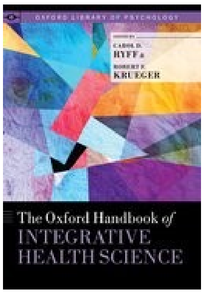

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CHAPTER

17 Psychosocial Life Histories and Biological Pathways to Bone Health

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Abstract

Low-trauma fractures of the hip and spine are a major cause of morbidity, disability, and early mortality in older Americans. The ability to resist fractures in later life is determined by accrual of bone mass during the growing years, its maintenance in adulthood, and rates of decline in older ages. Psychosocial and biological factors in each of these life stages can influence the risk of osteoporosis in later life. This chapter summarizes findings from The Study of Midlife in the United States (MIDUS) on associations of life-course socioeconomic conditions, social relationship histories, and psychological profiles with adult bone health. It then presents MIDUS evidence of links between physiological dysregulation and low bone strength and concludes with a description of research needed to infer and explicate the potentially causal roles for life-course psychosocial profiles in adult bone health and osteoporosis.

Keywords: bone strength, low-trauma fracture, bone mass, osteoporosis, MIDUS, psychosocial histories, bone health, bone mineral density, bone turnover, physiological dysregulation

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Introduction

Osteoporosis, defined as compromised bone strength predisposing to increased risk of low-trauma fracture, also referred to as fragility fracture (NIH Consensus Development Program, 2000), affects more than 10 million Americans aged 50 years or older (Wright et al., 2014) and has a large public health impact worldwide (Cummings & Melton, 2002; World Health Organization, 2003a). Among postmenopausal women, one in two will have an osteoporosis-related low-trauma fracture in her lifetime, as will approximately one in five older men (US Preventive Services Task Force, 2011), resulting in fragility fractures that occur every 3 seconds worldwide. A fracture that results from a fall from standing height, such as while walking at usual speed, turning, reaching, or bending, counts as a low-trauma or fragility fracture and is diagnostic of osteoporosis. Low-trauma fractures, especially of the hip and spine, are a major cause of morbidity, physical disability, and early mortality in older Americans (Quah, Boulton, & Moran, 2011), and their economic impact is projected to increase worldwide in the coming decades as the world's population ages (Burge et al., 2007; Cheng et al., 2011; Harvey, Dennison, & Cooper, 2010). In 2005, in the United States 2 million osteoporotic fractures occurred, resulting in expenditure of $17 billion, with men accounting for a quarter of these costs. It is anticipated that by the year 2020, there will be 20 million men and 41 million women in the United States with osteoporosis or osteopenia (i.e., low bone mineral density [BMD]), and that fracture-related costs will rise 50% by the year 2025 (Burge et al., 2007; National Osteoporosis Foundation, 2002).

In addition to the graying of the population, individual exposures to social and psychological stresses in daily life have been rising steadily due to changing economies, declining real wages, work–family tensions, terrorism, frequent wars, and more recently the Great Recession (Ayers et al., 2012; p. 238 ↳ Glenn, Mitcheson, & Coleman, 2010; Holman & Silver, 2011; Levy & Sidel, 2013). Increasing migration into and within the United States also means smaller social support systems to help buffer the effects of life stresses (Miller McPherson, 2006). Adverse social and psychological environments, which have well-documented and strong links to a variety of health outcomes (House, Landis, & Umberson, 1988; Kubzansky & Kawachi, 2000; Pamuk, Makuc, Heck, Reuben, & Lochner, 1998), are not surprisingly also associated with increased fracture risk in older men and women (Bacon & Hadden, 2000; Farahmand et al., 2000; Forsen et al., 1999; Mussolino, 2005; Quah et al., 2011). Socioeconomic disadvantage, mental distress, and stressful life events have all been linked to increased fracture risk (Bacon & Hadden, 2000; Benetou et al., 2015; Farahmand et al., 2000; Fink, Kuskowski, & Marshall, 2014; Forsen et al., 1999; Mussolino, 2005; Quah et al., 2011).

