the nondiabetic range. The author noted that inflammation, particularly elevated IL-6 and C-reactive protein, may mediate the relationship between depression and hostility as well as risk of type 2 diabetes and cardiovascular disease, possibly because they increase insulin resistance.

### *Hostility and Social Relationships*

Hostility also has indirect effects on health by impacting quality of relationships. Hostile persons can undermine relationships through their mistrustful thoughts and antagonistic actions, and they are more likely to have negative social relations with others (T. W. Smith & Ruiz, 2002). Because of this, trait hostility has a serious impact on marriage and other important relationships. In their review, Kiecolt-Glaser and Newton (2001) noted that hostility assessed early in marriage predicted marital dissatisfaction several years later. Marital dissatisfaction can also have a negative impact on health. Their review revealed that high-stress marriages can slow wound healing, increase the risk of infectious disease, and even neutralize or lessen the effectiveness of vaccines (Kiecolt-Glaser & Newton, 2001). A 13-year longitudinal study of married women found that unsatisfying marriages increased cardiovascular risk during the study period (Gallo, Troxel, Matthews, & Kuller, 2003). Women with poor-quality marriages had higher rates of several markers for cardiovascular disease: low HDL cholesterol, high triglycerides, and higher BMI, blood pressure, depression, and anger.

The effects of marital tension seem to be particularly pronounced for women. In a recent study from Sweden, Orth-Gomer and colleagues (2000) followed 292 women for 5 years after an MI. They found that women with high levels of marital strife were nearly 3 times more

likely to have another heart attack or other coronary event as women who were married but not distressed. This relationship held even after adjusting for age, estrogen levels, education, and smoking.

In another recent study, Kiecolt-Glaser et al. (2005) found that couples who exhibited high levels of hostility had higher levels of circulating pro-inflammatory cytokines, and their rate of wound healing was 60% slower than for couples low in hostility. In the high-hostility couples, there were fewer cytokines at the wound site, where they were supposed to be, and high levels circulating systemically, where they were more likely to impair health and increase the risk of age-related diseases.

### *Summary*

The results of these recent studies suggest that hostility and hostility-related marital strife both increase the risk of cardiovascular disease and metabolic syndrome. These conditions can lead to premature mortality in abuse survivors who have a hostile worldview. Both of these conditions appear to be related to increased inflammation that may occur in the wake of violence or trauma. At least two studies suggest that women are particularly susceptible to these negative effects.

## SLEEP DISTURBANCES

The final sequelae of violence against women (VAW) I review is disrupted sleep. Sleep problems are common in trauma survivors. Although sleep disturbances are more likely in people with depression or PTSD and can be regarded as simply manifestations of these conditions, sleep researchers working with trauma survivors argue that sleep exerts an independent effect on health and should be considered separately (Krakow et al., 2000; Roberts et al., 2000). In addition, sleep difficulties exacerbate the effects of depression and PTSD and increase symptomatology (Krakow et al., 2000). Though preliminary, sleep disturbance does appear to be related to immune function as well. Although the exact mechanism is unclear, cytokines appear to have a role in regulating sleep, and the body responds to sleep deprivation by increasing pro-inflammatory cytokines (Groër, Davis, & Casey, 2005; Wilson et al., 2002).

Although a relatively new area of study within trauma research, a number of studies have documented disturbed sleep patterns in women who have experienced violence. For example, in a European community sample, 68% of sexual abuse survivors reported having sleep difficulties, with 45% having repetitive nightmares (Teegan, 1999). In a French sample, 33% of teens who had been raped indicated that they "slept badly" compared with 16% of the nonassaulted comparison group. Of the assaulted teens, 28% had nightmares (compared with 11%), and 56% woke during the night (compared with 21%; Choquet, Darves-Bornoz, Ledoux, Manfredi, & Hassler, 1997).

Hulme (2000) found that sleep problems among sexual abuse survivors were common in a primary-care sample. Fifty-two percent of sexual abuse survivors reported that they could not sleep at night (compared with 24% of the nonabused group), and 36% reported nightmares (compared with 13%). Intrusive symptoms were also common, with 53% of sexual abuse survivors reporting sudden thoughts or images of past events (compared with 18% of the nonabused group).

In a sample of battered women living in shelters ($N = 50$), 70% reported poor sleep quality, 28% went to bed very fatigued, and 40% woke up feeling very fatigued (Humphreys, Lee, Neylan, & Marmar, 1999). Furthermore, 82% described one or more of the following characteristics of disturbed sleep: many wakings over the course of the night, restless sleep, and early-morning waking. Six described vivid nightmares that included recent incidents of abuse.

