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Marriage, Health, and Immune Function: A Review of Key Findings
and the Role of Depression

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Review of Essential Findings

Marital relationships are strongly related to many aspects of physical health (Burman and Margolin 1992; Kiecolt-Glaser and Newton 2001). Not only are married individuals healthier than single, divorced or separated, and widowed individuals after controlling for income and age (Johnson et al. 2000; Verbrugge 1979), marital status has substantial predictive power for mortality from a range of chronic and acute conditions (Johnson et al. 2000; Verbrugge 1979). Compared to other social relationships, marital relationships tend to have a greater impact on an individual's emotional and physical well-being (Glenn and Weaver 1981). Indeed, a meta-analysis of autonomic, endocrine, and immune data suggests that family relationships, including marriage, are particularly important (Uchino et al. 1996).

A number of pathways have been proposed by which marriage can affect an individual's health (Burman and Margolin 1992; Kiecolt-Glaser and Newton 2001), many of which are bi-directional. Although selection undoubtedly plays a role, with healthier individuals more likely to marry and to stay married, the association between physical health and marriage remains after controlling for selection effects (Wu et al. 2003). Stress and social support are widely acknowledged to play a major role in accounting for both protective and deleterious correlates of marital status and quality (Burman and Margolin 1992; Graham et al. 2005a), with relatively direct mechanisms via physiological responses to stress (Umberson 1992) in addition to more indirect effects related to individual cognitions, affect, coping, and health behaviours (e.g., diet, sleep, exercise, and medication compliance).

The current review will focus on key findings linking marriage, immune functioning, and overall health. Throughout, the role of depression will be highlighted, as will be gender and other individual differences, such as trait hostility. The role of stress, social support, and coping

mechanisms will also be addressed. The current review is not exhaustive, but rather provides an overview of the importance of relationship factors. Another goal of this chapter is to encourage discussion and research on practical considerations related to diagnosis and intervention, such as the need for better characterization of relational processes in the DSM.

Biological Outcomes of Interest

Neuroendocrine Measures of Stress

Although marriage is typically considered to be beneficial or protective, marital conflict can function as both an acute stressor (e.g., a solitary argument) or chronic stressor (e.g., daily arguments for years). Such stress is associated with a number of changes in endocrine functioning, which can affect the immune system indirectly (Ader et al. 1991; Malarkey et al. 1994). Two pathways are key to maintaining homeostasis during stress: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system. Activation of these axes results in the release of stress hormones including cortisol, as well as catecholamines epinephrine and norepinephrine (Groth et al. 2000). Both cortisol and catecholamines are believed to play a significant role in the development of disease under conditions of chronic stress (Cohen et al. 1995).

Immune Measures

The immune system can be divided conceptually into natural (innate) and specific (adaptive) immunity. Natural immunity is a vital and almost immediate response to foreign invaders (e.g. bacteria and certain viruses), but one which is general and non-specific to pathogens. The key elements of natural immunity are neutrophils, macrophages, natural killer (NK) cells, and complement proteins. In contrast to natural immunity, specific immunity takes several days to engage but, once activated, is more efficient and effective than natural immunity.

The main cell type is the lymphocyte, which includes T-cells and B-cells. Two of the primary populations of T-cells are CD4 (helper) and CD8 (cytotoxic); CD4 cells are further subdivided as belonging to either Th1 (T-helper-1) or Th2 (T-helper-2) class, which are associated with different functional properties and produce different cytokines. Cytokines, which are produced by macrophages and other cells in addition to lymphocytes, are soluble proteins involved in communication between cells. Cytokines are a vital part of the immune system and are involved adaptive response to immune challenge including site-specific inflammation, fever, and improved wound healing (Rabin 1999). However, psychological stress also appears to stimulate cytokine production and chronically elevated amounts of certain cytokines are implicated in morbidity and mortality, especially in older adults. For example, increased levels of pro-inflammatory cytokines, such as IL-6, are associated with a variety of diseases, including cardiovascular disease, arthritis, Type-2 diabetes, and certain cancers (Kiecolt-Glaser et al. 2003b). IL-6 also triggers the increase of C-reactive protein (CRP), a general marker of inflammation associated with increased risk for myocardial infarction (Ridker et al. 2000).