We start this chapter with a discussion of the two major issues that are key to gaining insight into how the psychosocial environment might influence bone health and fracture risk: the need to adopt a psychosocial life history approach and the importance of going beyond measures of bone mass to gauge bone strength. Subsequently, the chapter describes new findings from the Midlife in the United States (MIDUS) study on the influences of various aspects of psychosocial life profiles and potential biological pathways on comprehensively assessed adult bone strength, placing the findings in the context of the current literature. We close with a discussion of possible future directions of inquiry to enrich further our understanding of factors that shape bone health in older ages.

Background

Although associations have been documented between the psychosocial environment of an older adult and his or her risk of fracture, until recently there was little evidence of links between psychosocial factors and low bone strength, the major reason for low-trauma fracture (Brennan et al., 2011; Lauderdale & Rathouz, 2003; Pearce et al., 2005; Varenna et al., 1999; Wang & Dixon, 2006). This suggests that social and economic factors might affect fracture risk through pathways not involving bone strength, such as increased body weight, which increases the impact forces in a fall, and disorders of gait and balance, which increase the likelihood of a fall. Furthermore, our understanding of the processes underlying the mind–bone connection had been hampered by the inconsistency of evidence of psychosocial influences on bone strength. For instance, low BMD is the major bone-related risk factor for fracture (Cummings et al., 1995), yet studies showed that men from low socioeconomic status (SES) groups have higher BMD in both the femoral neck and the lumbar spine than men from high SES groups (Elliot, Gilchrist, & Wells, 1996), and women from disadvantaged minority communities have higher BMD than their Caucasian counterparts (Araujo et al., 2007; Bachrach, Hastie, Wang, Narasimhan, & Marcus, 1999; Barrett-Connor et al., 2005; Cauley et al., 2005, 2007; Finkelstein et al., 2002).

There are several reasons for this inconsistency. For one, bone strength in later life depends critically on peak bone strength achieved in young adulthood (Cooper et al., 2006); thus, the psychosocial environment in younger years is likely to be as important, if not more important, than the late life psychosocial environment in influencing bone strength in older ages (when the risk of low-trauma fracture is highest). Yet, few studies had examined psychosocial influences in childhood and young adulthood on adult bone strength, and none examined the role of accumulated adversity over the life span and consistent psychosocial well-being on bone strength. Second, aspects of psychological well-being, such as positive affect, life satisfaction, and personal mastery, which have strong links with other physical health outcomes (Ostir, Markides, Black, & Goodwin, 2000), are likely also to positively influence bone strength. However, most previous studies focused on the influences of psychological ill-being, mainly depression and anxiety, while bone strength links with psychological well-being remained largely unexplored.

Third, BMD is a strong predictor of osteoporotic fracture risk, but it is only one of many bone-related factors that contribute to bone strength; most fractures occur in people who do not meet BMD criteria for osteoporosis (Marshall, Johnell, & Wedel, 1996; Siris et al., 2004). Factors such as bone size relative to body size and the dynamics of bone remodeling play a large role in determining bone strength and future fracture risk (Allolio, 1999; Sklarin, Arnaud, Genant, & Stone, 1996), and their associations with psychological and social factors has not been established. Data from MIDUS have been and continue to be used to fill some of these gaps in our understanding of the importance of psychosocial factors in the development of osteoporosis.

Life History May Be More Important Than Current Conditions

Psychosocial influences typically play out over the long term, and their impact on adult health and mortality is cumulative over years of exposure (Alwin & Wray, 2005; Barker & Osmond, 1986; Elo & Preston, 1992; Hatch, 2005; Wadsworth & Kuh, 1997). Cumulative psychosocial histories are also expected on bone health because bone strength in older ages (when the risk of fractures is highest) depends on bone mass accrual during childhood and young adulthood as well as the maintenance of bone mass during middle adulthood and bone loss in older adulthood (Hansen, Overgaard, Riis, & Christiansen, 1991; Janz, 2002). Empirical studies suggest that bone strength in older ages depends equally on peak bone strength achieved and maintained in young and middle adulthood and the rate of decline in bone strength in later years (Riis, Hansen, Jensen, Overgaard, & Christiansen, 1996). Psychosocial factors at each of these life stages are likely to leave their mark on bone strength, both directly and through influences on lifestyle choices. Childhood diet, physical activity, and smoking have each been linked to peak bone mass achieved (Janz, 2002; Javaid & Cooper, 2002; Stager, Harvey, Secic, Camlin-Shingler, & Cromer, 2006) and to BMD in later life (Rikkonen, Tuppurainen, Kroger, Jurvelin, & Honkanen, 2006), as has physical activity in young adulthood (Neville et al., 2002). These behavior choices are influenced by social and psychological factors operating at those life stages.

