

Entry Level Clinical Nutrition

May 2014 Update:

Is companionship an essential
nutrient? – Part II

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- *“There are many ways to destroy a person, but the simplest and most devastating might be solitary confinement. Deprived of meaningful human contact, otherwise healthy prisoners often become unhinged. They experience intense anxiety, paranoia, depression, memory loss, hallucinations and other perceptual distortions. Psychiatrists call this cluster of symptoms SHU syndrome, named after the Security Housing Units of many supermax prisons.”*

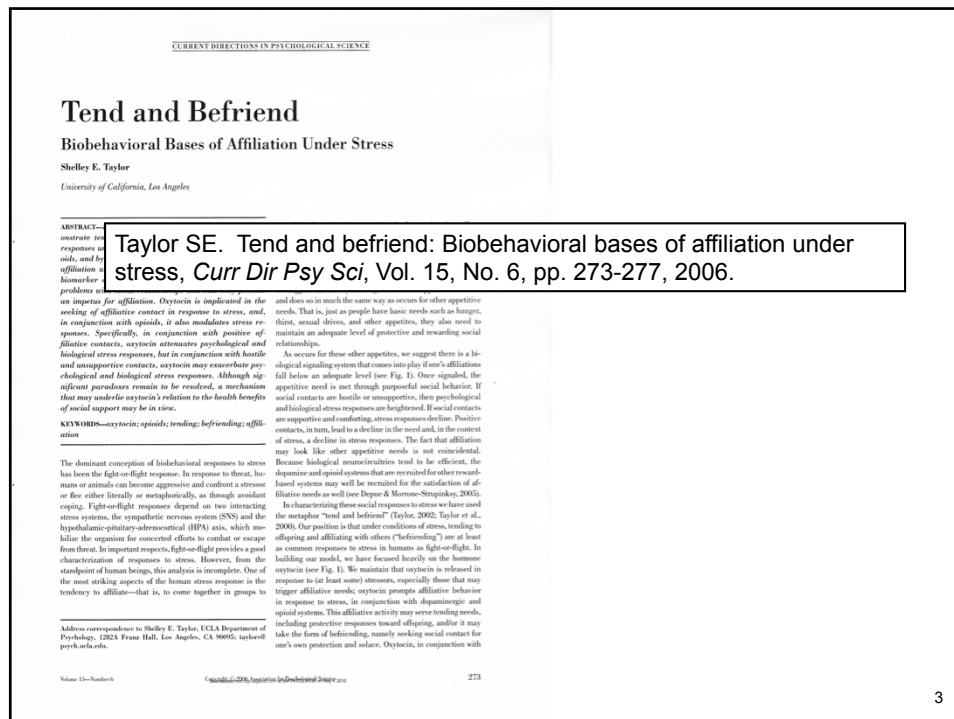
The Living Death of Solitary Confinement

By Lisa Guenther

The New York Times, August 26, 2012

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ELCN Update for May 2014 – Jeff Moss, DDS Is Companionship an Essential Nutrient – part 2



- **“In important aspects, fight-or-flight provides a good characterization of responses to stress. However, from the standpoint of human beings, this analysis is incomplete. One of the most striking aspects of the human stress response is the tendency to affiliate – that is, to come together in groups to provide and received joint protection in threatening times.”**

- **“From animal studies and our own data, we infer that there is an affiliative neurocircuitry that prompts affiliation, especially in response to stress. We suggest that this system regulates social-approach behavior and does so in much the same way as occurs for other appetitive needs. That is, just as people have basic needs such as hunger, thirst, sexual drives, and other appetites, they also need to maintain an adequate level of protective and rewarding social relationships.”**

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“Our position is that under conditions of stress, tending to offspring and affiliating with others (‘befriending’) are at least as common responses to stress in humans as fight-or-flight.”