There are several ways to obtain quantifiable measures related to immune functioning. Enumerative assays quantify cell numbers or percentages, as both the number (e.g., an absolute count of the number of NK cells) and the relative balance of different cells (e.g., the ratio of Th1-type cells to Th2-type cells) are relevant to the overall function of the immune system. In contrast, functional assays assess performance of particular cells, typically *in vitro*. While both enumerative and functional assays are influenced by acute stress, chronic and severe stress responses in humans tend to be more strongly and reliably associated with functional assays (Kiecolt-Glaser and Glaser 1995). Examples used commonly in psychological research with humans include the ability of NK cells to lyse (i.e., destroy) tumor cells and the ability of

lymphocytes to proliferate when stimulated with mitogens. Other assays include antibody responses to viruses and antibody and T-cell responses to vaccines. The amount of antibody or cytokine protein can be measured *in vitro* after stimulating cells or *in vivo* (e.g., amount of a particular cytokine in the circulating blood).

Marriage and Immune Functioning

Marital Relationships and General Health

Based on a large review of U.S. federal health data, married people have the lowest rates of disability due to chronic conditions (Verbrugge 1979). In terms of both acute and chronic conditions, separated and divorced individuals appear least healthy, followed by widowed, and then single individuals (Verbrugge 1979). In addition, the risk of mortality from a variety of conditions is typically lower among the married than the unmarried in a wide range of populations and after adjustment for income and biomedical risk factors (Goodwin et al. 1987; Gordon and Rosenthal 1995; Johnson et al. 2000). Null findings are rare and have typically occurred in contexts where the marital relationship is not as central to support provision, such as among first generation immigrants or residents of small, rural communities (Burman and Margolin 1992; House et al. 1988).

In general, the effect of marital status on both mortality and morbidity is substantially stronger for men than for women (Kiecolt-Glaser and Newton 2001). For example, nonmarried women have a 50% greater risk of mortality than otherwise comparable married women, compared to a 250% greater risk for nonmarried compared to married men (Ross et al. 1990). The increased risk of mortality associated with marital disruption is also often stronger for men (Kiecolt-Glaser and Newton 2001). Indeed, a particularly well-controlled and comprehensive study found that surviving one's spouse led to increased risk of mortality among men but not

women over a 10-year period (Helsing et al. 1981). There are several plausible explanations for why marriage confers greater health benefits to men than women. For one, wives tend to influence their spouses to improve health behaviors to a greater extent than do husbands (Umberson 1992). In addition, many married women do a greater percent of housework and childcare, with an particularly adverse impact on marital satisfaction for women with egalitarian ideals, and there is evidence such factors are associated with adverse cardiovascular and catecholamine responses (for a review, see Kiecolt-Glaser and Newton 2001). Women who become married are also more likely to cease employment and may suffer from a resulting loss of that social network (Johnson et al. 2000).

While being married confers health benefits, on average, the mere existence of a close relationship is not enough to be protective. Indeed, poor marital quality is strongly associated with worse health (Kiecolt-Glaser and Newton 2001). For example, in a population-based, prospective follow-up study conducted in Stockholm of women with coronary heart disease, marital stress worsened the prognosis 2.9 fold for recurrent coronary events (Orth-Gomer et al. 2000). Among patients with congestive heart failure, marital quality predicted 4-year survival as well as illness severity (Coyne et al. 2001). Similarly, greater dyadic conflict was associated with a 46% higher relative death risk among female hemodialysis patients (Kimmel et al. 2000).

While men appear to benefit more from being married overall, the weight of evidence suggests that women suffer more from poor marital quality. For example, in a large sample randomly selected from members of an HMO, companionship in marriage and equality in decision making were associated with a lower risk of death over 15 years among women but not men (Hibbard and Pope 1993). Similarly, in another large study, women who reported that they had considerable conflicts with their husbands and who also reported work conflict had a 2.54-

fold risk of work-related disability related to a variety of health problems in the ensuing six years; neither work nor marital conflict was a risk factor for men (Appelberg et al. 1996). There are a variety of reasons why women and men may respond differently to marital quality. For a comprehensive review see Kiecolt-Glaser and Newton (2001). One difference of note is that women's self-representations tend to be characterized by greater relational interdependence (Cross and Madson 1997). In addition, women tend to spend more time thinking about marital events than do men (Burnett 1987; Ross and Holmberg 1990). For these reasons, conflictual marriages may dampen the benefits of being married more for women than men.