The richness of psychosocial assessments at various life stages in MIDUS provides an exciting opportunity to bring a life course perspective to the role of the psychosocial environment on adult bone health.

Bone Size and Bone Turnover Also Affect Bone Strength

Although BMD is the strongest predictor of fracture risk, several other factors play important roles, so much so that the majority of hip fractures occur in people who do not meet BMD criteria for osteoporosis (Marshall et al., 1996; Siris et al., 2004), and fracture rate differences between demographic groups are not consistent with BMD differences (P. D. Ross et al., 1991). It is apparent that BMD on its own does not adequately reflect bone strength and capture fracture risk. Analogous to the strength of engineering structures, the structural strength of bone depends not only on material density (i.e., BMD), but also on bone size and thickness (Gluer et al., 1994; Martin, 1993). Moreover, with respect to fracture risk, absolute structural strength is not as important as strength relative to the size of the load: Structures exposed to larger loads need to be stronger than structures exposed to less heavy loads. In humans, the load that bone is exposed to (during impact from a simple fall from standing height) depends on both body height and body weight (Hayes et al., 1993; Robinovitch, Hayes, & McMahon, 1991). Not surprisingly, both bone size and body size play important roles in hip fracture risk, independent of BMD (Allolio, 1999).

We have developed and validated composite indices of femoral neck strength that incorporate bone size, body size, and BMD, which can be constructed from routine Dual-energy X-ray Absorptiometry (DXA) scans of the hip (Karlamangla, Barrett-Connor, Young, & Greendale, 2004). The composite strength indices are negatively correlated with hip fracture risk in older women, and their size components (bone size relative to body size) provide fracture prediction information that is independent of BMD (Karlamangla, Barrett-Connor, et al., 2004). These strength indices may also explain the BMD–fracture discrepancy between ethnic groups. For instance, Japanese women have lower hip fracture rates than Caucasian women, despite having lower BMD (P. D. Ross et al., 1991); a comparison of their composite strength indices reveals that the strength indices are 0.64 to 0.66 standard deviations *higher* in Japanese women than in Caucasian women (Ishii, Cauley, et al., 2012).

Few studies have examined how bone size and bone structural strength indices change over time as adults age and how they are influenced by psychosocial factors. One recent longitudinal study found that bone size increases with age in postmenopausal women, possibly to compensate for declines in BMD (Ahlborg, Johnell, Turner, Rannevik, & Karlsson, 2003). We found that even though BMD decreases in postmenopausal women over time, composite strength indices decline much less slowly or remain stable over 3–4 years of follow-up because of compensatory increases in bone size (Karlamangla, Black, et al., 2004). These findings demonstrate the importance of looking beyond BMD to assess bone strength and changes in bone strength over time.

While BMD and bone composite strength indices reflect current bone strength, biochemical markers of bone turnover assess ongoing change in bone strength (Christiansen, Riis, & Rodbro, 1987). Bone is a dynamic tissue that is constantly p. 240 ↳ being broken down and re-formed (i.e., remodeled) throughout life. Bone remodeling or turnover occurs via the coupled processes of bone resorption (by osteoclast cells) and bone formation (by osteoblast cells) (World Health Organization, 2003b). When formation exceeds resorption, there is net increase in bone mass and bone strength, but if resorption exceeds formation, then there is net loss of bone mass and consequent reduction in bone strength (Looker et al., 2000).