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The oxytocin connection

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- **“In building our model, we have focused heavily on the hormone oxytocin. We maintain that oxytocin is released in response to (at least some) stressors, especially those that may trigger affiliative needs; oxytocin prompts affiliative behavior in response to stress, in conjunction with dopaminergic and opioid systems. This affiliative activity may serve tending needs, including protective responses toward offspring, and/or it may take the form of befriending, namely seeking social contact for one’s own protection and solace.”**

8

- **“Oxytocin, in conjunction with positive social contacts, attenuates biological stress responses (sympathetic nervous system, hypothalamic/pituitary/adrenal axis) that can arise in response to social threats.”**

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- **“We found that women who were experiencing gaps in their social relationships had elevated levels of oxytocin. Specifically, women with high levels of oxytocin were more likely to report reduced contact with their mothers, their best friends, their pets, and social groups to which they belonged. In addition, those with significant others were more likely to report that their partners were not supportive, did not understand the way they felt about things, and did not care for them. Poor quality of the marital relationship and infrequent display of affection by the partner were also associated with higher levels of plasma oxytocin. Thus, oxytocin appears to signal relationship distress, at least in women.”**

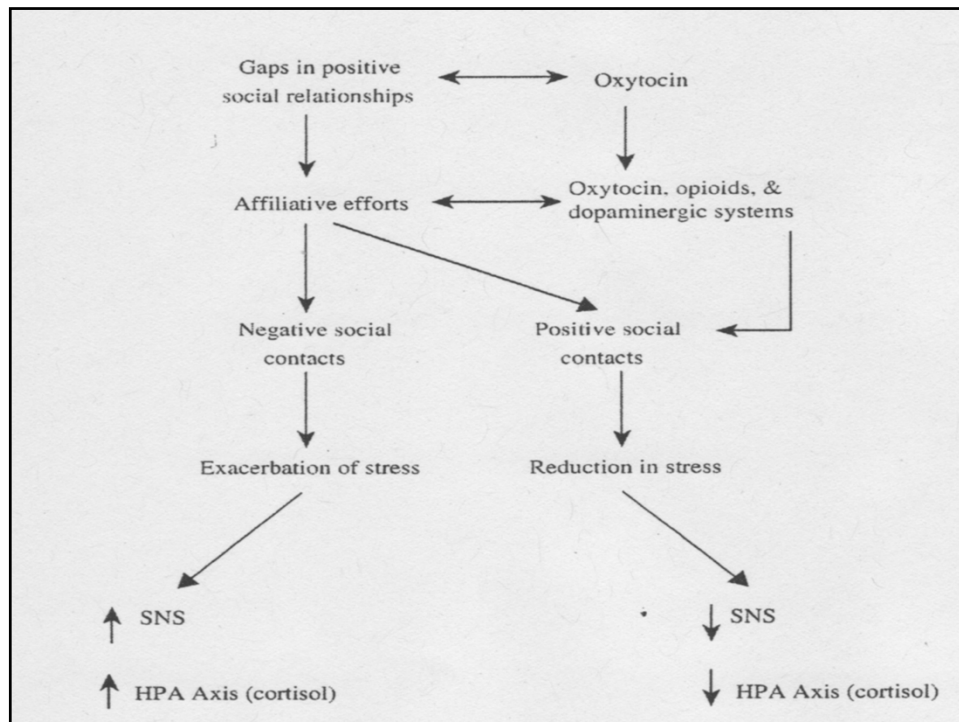
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- **“Plasma oxytocin was not related to general psychological distress, only to gaps or problems in positive relationships; and whereas oxytocin appeared to signal gaps in relationships, levels of the stress hormone cortisol were not similarly elevated. These points suggest that oxytocin may be distinctively related to relationship distress.”**

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- **“If oxytocin is related to social distress, then as an affiliative hormone, oxytocin may provide an impetus for social contact to ameliorate stress. There is manifold evidence that oxytocin, indeed, promotes affiliation, most of which has come from animal studies.” Exogenously administered oxytocin has been related to increases in physical proximity, increased maternal behavior, grooming, and preferences for conspecifics in whose presence elevated oxytocin was experienced. Oxytocin is also thought to underlie affiliative activities in humans as well, including maternal behavior and social bonding more generally.”**

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The impact of oxytocin on stress related factors

- **“The next link in the model relates oxytocin to stress responses. Animal studies have shown that exogenous administration of oxytocin or stimulation of oxytocin secretion decreases sympathetic reactivity, blood pressure, pain sensitivity, and corticosteroid levels, among other findings suggestive of a reduced stress response.”**

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- **“...among breastfeeding women who have high levels of oxytocin, among women reporting more frequent hugs from partners, and among men receiving exogenous oxytocin, psychological and biological stress responses were lower.”**

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What about low oxytocin?

- **“Those with low levels of plasma oxytocin showed an increase in cortisol in response to the social threat and a decrease during recovery.”**

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Why is high oxytocin associated with high relationship stress and low stress responses?