Marital Status and Immune Functioning

Several of the first studies of marriage and immune functioning were designed in part to explain the particularly strong association between marital disruption and health. One study found that married women had better immune function than comparable recently separated or divorced women (Kiecolt-Glaser et al. 1987), with the latter showing higher antibody titers in response to *in vitro* stimulation with Epstein-barr virus (EBV), and lower percentages of natural killer (NK) cells (Kiecolt-Glaser et al. 1987). These effects were not explained by differences in drug or alcohol use, diet, or sleep. Similar results were found with men, with divorced or separated men showing higher antibody titers to two herpesviruses, indicating poorer immune system control over viral latency (Kiecolt-Glaser et al. 1988).

Several studies have shown dysregulation of immune functioning following the death of a spouse (Bartrop et al. 1977), mirroring data showing increased mortality among bereaved individuals. Although the majority of studies linking bereavement and specific immune measures have been of older women, the association between bereavement and health in younger individuals is likely to be even stronger; younger people are at greater risk for both mortality and

morbidity from spousal bereavement than older individuals (for a review, Schulz and Rau 1985), perhaps due to differences in their expectations of the preparedness of their social networks to provide support following this event. Depressive symptoms common among the bereaved may play a substantial role in the association between bereavement and immunity: More severe depressive symptoms among bereaved women are associated with a less adaptive pattern of immune response (Irwin et al. 1987). Thus, it is possible that depressive symptoms mediate immune responses to bereavement. However, other explanations for such associations are also possible, including third variables, such as genetics, that might influence both depressive and immune responses to stress.

Marriage Quality and Immune Functioning

In the last 10 years or so, research on the immune impact of marital factors has focused on aspects of relationship quality rather than marital status. One commonly used indicator of marital quality is self-reported satisfaction with marriage. In the studies described previously comparing married men and women with separated or divorced individuals, lower marital satisfaction was associated with several indicators of poorer immune functioning (Kiecolt-Glaser et al. 1987; Kiecolt-Glaser et al. 1988). Again, depression seems to play a role: Poorer marital quality was related to greater depression, which was also associated with poorer immune functioning (Kiecolt-Glaser et al. 1988). Because these studies were retrospective, they did not examine depression as a mediator of a causal relationship, nor have more recent studies tested this hypothesis to our knowledge. A subsequent section in this chapter reviews more fully other literature relevant to the possible role of depression.

In addition to self-report measures of marital satisfaction, marital quality has increasingly been assessed using observations of behavior during couple interactions. Although several

studies have explored positive interactions – such as support provision and general positive behavior – hostile behaviors, such as interrupting and criticizing, appear to be more predictive of physiological outcomes. Hostile behaviors during marital discussions are associated with adverse changes in blood pressure, endocrine levels, and immune responses (Ewart et al. 1991; Kiecolt-Glaser et al. 1993; Malarkey et al. 1994). For example, using a sample of healthy newlywed couples with high marital satisfaction overall, subjects who exhibited more negative or hostile behavior during a 30-minute discussion of marital problems showed greater decrements over 24 hours as compared to other subjects on four immune measures (Kiecolt-Glaser et al. 1993).

Such findings have been replicated with a variety of populations and by a number of different labs. In addition to our newlywed sample, for example, older couples also show endocrine and immune dysregulation following marital conflict discussion (Kiecolt-Glaser et al. 1997), with both men and women who demonstrated more negative behavior evidencing the poorest immunological responses across three assays. In another marital interaction study, wives responded to a 45-minute conflictive discussion task with greater increases in depression, hostility, and systolic blood pressure than husbands (Mayne et al. 1997). In addition, women's lymphocyte proliferative responses decreased following conflict, while men's increased (Mayne et al. 1997).

Overall, as with the gender differences in response to marital conflict, the relationship between physiological change and negative marital behavior has typically been stronger for women than for men (e.g., Kiecolt-Glaser et al. 1996; Malarkey et al. 1994; Mayne et al. 1997). These differences between wives and husbands do not seem to be a function of gender differences in broader physiological patterns of responding to acute stress (Kiecolt-Glaser and Newton 2001).