In older adults, loss of bone mass results from an excess of resorption over formation; as such, higher levels of turnover markers reflect greater ongoing declines in bone mass and strength (Dresner-Pollak et al., 1996) and predict greater fracture risk, independent of current BMD (Delmas, Eastell, Garnero, Seibel, & Stepan, 2000; Garnero, 2000; Gerdhem et al., 2004; Sornay-Rendu, Munoz, Garnero, Duboeuf, & Delmas, 2005). However, because bone formation is coupled to bone resorption, both resorption and formation markers are elevated in individuals losing bone, both old (Dresner-Pollak et al., 1996) and young (Kahl et al., 2005). The two markers are also increased in individuals who are laying down net new bone and increasing their bone strength, such as growing children (Szulc, Seeman, & Delmas, 2000); young women with anorexia nervosa on a nutritional rehabilitation program (Viapiana et al., 2007); and older men receiving strength training (Sartorio et al., 2001). Thus, the level of formation markers alone, or resorption markers alone, does not reflect the direction of ongoing change in bone mass.

Bone metabolic balance indices, on the other hand, which combine formation and resorption markers to reflect the excess of formation over resorption, can and have been used to assess the direction and magnitude of ongoing change in bone mass (Eastell et al., 1993; Prouteau, Pelle, Collomp, Benhamou, & Courteix, 2006; Sartorio et al., 2001; Satoh, Soeda, & Dokou, 1995; Takahashi, Naitou, Ohishi, & Nagano, 2003; Whipple et al., 2004). Thus, bone composite strength indices and bone metabolic balance indices provide a more complete assessment of current and future bone strength and fracture risk than does a single snapshot of BMD. Prior to MIDUS, no studies had examined psychosocial life history associations with either composite strength indices or bone metabolic balance indices.

New Evidence From MIDUS

Psychosocial Life Histories and Adult Bone Strength

Our conceptual model of the pathways from psychosocial life history to bone strength goes through regulatory physiology, lifestyle choices, and medications to affect the metabolic balance between bone resorption and formation and thus to bone strength. As indicated in Figure 17.1, these factors also affect gait and balance and the risk of falls, which combine with bone strength to determine fracture risk. For simplicity of presentation, Figure 17.1 shows only the effects of psychosocial stressors. Positive psychosocial advantage is postulated to work along the same pathways, but leads to opposite effects: better health behaviors, well-regulated physiology, positive bone balance (in favor of bone formation over resorption), enhanced bone strength, and fewer fractures. While effects on metabolic bone balance are expected to be from concurrent psychosocial and health behavior states, effects on bone strength (and thus, on fracture risk) are expected to be cumulative over time.

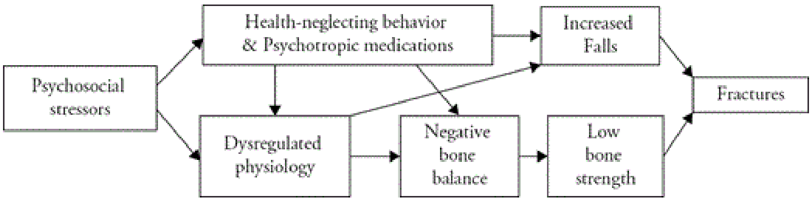

Figure 17.1 Conceptual model of pathways from psychosocial adversity to bone strength.

In this section, we summarize findings from MIDUS on associations of life course socioeconomic conditions, social relationship histories, and psychological profiles with adult bone health measures, BMD, markers of bone turnover, and composite indices of bone strength and place these findings in the context of the current literature.