- **“The fact that high levels of oxytocin can be associated both with relationship distress and with reduced stress responses appears inconsistent. One hypothesis is that bursts of oxytocin, as may occur in response to anticipated or actual social contact or exogenous administration of oxytocin, reduce stress responses but that elevated oxytocin in plasma, which likely represents trace evidence of some preceding process, is associated with relationship distress.”**

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Gender differences in relation to oxytocin

- **“The effects of oxytocin on social behavior have been heavily studied in estrogen-treated female animals and in women. The evidence that oxytocin plays an important role in male social relationships is less plentiful.”**

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Why does a gender difference exist?

- **“There are several reasons to believe that oxytocin may play a more important role in influencing women’s social behavior than men’s, especially under stress. At the time when human stress responses evolved, work was largely sex segregated, with women more responsible for childcare. Thus, selection pressures for responses to threat that benefit both self and offspring may have been greater for females than for males – favoring social responses to stress in women especially.”**

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- **“Women’s consistently stronger affiliative responses to stress compared to those of men is consistent with this point. Estrogen strongly enhances the effects of oxytocin, which is also consistent with a greater role for oxytocin in women’s behavior than in men’s.”**

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Social interactions and inflammation

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Neural sensitivity to social rejection is associated with inflammatory responses to social stress

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Contributed by Shelley E. Taylor, June 25, 2010 (sent for review April 21, 2010)

Although stress-induced increases in inflammation have been implicated in several major disorders, including cardiovascular disease and depression, the neurocognitive pathways that underlie inflammatory responses to stress remain largely unknown. To examine these processes, we recruited 124 healthy young adult participants to complete a laboratory-based social stressor while markers of inflammatory activity were obtained from oral fluids. A subset of participants ($n = 31$) later completed an fMRI session in which their neural responses to social rejection were assessed. As predicted, exposure to the laboratory-based social stressor was associated with significant increases in inflammatory activity. Moreover, individuals with greater neural sensitivity to social rejection also showed greater increases in inflammatory activity during the stressor. These findings suggest that neural sensitivity to social rejection is associated with inflammatory responses to social stress.

anterior cingulate | insula | inflammation | depression | disease

Psychological stress is intimately related to human health and well-being. It increases susceptibility to the common cold (1), elevates risk for several major diseases (2), and is a strong, independent predictor of morbidity and mortality. In a recent epidemiological study, for example, males experiencing high levels of stress were 32% more likely to die during a 252 assessment period than were those experiencing low levels of stress (3). Stress may affect health in part by up-regulating inflammatory processes that have been implicated in the onset or progression of several disorders, including asthma, rheumatoid arthritis, cardiovascular disease, and depression (4–8). Although many stressors can have this effect, animal and human research has shown that social stressors are particularly strong triggers of inflammation (9–11). Exposure to everyday social stress in humans, for example, is associated with elevated inflammatory activity (12–15) and with the up-regulated expression of genes that promote inflammation (16). In addition, controlled laboratory studies have shown that acute social stressors—specifically ones that involve social evaluation and the possibility of social rejection—elicit significant increases in proinflammatory cytokines, a key mediator of the inflammatory response (17, 18).

Despite evidence that social stressors may trigger inflammation, the neurocognitive pathways that underlie this effect remain unknown. In particular, no studies to date have investigated the neural regions associated with differences in inflammatory responding to acute social stress. The brain plays a critical role in appraising social stressors, as well as in modulating the immune system's response to stressors that involve social or physical threat (19–21). Differences in inflammatory responses to social stress may thus be explained, at least in part, by individual differences in activity in neural regions that process social threat-related information.

Insofar as stressors involving the possibility of social rejection up-regulate inflammatory activity (17, 18), neural regions involved

in processing rejection-related distress may relate to individuals' magnitude of inflammatory responses to social stress. On the basis of prior research, these brain regions include the dorsal anterior cingulate cortex (dACC) and the anterior insula. Exposure to an acute episode of social rejection or to rejection-related cues has been shown to activate both the dACC and the anterior insula (22, 23); greater activity in the dACC, in turn, has been associated with greater self-reported feelings of social distress (e.g., "I felt rejected") (22, 24). Exposure to social-evaluative threat also has been shown to activate the dACC (25). Thus, neural regions associated

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- **“Exposure to everyday social stress in humans, for example, is associated with elevated inflammatory activity and with the up-regulated expression of genes that promote inflammation. In addition, controlled laboratory studies have shown that acute social stressors – specifically ones that involve social evaluation and the possibility of social rejection – elicit significant increases in proinflammatory cytokines, a key mediator of the inflammatory response.”**

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Experimental protocol

- **“...we recruited 124 healthy young adult participants to complete a laboratory-based social stressor while markers of inflammatory activity were obtained from oral fluids. A subset of participants (n = 31) later completed an fMRI session in which their neural responses to social rejection were assessed.”**

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What were the results of the experiment?