Individuals high in trait hostility are also more likely to show greater endocrine and immune responses to marital conflict, and only in part because they show more negative conflict behaviors during marital interactions (Newton et al. 1995; Mayne et al. 1997). Indeed, another study found no significant association between behaviorally-coded affect during conflict and cardiovascular, immune, or cortisol data except among husbands who were high on cynical hostility (Miller et al. 1999).

In addition to their relevance to health, these findings have important implications for understanding marital stability. Evidence following up with participants from our study of newlyweds suggests that stress hormone responses can predict marital satisfaction and divorce. Those with higher stress hormones throughout the day as measured in their first year of marriage, not necessarily those linked to a conflict discussion, were more likely to subsequently divorce (Kiecolt-Glaser et al. 2003a). Moreover, higher stress hormone reactivity in response to the problem-solving discussion was associated with poorer marital satisfaction 10 years later (Kiecolt-Glaser et al. 2003a).

For some individuals, the marital relationship is chronically stressful not because of conflict or hostility per se, but because of the health status of the partner. Individuals who are caregiving for spouses with Alzheimer's and other forms of dementia experience chronic stress, report low levels of social support, and are at elevated risk for depressive symptoms and affective disorders even after the death of their spouse (Esterling et al. 1994). As compared to sociodemographically similar controls, caregivers report more days of infectious illness (Kiecolt-Glaser et al. 1991), evidence poorer immune responses to virus and vaccine challenges (Vedhara et al. 1999; Glaser et al. 2000), and evidence slower healing of laboratory induced wounds (Kiecolt-Glaser et al. 1995). In addition, both current and former caregivers show evidence of

dysregulated inflammation. For example, caregivers have poorer NK cell responses to cytokines *in vitro* (Esterling et al. 1994; Esterling et al. 1996), show a substantially greater increase in IL-6 over a 6-year period (Kiecolt-Glaser et al. 2003b), and show a stronger association between pain and C-reactive protein (Graham et al., 2005c) as compared to non-caregivers. Relational processes appear to play a strong role in the adverse impact of caregiving. Caregivers who are most bothered by dementia-related behaviors of their spouse show the most uniformly negative changes in immune functioning (Kiecolt-Glaser et al. 1991) and poor NK cell responses among caregivers are associated with less positive social support and less emotional closeness among social contacts (Esterling et al. 1996).

The Role of Mental Health

Overall, those who are married enjoy better mental health than those who are not (Kessler and McRae 1984; Pearlin and Johnson 1977; Thoits 1986). Much research has focused specifically on depressive symptoms, which are lower among the married than the unmarried overall (Wu et al. 2003). Although this association between marriage and better mental health is partially explained by selection effects (Overbeek et al. 2003), a substantial amount appears to be explained by the health advantages of being married (Horowitz et al. 1996; Wu et al. 2003). However, as noted earlier, not all marriages are created equal. Indeed, unmarried people are happier, on average, than those who are unhappily married (Glenn and Weaver 1981). Moreover, among the married, those in less conflictual marriages report greater overall mental health (Berry and Worthington 2001). One study found that those reporting marital discord had a 10-fold increase in risk for depressive symptoms (O'Leary et al. 1994). Similarly, data from a large epidemiological study demonstrated that unhappy marriages were associated with a 25-fold increase in major depressive disorder over untroubled marriages (Weissman 1987).

The magnitude of the association between marital distress and depressive symptomatology is comparable for women and men (O'Leary et al. 1994). However, recent prospective work suggests that poor marital quality is more likely to lead to depression for women than for men (Fincham et al. 1997), which may partly explain why marital quality tends to have greater impact on women's physical health and immunity specifically. Marital dissolution is also strongly associated with increases in depression and depressive symptoms for both men and women (Wade and Pevalin 2004). For example, a large longitudinal study of older adults found a 9-fold increase in major depression and a 4-fold increase in depressive symptoms among the recently bereaved as compared to married individuals (Turvey et al. 1999). A rise in depressive symptoms following bereavement is particularly common among those for whom the loss of spouse was unexpected (Carnalley et al. 1999) and for whom social support is lacking (Wortman et al. 2004).