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Socioeconomic Histories and Adult Bone Strength

Several prospective cohort and population-based studies have demonstrated that fracture incidence in older adults is inversely associated with current SES, and this association is seen with different measures of SES, including education level, income, housing type (one-family home vs. apartment), and employment status (Bacon & Hadden, 2000; Crandall et al., 2014; Farahmand et al., 2000; Wilson, Chase, Chrischilles, & Wallace, 2006; Zingmond, Soohoo, & Silverman, 2006). However, the longest duration of follow-up in these studies was 5 years, and at least one case–control study failed to find an association between education level and hip fracture risk (Vestergaard, Rejnmark, & Mosekilde, 2006). In direct contradiction to the SES–fracture associations seen in these studies, men from lower SES groups had higher BMD in both the femoral neck and lumbar spine than men from higher SES groups in one study (even after adjusting for manual labor) (Elliot et al., 1996). Mexican American women with lower income also had higher BMD than women from high-income groups in a second study (Lauderdale & Rathouz, 2003). However, other cross-sectional studies have found the expected positive association between SES and BMD (Gur, Sarac Aşü, Nas, & Cevik, 2004; Lim et al., 2005; Varenna et al., 1999; Wang & Dixon, 2006), although these associations appear to be stronger in Caucasians than in minority communities (Gur et al., 2004; Lauderdale & Rathouz, 2003).

Almost all of these studies have been in older women at risk for osteoporotic fractures. A few studies have examined SES–BMD relationships in younger groups; one in Lebanese children and one in schoolgirls from Delhi, India, found that children from higher SES families had higher BMD (Arabi et al., 2004; Marwaha et al., 2007), and one in Spain found the largest SES differences in BMD by age were in 20- to 39-year-olds (del Rio Barquero et al., 1992).

Using data from MIDUS, we demonstrated that socioeconomic advantage in childhood and higher level of adult education were independently associated with greater adult BMD in the lumbar spine (Crandall, Merkin, et al., 2012). Further, in non-Hispanic white men, childhood socioeconomic advantage was also associated with higher composite indices of femoral neck strength relative to load (Karlamangla et al., 2013), thus demonstrating links with both cortical bone (in the femoral neck) and trabecular bone (in the lumbar spine). In 729 participants (mean age 57 years, range 34–85 years) from the MIDUS biomarker project, after adjusting for numerous covariates (age, menopausal transition stage, race, gender, body weight, smoking, physical activity in three life stages [high school, young adulthood, and at time of BMD measurement], and clinical site), BMD in the lumbar spine was 0.27 standard deviations (*SD*) higher at the 90th compared to the 10th percentile of the childhood socioeconomic advantage score, composed from parental education, self-rated financial status relative to others, and not being on welfare ($p = .009$), and 0.24 *SD* higher in college graduates compared to participants without college education ($p = .01$). Neither childhood advantage nor adult education level was associated significantly with BMD in the femoral neck (Crandall, Merkin, et al., 2012).

Although BMD in the femoral neck is the more important determinant of hip fracture risk (than lumbar spine BMD), as discussed previously, it is not the only driver of femoral neck bone strength, and bone size and body size also play important roles in determining the risk of hip fracture. Since psychosocial adversities have been linked to increased body weight, it is important to examine the relationship between life histories of adversity and comprehensively assessed bone strength that incorporates body size and bone size in addition to BMD. In the MIDUS sample, childhood socioeconomic advantage was, indeed, associated positively with all three composite indices of femoral neck strength in non-Hispanic white men but not in the other three race/gender groups: In white men, for every *SD* increment of childhood advantage score, femoral neck composite strength indices increased by 0.18 *SD* to 0.26 *SD* (*p* values .0009 to .04) (Karlamangla et al., 2013).

In contrast to childhood socioeconomic advantage and adult education, adult current financial advantage (composed from family-adjusted poverty-to-income ratio, self-assessed current financial situation, having enough money to meet needs, and ease in paying bills) was *not* associated with either lumbar spine or femoral neck BMD. However, although not associated with BMD, current financial adversity was significantly associated with increased bone turnover in men (Crandall, Miller-Martinez, et al., 2012). Increased bone turnover, which is an indicator of ongoing loss of bone mass and bone strength, was also seen in minority race women compared to white women (Crandall, Miller-Martinez, et al., 2012), consistent
p. 242 with the hypothesis that social stresses negatively affect bone ↳ metabolic balance (between resorption and formation), which over time would lead to lower bone strength later in life. The size of the associations of financial adversity with increased turnover was substantial and comparable in magnitude to the effects of many osteoporosis medications (Crandall, Miller-Martinez, et al., 2012).