- **“As predicted, exposure to the laboratory-based social stressor was associated with significant increases in two markers of inflammatory activity, namely a soluble receptor for tumor necrosis factor- α (sTNF α RII) and interleukin-6 (IL-6).”**

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- **“In the neuroimaging subsample, greater increases in the sTNFαRII (but not IL-6) were associated with greater activity in the dorsal anterior cingulate cortex and anterior insula, brain regions that have previously been associated with processing rejection-related distress and negative affect. These data thus elucidate a neurocognitive pathway that may be involved in potentiated inflammatory responses to acute stress.”**

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Negative and competitive social interactions are related to heightened proinflammatory cytokine activity

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Contributed by Shelley E. Taylor, December 19, 2011 (sent for review November 2, 2011)

Research has consistently documented that social relationships influence physical health, a link that may implicate systemic inflammation. We examined whether daily social interactions predict levels of proinflammatory cytokines IL-6 and the soluble receptor for tumor necrosis factor (sTNFαRII) and their reactivity to a social stressor. On daily diaries, social interaction challenges, 25- and 30-min social interaction and sTNFαRII levels of these from the and one proinflammatory cytokine activity.

competition | social stress | immunology

Research has consistently documented that social relationships influence physical health (1, 2). People who are more socially integrated live longer (3) and are less likely to experience specific disease outcomes, including heart attacks (4) and upper respiratory illness (5). One way social relationships may influence health is through inflammation, a natural, early response of the immune system that is essential to fighting infections and repairing injured tissue. Communication molecules known as proinflammatory cytokines coordinate and promote inflammatory processes. Although acute inflammation is adaptive, chronic inflammatory activity can contribute to adverse health outcomes. Specifically, increases in proinflammatory cytokines IL-6 and TNF-α have been linked to hypertension (6), atherosclerosis (7), coronary heart disease (8, 9), depression (10), diabetes (11), and some cancers (12, 13).

Social ties have also been linked to aspects of inflammation, and they may play a role in the relationship between inflammation and health. People who are socially integrated or have larger social networks have been found to have lower plasma levels of IL-6 and C-reactive protein (CRP), a byproduct of IL-6 activity (14). A cold and conflict-ridden early family environment has been tied to elevated levels of CRP in adulthood (15). Chronic relationship stress characterized by conflict, mistrust, and instability, although not consistently related to basal levels of proinflammatory cytokines, have been tied to greater lipopolysaccharide-stimulated IL-6 production *in vitro* (16). Similarly, hostile married couples engaging in a conflict interaction in the laboratory had higher levels of IL-6 24 h later compared with those engaging in a supportive interaction (17), and married women with rheumatoid arthritis who experienced more spousal criticism showed an increase in IL-28, a marker of disease activity, when experiencing interpersonal stress (18).

Several important issues need to be addressed, however. First, as yet, it is unknown whether studies relating chronic relationship stress and acute evaluative stress episodes translate to natural

settings and to the experiences of everyday social interactions. Second, most studies investigating potential links between social relationships and inflammation have been cross-sectional, assessing social relationships or manipulating social interactions at one point in time; prospective evidence is needed. Third, it is unknown

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1878-1882 • PNAS | February 7, 2012 • vol. 109 | no. 6

www.pnas.org/cgi/doi/10.1073/pnas.1120972109

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- **“Similarly, hostile married couples engaging in a conflict interaction in the laboratory had higher levels of IL-6 24 h later compared with those engaging in a supportive interaction, and married women with rheumatoid arthritis who experienced more spousal criticism showed an increase in sIL-2R, a marker of disease activity, when experiencing interpersonal stress.”**

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- **“One-hundred twenty-two healthy young adults completed daily diaries for 8 d that assessed positive, negative, and competitive social interactions. Participants then engaged in laboratory stress challenges, and IL-6 and sTNF α RII were collected at baseline and at 25- and 80-min poststressor, from oral mucosal transudate.”**