The association between marital relationships and depressive symptoms has important implications for physical health. Clinical depression is generally associated with immune dysregulation as evidenced by a number of indicators. Importantly, depression can directly increase production of pro-inflammatory cytokines, including IL-2, IL-6 and tumor necrosis factor- α (for a review, see Kiecolt-Glaser and Glaser 2002) which, when chronically elevated, play a pathogenic role in a range of diseases (Kiecolt-Glaser et al. 2003b). In addition to direct physiological alterations, depression affects health indirectly by influencing health-related behaviors, including alcohol use, sleep, diet, and exercise (Kiecolt-Glaser & Glaser, 1988). Depression also affects subjective reports of physical health: After controlling for objective indicators of physical health, those who are depressed tend to report worse perceived current health and greater bodily pain than those who are not depressed (Wells et al. 1989). This may be

a reflection of physical symptoms related to depression and/or cognitive differences in how depressed individuals perceive their health (Pinquart 2001). Given that depression affects a variety of health behaviors, physiology, and subjective experience of health, the association between marriage and depressive symptoms may be a key pathway linking close relationships and health (Kiecolt-Glaser and Newton 2001).

Future Research and Clinical Implications

The institution of marriage and gender roles associated with marriage change over time. Although a majority of U.S. households (52%) are headed by married couples, the number of households headed by couples who cohabit as if married has increased to 5.5 million from 3.2 million in 1990 (Simmons and O'Connell 2003). Of these, over 11% are same-sex couples (Simmons and O'Connell 2003). Both heterosexual and same-sex cohabiting partners represent a largely unstudied population. Data on the mental and physical health effects of cohabitation have been inconsistent. Some studies have found that the self-reported health of cohabitators is greater than that of singles, but not as good as that of married individuals (Joung et al. 1995). Recent data suggests that cohabiting partners share most of the physical and psychological advantages of married people, after controlling for income and age (Wu et al. 2003). Research comparing cohabiters to married individuals may be particularly useful in determining precisely what aspects of close relationships are protective for health and immune functioning.

A growing body of research suggests that psychopharmacological, psychotherapeutic, and behavioral interventions can reduce the impact of stress on immune parameters (Kiecolt-Glaser et al. 2002). The particularly potent effects of marital distress on immune and health outcomes suggest that couple-based interventions targeting relevant aspects of the marital relationship may effectively improve mental and physical health. For example, an intervention

targeting marital communication has been shown to reduce cardiovascular responses during a relationship problem discussion in those with hypertension (Ewart et al. 1984). To our knowledge, no similar evidence is available in terms of the effects of such an intervention on immune parameters.

Another important and related element of couple interventions is the degree to which couples discuss their emotional reactions to stress. Disclosure of emotions is related to better perceived partner responsiveness and, in turn, with couple's feelings of intimacy (Laurenceau et al. 1998). Robust mental and physical effects of written emotional disclosure about stressful events have been found in both clinical and non-clinical populations (Pennebaker 1997; Smyth et al. 1999). Preliminary evidence suggests that changes in immune functioning play a role (Booth and Petrie 2002), while changes in health behaviors do not appear to be relevant (Stone et al. 2000). Although most of these interventions have involved non-directed, journal-type writing, preliminary evidence with chronic pain patients suggests that writing in a directed way about angry feelings specifically can be beneficial in terms of pain severity, control over pain, and depression (Graham et al., 2005b). Treatment group participants in this study expressed anger in letters, which were often addressed to a spouse. Individual variation in response to any intervention focused on interpersonal processes is likely (Kiecolt-Glaser et al. 2002) and needs particular attention before interventions designed around couple interactions should be implemented in practice.

Given the relationship between marital distress, depression, and immune functioning, marital interventions should include measures of depression to determine if depressive symptoms mediate effects of improved marital quality on immune function. The potential role of other variables, such as stress responses and genetics, should also be examined. In addition, it is

noteworthy that there is a lack of research assessing the immune effects of interventions targeting depression directly, with the majority of psychosocial interventions focused on stress reduction. There is also great need for additional research with older populations, who are at greater risk of morbidity and mortality resulting from dysregulated immune functioning (Kiecolt-Glaser et al. 2003b). Finally, to the extent that future interventions are successful, assessing their effects on health longitudinally would also be ideal.