In summary, these findings from MIDUS demonstrate the importance of taking a life course approach, with cumulative effects of earlier socioeconomic conditions seen on current bone strength and effects of current adversity primarily seen on current bone metabolic balance, which, if sustained, would be expected to affect bone strength in the future. They also highlight the need to look comprehensively at bone strength and not focus exclusively on bone mass or density since psychosocial and even behavioral factors may influence bone mass and body size in different directions.

Social Relationship Histories and Adult Bone Strength

Prior to MIDUS, there had been no studies of the direct links between the number or quality of social relationships and bone strength. However, social integration or support has modest links to greater physical activity/exercise (Cohen, Gottlieb, & Underwood, 2000), and life histories of physical activity /exercise are associated with increased BMD, bone size, and bone strength indices (Faulkner et al., 2003; Forwood et al., 2006; Janz et al., 2007), suggesting at least one pathway by which social relationships over the life course could influence adult bone strength.

The MIDUS data confirmed that childhood in single-parent families is, indeed, linked to lower adult bone strength relative to load, even after controlling for childhood and adult socioeconomic circumstances and health behaviors: Indices of femoral neck strength relative to load were 0.25 to 0.40 *SD* lower per each additional year in a single-parent household ($p < .05$) (Crandall et al., 2015). Previous studies have shown that each *SD* increment in the femoral neck composite strength indices was associated with 34–41% relative decrement in the rate of fracture in women going through the menopausal transition (Ishii, Greendale, et al., 2012) and 57–66% relative decrement in the risk of hip fracture over 10 years in postmenopausal women (Karlamangla, Barrett-Connor, et al., 2004). The differences in composite strength indices observed in MIDUS between single-parent and two-parent childhoods would therefore imply that women who experience 9 or more years of single parenting in childhood will be at 14–19% relative increase in fracture rate when going through the menopausal transition and 31–41% relative increase in 10-year hip fracture risk after menopause. Since in 2012 only 64% of American children resided with both parents (Federal Interagency Forum on Child and Family Statistics, 2013), these findings carry important implications for the bone health of future cohorts of adults.

Adult marital histories and marital quality were also related to bone health in the MIDUS cohort. Spine BMD was lower in men who reported getting married early and in men who reported one or more marital breakups, compared to men who reported neither. Compared to stably married men, men who had experienced marital disruptions had 0.62–0.66 *SD* lower BMD in the lumbar spine ($p < .05$), and men who had never married had 0.47 *SD* lower spine BMD ($p < .01$). Among men married at least once, every year decrement in age at first marriage (if first married under age 25) was associated with 0.07 *SD* decrement in lumbar spine BMD ($p < .05$) (Miller-Martinez et al., 2014).

While marital trajectories were less consequential to women's bone health, women who said their spouses/partners were supportive had higher BMD than women who reported less support from their spouses. In women who were married at least once, adjusted for support from other sources (friends and other family members), each point increase in spouse support (on a 4-point rating scale) was associated with 0.35 *SD* higher lumbar spine BMD ($p < .01$). These gender differences in the bone health implications of marital life histories and marital quality are consistent with prior evidence that marriage is associated with better physical health, but more so in men than in women. In addition, for women, the quality of the marriage is more important to health than just being married because unhappily married women suffer more distress than those never married (C. E. Ross, Mirowsky, & Goldsteen, 1990).

These findings from MIDUS again highlight the need to adopt a life course approach to psychosocial exposures and to focus not exclusively on bone mass when assessing bone strength and the risk of fragility fracture.