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- **“Negative social interactions predicted elevated sTNF α RII at baseline, and IL-6 and sTNF α RII 25-min poststressor, as well as total output of sTNF α RII. Competitive social interactions predicted elevated baseline levels of IL-6 and sTNF α RII and total output of both cytokines.”**

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- **“The present findings raise the questions of why daily social experiences are related to inflammation and by what routes. Negative and competitive social interactions represent daily interpersonal stressors, which are reported to be the most frequent type of stressor experienced in people’s daily lives and are more predictive of negative physical and mental health than other types of stressors. Frequent repeated exposure to such stressors may create chronic stress, which leads to low-grade chronic systemic inflammation.”**

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Some big picture thoughts

- **“It is unlikely that the specific stressors over the short time span of the present study have any health effects, especially in a young healthy population. Moreover, some inflammation is desirable, as it promotes healing of physical injury. However, recurrent and repeated activation of the inflammatory response is deleterious to health.”**

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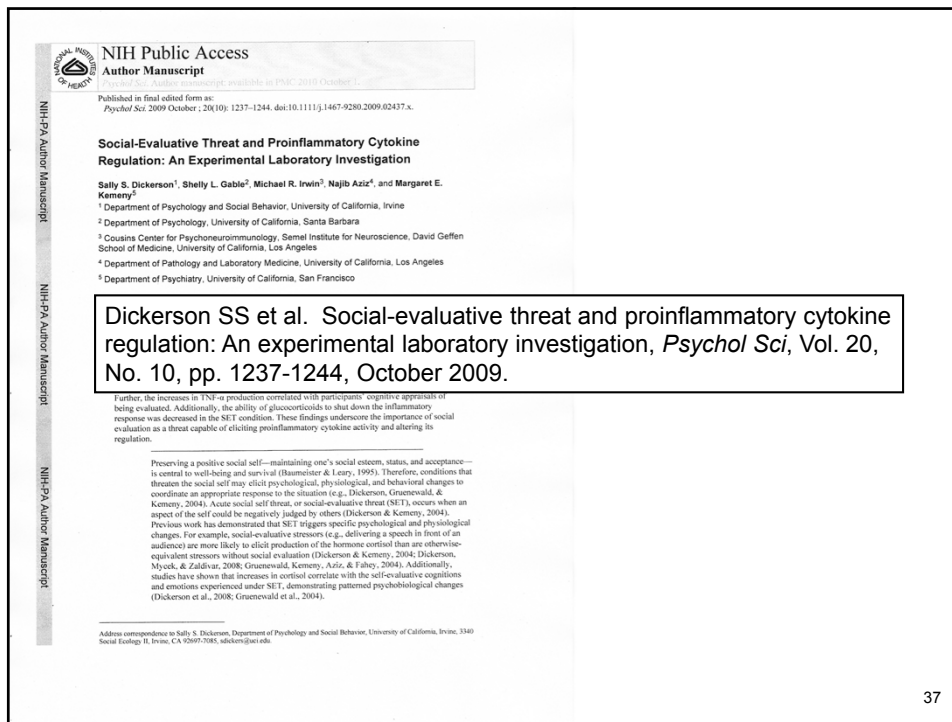
- **“Thus, cumulatively, a greater number of daily negative and competitive social interactions may, over time, predict inflammation-related disorders and exacerbate existing illnesses that are sensitive to inflammation. This is an important direction for future research.”**

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Social interactions,
inflammation, and
glucocorticoids

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ELCN Update for May 2014 – Jeff Moss, DDS Is Companionship an Essential Nutrient – part 2



- **“Social threats may not only increase proinflammatory activity, but also alter the regulation of this response. High levels of glucocorticoids (cortisol or its synthetics, hydrocortisone and dexamethasone) typically inhibit the production and expression of proinflammatory cytokines. Although social threat can elevate glucocorticoids in humans and in nonhuman animals, certain threats may interfere with the glucocorticoid-driven inhibitory process, thereby leading to simultaneous elevations in glucocorticoid and proinflammatory activity.”**

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- **“Indeed, social threat can modulate the ability of glucocorticoids to shut down inflammatory processes in nonhuman animals. In other words, social stressors can decrease the ability of glucocorticoids to reign in proinflammatory responses (i.e., decrease glucocorticoid sensitivity): As a result of down-regulation of glucocorticoids receptors on immune cells that produce proinflammatory cytokines, glucocorticoids become less able to alter (inhibit) the activity of these cells.”**

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“Decreases in glucocorticoid sensitivity may be specific to social threat, as other stressors have not induced these immunoregulatory changes.”