In a study of sleep disorders in sexual assault survivors, 80% had either sleep-breathing or sleep-movement disorders. Both of these disorders were linked to higher levels of depression and suicidality, and women who had both types of sleep disorders had the most severe symptoms. The authors speculated that fragmented sleep potentiated the symptoms for women after a sexual assault, stretching their fragile coping abilities to the breaking point (Krakow et al., 2000).

### Depression

Sleep difficulties intersect with depression in a number of ways. Data from a large sample of older adults ($N$ = 2,370) indicated that sleep disorders were strongly associated with the risk of major depression. Early-morning waking was the sleep disturbance most consistently related to depression over time (Roberts et al., 2000). Sleep difficulties also predicted a longer course of depression. In a 10-year study of outcomes of depression treatment, those with severe fatigue and trouble sleeping were more likely to have a chronic course of depression (Moos & Cronkite, 1999).

Depression also impacts sleep architecture. Sleep architecture refers to the percentage of time that people spend in various sleep stages and the distribution of those stages throughout the night (Morin & Ware, 1996). The alteration most likely in depressed individuals is an alteration of REM-sleep parameters. Specifically, depressed people are more likely to have longer periods of REM earlier in the night than are nondepressed people (referred to as a "short REM latency"). They are also likely to have increased percentages of REM sleep and less deep sleep as a result (Morin & Ware, 1996).

One study examined the relationship between sleep architecture and depression (Perlis et al., 1997). Using canonical correlation, the authors found that severe depression drastically reduced the amount of time spent in Stage 4 (delta) sleep. Furthermore, depressed patients have more REM sleep, and REM sleep occurs earlier in the night (Perlis et al., 1997; Ware & Morin, 1997). Antidepressants, particularly tricyclics and MAO inhibitors, decrease the percentage of REM sleep, and prolong the latency to first REM sleep. Cognitive-behavioral therapy may also produce these changes (Ware & Morin, 1997).

### PTSD

Sleep disorders are also common in PTSD, with disturbed sleep and nightmares being key symptoms (Morin & Ware, 1996). PTSD also appears to have a relationship to REM latency, but this relationship is unclear. Some survivors have a shortened REM latency, whereas others have a lengthened REM latency. The reactions of particular trauma survivors tend to vary by both the recency of the traumatic event and the severity of current PTSD (Morin & Ware, 1996).

Sleep problems may also keep symptoms of PTSD active. In a study of 23 patients who suffered from chronic nightmares and obstructive sleep apnea, patients who had completed a treatment program for their sleep problems ($N$ = 14) were compared with patients who had dropped out of the program ($N$ = 9). Twenty-one months later, those who completed the program had substantially improved sleep compared with those who had not. When the patients with PTSD were compared with the PTSD/no-treatment patients, those in the treatment group had 75% improvement in their PTSD symptoms. In contrast, the 6 patients in the PTSD/no-treatment group reported a 43% worsening of symptoms. The authors concluded that treating sleep difficulties appeared to also improve PTSD symptoms and recommended a full evaluation of sleep in patients with PTSD (Krakow et al., 2000).

### How Sleep Impacts Health

Poor sleep quality has a profound effect on health. It compromises immune, metabolic, and neuroendocrine function, chronically activates the HPA axis, and even increases mortality risk (Carmichael & Reis, 2005). In a meta-analysis of 19 studies, Pilcher and Huffcutt (1996) found that sleep deprivation strongly impacts functioning in three broad categories: motor functioning, cognitive functioning, and mood, with the most severe effect being on mood. Indeed, sleep-deprived subjects reported moods that were three standard deviations lower than their non-sleep-deprived counterparts. Interestingly, partial sleep deprivation was more damaging than total sleep deprivation. People with chronically poor sleep also have more car accidents. Among people with chronic conditions, lack of sleep predicted greater functional disability and decreased quality of life. Not surprisingly, people with poor sleep use more medical services than their non-sleep-deprived counterparts (Stepanski, Rybarczyk, Lopez, & Stevens, 2003).

M.T. Smith and colleagues noted the overlap between sleep and pain, with the relationship most likely being bidirectional: pain interferes with sleep and sleep disturbances increase the experience of pain (Smith et al., 2000). Sleep problems may also reduce a patient's ability to cope with chronic pain. In their study of 51 people with chronic pain, 88% reported some dissatisfaction with their sleep. Presleep cognitive hyperarousal was the best predictor of sleep quality regardless of pain severity. This included racing thoughts, intrusive thoughts, depressive cognitions, and worry.