Chronically ill populations are another important direction for future research, both to determine the impact of psychosocial factors on health and to develop meaningful interventions. Although aspects of marriage have been studied in populations with illnesses of particular immunological relevance – such as rheumatoid arthritis, HIV, mouth ulcers, and certain cancers – there is little direct evidence linking those health outcomes to specific immune parameters (Kiecolt-Glaser and Newton 2001). Marital interaction unquestionably alters symptom expression in a number of chronic conditions. For example, men and women reporting lower marital quality evidence increased risk of periodontal disease and dental cavities (Marcenes and Sheiham 1996). Similarly, large prospective epidemiological studies have implicated marital strain as a factor in the development of ulcers (e.g., Levenstein et al. 1999). Thus far, most studies of health populations have not included direct measures of endocrine and/or immune functioning, which would allow for clearer delineation of mediating factors. However, this direction is promising. For example, interpersonal stress has been linked to both endocrine and immune alterations among those with rheumatoid arthritis, changes which were associated with clinician-rated disease activity as well as self-reported joint tenderness in well-designed prospective studies (Waltz et al. 1998). Similarly, preliminary work indicates that psychological stress predicts NK cell lysis and NK response to cytokine stimulation among cancer patients

(Andersen et al. 1998); however, this is only one avenue by which the immune system defends against malignancy and research employing other measures will be valuable.

In addition to studies with clinical populations, further evidence of the clinical relevance of immune alterations will be helpful in understanding the full impact of marital stress. There is a particular need for longitudinal studies demonstrating that immune dysregulation observed during partner conflict is predictive of morbidity and mortality in the long-term. Within short-term research designs, the utilization of outcomes with clear clinical relevance will strengthen our ability to interpret immunological changes. Wound-healing is one such outcome. Recent work from our laboratory on the effects of marital interactions has assessed healing of experimentally induced wounds. Couples who demonstrated consistently higher levels of hostile behavior during across both conflictive and supportive interactions healed wounds at 60% of the rate of low hostile couples (Kiecolt-Glaser et al. 2005). Use of such methodologies provides clinically relevant data over a relatively short period of time.

Finally, another important area for future research on the association between marital factors and immune functioning is positive and supportive aspects of relationships (Robles and Kiecolt-Glaser 2003). Although research to date suggests that hostile and negative behavior is more toxic to health than supportive behaviors are beneficial or protective (Kiecolt-Glaser and Newton 2001), the effects of positive marital interactions may be underestimated because the methods used in most research may promote negativity (e.g., by focusing on conflict discussions) and limit opportunities for couples to display supportive behavior. One important question will be whether the impact of conflict behaviors is buffered in typically supportive marriages, and exacerbated in those where support is low (Bradbury et al. 1998). Positive support provided by close relationships is associated with more adaptive immune function (Uchino et al. 1996), often

apparently by buffering the effects of stress (for a review see Graham et al. 2005a). In addition, there are other well-validated and important measures of marital quality, such as partner closeness, that are assessed with pictorial diagrams and unobtrusive reaction time tests (Aron et al. 1992). The health impact of such measures has not been studied at all, to our knowledge, and will make a valuable addition to our understanding of close relationships, immunity, and health.

Conclusion

The evidence reviewed suggests that immune functioning plays an important role in the association between marital factors and health. Both the state of being married and marital satisfaction are associated with adaptive immune responses and better overall health, while marital disruption and hostile marital interactions are associated with dysregulation of immune functioning based on a range of markers. While there are many processes at work, which are frequently bi-directional, stress appears to play a significant role in accounting for these associations; for example, it is likely that being happily married buffers the effects of life stress, especially for men, while marital conflict is itself a powerful psychosocial stressor, especially for women. Marital conflict appears to be particularly toxic in terms of immune functioning for those who tend to have frequent and intense hostile reactions to stress. In addition, changes in depression may help account for the association between marital factors and health: as described earlier, marriage, marital disruption, and marital conflict are strongly associated with depressive symptomatology, which is also associated with the dysregulation of immune functioning both directly via physiological mechanisms and indirectly via health behaviors. Even as societal patterns of marriage change, key partnerships with close others remain and retain the power to affect us negatively as well as positively. In developing the next edition of the DSM, additional consideration of relational risk factors and disorders is warranted. Moreover, greater

understanding of the scope, mediating factors, and impact of marriage and close partnerships on health and immunity will be essential as we strive to develop targeted interventions to improve both psychological and physical well-being.

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