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Loneliness and inflammation

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Article in Press
Available online at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: www.elsevier.com/locate/psyneuen

Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women

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Received

KEYWORDS
Loneliness
Cytokines
Interleukin
Interleukin-6
Interleukin-10
Monocyte chemoattractant protein-1
Salivary cortisol
Mental stress

Hackett RA et al. Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women, *Psychoneuroendocrinology*, published online ahead of print 2012.

1. Introduction

The impact of loneliness on health has become increasingly well recognised. Loneliness is independently predictive of mortality (Perrine et al., 1997; Patterson and Vennart, 2010; Shrivastava and Ayalan, 2010; Tinsley et al., 2011) and increases the risk of having a heart condition (Sorkin et al., 2002). There is some evidence that the effects of loneliness may be differentially experienced by men and women, although the literature on gender differences in loneliness levels is mixed (Pinquart and Sörensen, 2001; Thoresen, 2009). For example, Thurston and Kubzansky (2009) showed that loneliness was prospectively linked with incident coronary heart disease (CHD) over a 19-year follow-up period, after controlling for standard risk factors. But effects were only found in women, and not in men.

Identification of the biological mechanisms through which loneliness might impact health would clarify the processes

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0306-4530/\$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psyneuen.2012.03.016

Please cite this article in press as: Hackett, R.A., et al., Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women, *Psychoneuroendocrinology* (2012), http://dx.doi.org/10.1016/j.psyneuen.2012.03.016

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- **“Loneliness has been linked with changes in cardiovascular processes such as elevated systolic blood pressure, greater diastolic blood pressure reactions to acute stress in women, elevated total peripheral resistance, lower heart rate variability and decreased cardiac output.”**

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- **“Ong et al recently reported that loneliness was associated with greater blood pressure responses to social evaluative threat and with delayed post-stress recovery, and that this effect was accentuated by greater age. Elevated cortisol levels have been observed in both lonely students and lonely adults.”**

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- **“One explanation is that loneliness may compromise the regulation by glucocorticoids (GCs) on pro-inflammatory transcription pathways.”**

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Study protocol

- **“Saliva samples and blood were taken from 524 healthy middle-aged men and women from the Whitehall II cohort at baseline, immediately after the stress tasks and 45 min later. Loneliness was measured using the revised UCLA loneliness scale.”**

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Results

- **“We reasoned that if inflammation contributes to the impact of loneliness on disease risk, then loneliness would be positively associated with inflammatory responses to laboratory stress. The results of the study were partly consistent with larger IL-6 and IL-1Ra responses to psychological stress and greater MCP-1 levels in women, independently of age, grade of employment, BMI and smoking status. But no associations were observed in men.”**

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What is MCP-1?

- **“MCP-1 is a pro-inflammatory chemokine that is known to play a major role in the development of cardiovascular disease.”**

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- **“Interestingly, increases in MCP-1 were more sustained in women than men, consistent with the heightened cytokine responses. Loneliness was positively associated with elevated MCP-1 concentrations in women throughout the session, which were maintained from baseline to recovery.”**

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- **“The observed relationship between loneliness and heightened inflammation in women extends the findings of a previous analysis in which diastolic blood pressure reactivity to stress was positively associated with loneliness in women but not in men. It may be that the inflammatory processes which are implicated in coronary atherogenesis are particularly sensitive to the effects of loneliness in women. This idea is consistent with results from a recent large epidemiological study which found chronic loneliness to be prospectively associated with incident CHD in women but not in men.”**

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- **“The greater sensitivity of women to the impact of loneliness on biological responses may result from gender differences in the importance of social relationships to the maintenance of well-being.”**

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- **“Taylor et al. have argued that females employ a ‘tend-and-befriend’ response to stress, prioritizing the creation and maintenance of social relationships in managing adversity. This pattern may make women more sensitive to the effects of loneliness, potentially accounting for the heightened inflammatory stress responses observed in lonely women, despite there being no differences in loneliness scores between men and women.”**

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What about salivary cortisol?

- **“In contrast with the cytokine and chemokine results, cortisol responses to stress showed an inverse association with loneliness in women.”**

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Is low cortisol with loneliness a good thing or a bad thing?