The deleterious effects of disturbed sleep have also been found in samples of survivors of VAW. In a sample of female rape survivors with PTSD, trauma-related sleep disorders had an independent impact on health, even after controlling for both depression and PTSD (Clum, Nishith, & Resick, 2001).

### *Summary*

Disturbed sleep is a comorbid condition in VAW survivors that is frequently undiagnosed, may exacerbate depression and PTSD, and is related to increased health problems and decreased quality of life. These findings suggest that sleep be evaluated in VAW survivors and that sleep disorders not simply be attributed to either depression or PTSD. Improving sleep quality will likely result in lower levels of symptoms and improved health overall.

## ANTI-INFLAMMATORY TREATMENT APPROACHES

The recent studies cited above suggest that inflammation may be increased in women who have experienced violence. Three common sequelae—depression, hostility, and sleep disturbances—appear to increase inflammation and impair health in abuse survivors. This research suggests that reducing inflammation may help to lessen the severity of symptoms. The depression literature already indicates that many of the treatments that we know are effective in alleviating depressive symptoms also appear to be anti-inflammatory, and this may be another mechanism for their efficacy. For example, the selective serotonin reuptake inhibitor class of antidepressants have been found to lower levels of C-reactive protein in cardiac patients with major depression (O'Brien, Scott, & Dinan, 2006). This anti-inflammatory effect was independent of whether depression resolved in these patients.

Along these same lines, a large population study found that people with high serum levels of long-chain omega-3 fatty acids (EPA and DHA) had low levels of pro-inflammatory cytokines (IL-6, IL-1, TNF-α) and lower levels of C-reactive protein. They also had higher levels of anti-inflammatory cytokines, resulting in lower levels of inflammation overall (Ferrucci et al., 2006). Also, several recent population studies have indicated that high levels of EPA and DHA may be protective of mental health. These studies found that populations with higher levels of EPA and DHA in their diets (usually from eating fatty fish) had lower levels of major depression (Tanskanen et al., 2001), postpartum depression (Hibbeln, 2002), bipolar disorder (Noaghiul & Hibbeln, 2003), and even future suicide risk (Sublette, Hibbeln, Galfalvy, Oquendo, & Mann, 2006).

Even cognitive therapy is arguably anti-inflammatory. Two recent studies have demonstrated that negative beliefs, such as hostility, can increase the levels of pro-inflammatory cytokines—especially IL-6 (Kiecolt-Glaser et al., 2005; Suarez et al., 2004). Cognitive therapy is a treatment for depression with known efficacy (Rupke, Blecke, & Renfrow, 2006). The primary goal of cognitive therapy is to reduce negative cognitions. Because negative cognitions increase inflammation, reducing their occurrence will have physical effects as well—primarily reducing inflammation.

Although these findings are preliminary, treatments that are anti-inflammatory show promise as primary or adjunct treatments in trauma survivors. Although cognitive therapy and antidepressants have been used successfully with trauma survivors (Kendall-Tackett, 2003), EPA and DHA have not been tried, to my knowledge. But this may prove to be an effective addition to our treatment regimens and would be a fruitful avenue to explore.

## OVERALL SUMMARY

Depression, hostility, and sleep disturbances are common sequelae of abuse and violence. In addition to their negative impact on day-to-day functioning, they can also act as chronic stressors in survivors of violence against women. Each of these can have a profound impact on health, in part, by raising levels of pro-inflammatory cytokines, and can continue to impact VAW survivors long after the abuse has ended. Treatments that reduce inflammation may be a promising way to alleviate depressive and trauma symptoms and to also decrease the risk of subsequent health problems. Cognitive-behavioral therapy is another approach with proven efficacy in reducing depression and hostility and in improving sleep quality. Although these sequelae overlap and tend to co-occur, they are distinct and should be evaluated and addressed separately.

## IMPLICATIONS FOR PRACTICE, POLICY, AND RESEARCH

- Depression, hostility, and sleep disturbance should be evaluated in all women with a history of violence.
- Each of these should be specifically addressed in treatment as reducing these will improve overall health.]
- Research on violence against women should include immune system measures, especially measures of pro-inflammatory cytokines—particularly IL-1β, IL-6, and TNF-α.
- Research on treatment effectiveness should also include cytokine levels as outcome measures because these may predict women's long-term health.
- High levels of pro-inflammatory cytokines increase the risk of various illnesses, including cardiovascular disease and metabolic syndrome.
- Treatments that are anti-inflammatory show promise in improving the health of women who have experienced violence.

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