- **“These findings suggest that lonely people show insufficient glucocorticoid (GC) signaling to inhibit inflammatory responses under stress, not because of attenuated GC receptor sensitivity but decreased hormone release. Thus, decreased cortisol responses to stress, reduced GC receptor sensitivity, and increased activity of pro-inflammatory transcription pathways may all contribute to heightened inflammatory responses in lonely individuals.”**

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Hackett et al conclude:

- **“The impact of loneliness on health in women may be mediated in part through dysregulation of inflammatory and neuroendocrine systems.”**

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Loneliness and mortality

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ELCN Update for May 2014 – Jeff Moss, DDS Is Companionship an Essential Nutrient – part 2

ORIGINAL INVESTIGATION

ONLINE FIRST

Living Alone and Cardiovascular Risk in Outpatients at Risk of or With Atherothrombosis

Jacob A. Udell, MD, MPH, Philippe Gabriel Steg, MD, Benjamin M. Scirica, MD, MPH, Sidney C. Smith Jr, MD, E. Magnus Ohlsson, MD, Kim A. Eagle, MD, Shinya Goto, MD, Jong H Cho, MD, Deepak L. Bhatt, MD, MPH, for the Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators

Udell JA et al. Living alone and cardiovascular risk in outpatients at risk of or with atherothrombosis. Arch Intern Med. 2012;Published online June 18, 2012

ember 1, 2003, through December 31, 2004, and followed up to 4 years for cardiovascular events. Events were examined by living arrangement with risk adjustment for age, sex, clinical risk factors, therapy, preexisting vascular disease, and sociodemographic factors. Effect modification was tested by age, sex, employment, ethnicity, education, and geography.

Results: Among the 44 573 REACH participants, 8304 (19%) were living alone. Living alone was associated with higher 4-year mortality (14.1% vs 11.1%) and cardiovascular death (8.6% vs 6.8%; log-rank $P < .01$ for both comparisons); however, there was significant effect modification.

Conclusions: In an international outpatient population with atherothrombosis aged 45 years or older, living alone was associated with increased mortality among all but the most elderly patients, although this observation warrants confirmation.

Arch Intern Med.
Published online June 18, 2012.
doi:10.1001/archinternmed.2012.2782

SOCIAL ISOLATION, OR AN ABSENCE of real or perceived social support, may be associated with poor health consequences, including cardiovascular (CV) disease.¹⁻³ The degree to which people are integrated with others may be as strongly predictive of incident myocardial infarction (MI) and coronary heart disease (CHD) survival as smoking, elevated cholesterol levels, and hypertension.⁴⁻⁶ Moreover, the risk associated with living alone is relevant given that approximately 1 in 7 American adults are living alone.^{7,8} To some, living alone may have associated social and economic benefits but also potential drawbacks, including social mobility and isolation,^{9,10} as predicted by Sorokin¹¹ in the early 20th century. Increasingly, individuals in developed and developing countries are living away from extended family or friends, participating in mobile employment, and communicating remotely. There is substantial epidemiological evidence that social isolation may alter neurohormonal-mediated emotional stress, influence health behavior, and effect access to health care.

See related article

resulting in association with, or acquisition of, CV risk.^{12-15,16-17} Prior CV risk estimates associated with social isolation vary considerably owing to the difficulty in reliably and precisely estimating multidimensional psychosocial measures among diverse settings. To our knowledge, no prior report has comparatively studied the risk associated with social isolation among an internationally diverse population of outpatients with varying CV and sociodemographic risk factors, including employment, education, and geo-

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- **“In conclusion, living alone was independently associated with an increased risk of mortality and CV death in an international cohort of stable middle-aged outpatients with or at risk of atherothrombosis.”**

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Can the same be said for individuals over 60 years of age?

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ORIGINAL INVESTIGATION
ONLINE FIRST

Loneliness in Older Persons

A Predictor of Functional Decline and Death

Carla M. Perissinotto, MD, MHS; Bena Stijacic-Cenzer, MA; Kenneth E. Covinsky, MD, MPH

Perissinotto CM et al. Loneliness in older persons: A predictor of functional decline and death. Arch Intern Med. 2012; Published online June 18, 2012.

Retirement Study: a nationally representative study of older persons. Baseline assessment was in 2002 and follow-up assessments occurred every 2 years until 2008. Subjects were asked if they (1) felt left out, (2) felt isolated, or (3) lack companionship. Subjects were categorized as not lonely if they responded hardly ever to all 3 questions and lonely if they responded some of the time or often to any of the 3 questions. The primary outcomes were time to death over 6 years and functional decline over 6 years on the following 4 measures: difficulty with instrumental number of activities of daily living

(41.2% vs 28.2%; adjusted RR, 1.28; 95% CI, 1.08-1.52); experience decline in mobility (38.1% vs 29.4%; adjusted RR, 1.38; 95% CI, 0.99-1.91); or experience difficulty in climbing (40.8% vs 27.9%; adjusted RR, 1.31; 95% CI, 1.10-1.57). Loneliness was associated with an increased risk of death (22.8% vs 14.2%; adjusted HR, 1.45; 95% CI, 1.11-1.88).

Conclusion: Among participants who were older than 60 years, loneliness was a predictor of functional decline, or lack of companionship. While persons who are lonely are more likely to experience depressive symptoms, feelings of loneliness are only weakly associated with enjoyment, energy, and motivation—emotions that are central to a

“Loneliness is a common source of suffering in older persons. We demonstrated that it is also a risk factor for poor health outcomes including death and multiple measures of functional decline. It persisted after accounting for a large number of confounders including illness severity and depression.”

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Other studies have shown that measures of social isolation—the number of social contacts and the amount of social engagement—are associated with poor health outcomes. Yet, these quantitative measures of relationships may not adequately capture the distress that an individual may subjectively feel. The con-

See also pages 0120024 and 0120030

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Some concluding thoughts

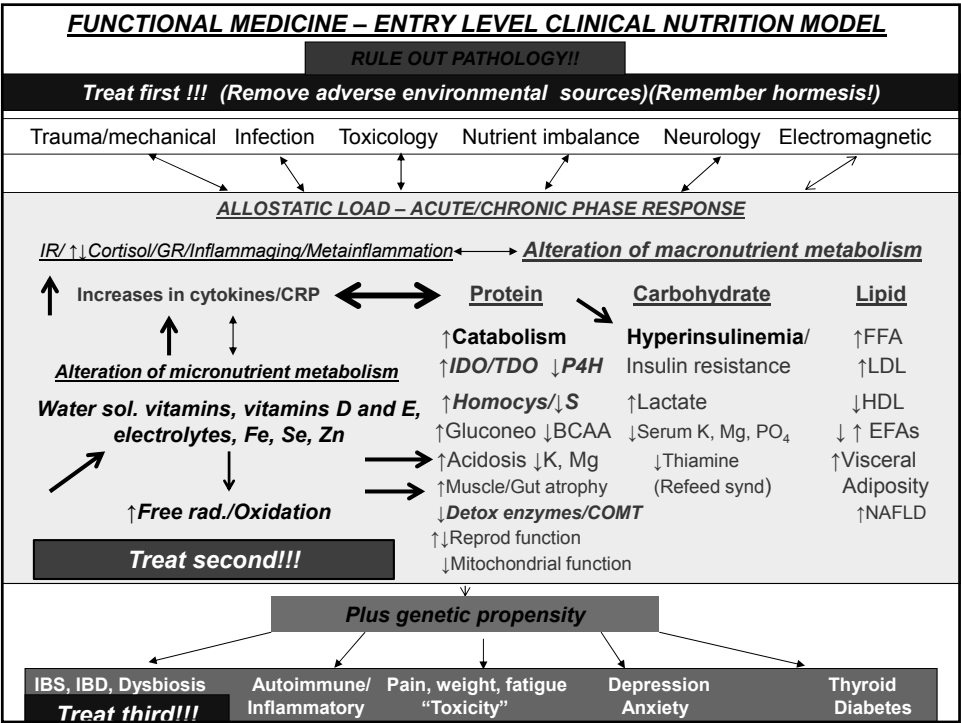
61

- ***To fully understand the needs of patients who are being considered in this series, I feel we must add a new “mantra” – “biochemical sociology” – the study of the biochemistry of social interactions.***

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- If we can keep this new mantra in mind as we address patient needs, particularly those that relate to chronic inflammation and all the downstream effects of chronic inflammation such as insulin resistance, sarcopenia, GI dysfunction, etc, we will realize that recommending exercise is no longer enough. We must also consider who the exercise is done with. We will realize that dietary recommendations are no longer enough. We must also consider who the diet is eaten with. We will realize that supplements are no longer enough. We must also consider attitudes about supplementation of other key people in patients’ lives.

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Is Companionship an Essential Nutrient – part 2