Psychological Well-Being Can Positively Influence Bone Health

p. 243 Good psychological health (such as positive affect, life satisfaction, personal mastery, and ↳ strong self-efficacy belief) and social resources (such as a supportive environment) are associated with reduced risks for a variety of physical health outcomes, including hypertension (Ostir, Berges, Markides, & Ottenbacher, 2006); diabetes mellitus (Norberg et al., 2007); cardiovascular disease (Ostir, Markides, Peek, & Goodwin, 2001); functional decline (Bassuk, Glass, & Berkman, 1999; Ostir et al., 2000; Seeman, 1996); and mortality (Koivumaa-Honkanen et al., 2000; Pressman & Cohen, 2005; Seeman et al., 1993; Seeman, Kaplan, Knudsen, Cohen, & Guralnik, 1987). Psychological and social well-being are also linked to better neuroendocrine and inflammatory profiles (Friedman, Hayney, Love, Singer, & Ryff, 2007; Friedman et al., 2005; Seeman & McEwen, 1996; Steptoe, Wardle, & Marmot, 2005), which in turn are associated with better bone health (Cauley et al., 2007; Greendale, Unger, Rowe, & Seeman, 1999). Psychological and social well-being at different points of the life course could therefore have positive influences on bone strength and counteract negative influences from psychosocial adversity at other times, yet the associations between positive well-being and bone strength have not been adequately examined. Previous studies of psychological influences on bone have instead focused on psychological ill-health, especially depression and anxiety.

Several studies have found links between psychological ill-health and fracture risk. Depression is associated with increased fracture risk (Mussolino, 2005; Sogaard et al., 2005; Whooley et al., 1999), as are anxiety disorder and use of anxiolytics (Colon-Emeric, Biggs, Schenck, & Lyles, 2003). Mental distress, based on self-reported life dissatisfaction, nervousness, loneliness, sleep disorder, troubled and uneasy feelings, depression, and impairment attributable to psychological constraints, was prospectively associated with increased fracture risk over 3 years of follow-up in women 50 years or older (Forsen et al., 1999).

The relationship of psychological health with BMD, however, is not as clear. While several studies have found that that both past and current depression are associated with low BMD (Furlan et al., 2005; Michelson et al., 1996; Robbins, Hirsch, Whitmer, Cauley, & Harris, 2001; Schweiger et al., 1994; Wong et al., 2005) and greater longitudinal decline in BMD (Coelho, Silva, Maia, Prata, & Barros, 1999; Diem et al., 2013; Schweiger, Weber, Deuschle, & Heuser, 2000), other large studies have found that the association is either not present (Reginster, Deroisy, Paul, Hansenne, & Ansseau, 1999; Sogaard et al., 2005; Whooley, Cauley, Zmuda, Haney, & Glynn, 2004; Whooley et al., 1999) or present only in young men and not in young women (Mussolino, Jonas, & Looker, 2004). Again, these findings may have been confounded by differences in body weight: Depression is associated with higher body weight, and heavier people need greater bone density to avoid fractures.

Not surprisingly, one cross-sectional study in perimenopausal Australian women found no BMD–depression association before adjusting for body weight, but depressed women had lower BMD *after* adjusting for body weight (Jacka et al., 2005). However, controlling for body weight may not be appropriate because body weight is not only a confounder but also a mediator of the link to bone health, as increased body weight can stimulate increases in bone mass by increasing skeletal loading (Ehrlich & Lanyon, 2002). Composite strength indices that combine bone size relative to body size (height and weight) with BMD directly account for both weight-related concerns (the causal link from body weight to bone mass and the need for greater bone mass to protect against greater impact forces in heavier individuals), but prior to MIDUS no studies had looked at the links between psychological health and bone size or strength indices.

On the positive psychology side, there is a general paucity of data on links between psychosocial well-being and bone health. One case–control study found life satisfaction was strongly associated with reduced fracture risk (Peel, McClure, & Hendrikz, 2007), and we have shown that high-functioning, community-living, older adults who score higher on a happiness measure had a lower risk of incident fractures over 7 years of follow-up (Karlamangla, Greendale, Singer, & Seeman, 2003). On the other hand, one small study in 102 Portuguese white women found no association between low BMD and the psychological general well-being index (Coelho et al., 1999). However, relationships between psychological well-being and bone strength may be masked in a study of well-being's relationship with BMD because of the importance of bone size and body size in assessing bone strength. No studies prior to MIDUS had examined bone size or bone strength indices in relationship with indices of psychological well-being.

The MIDUS data did indeed show, for the first time ever, that multiple domains of psychological well-being
p. 244 (positive affect, positive relationships, self-acceptance, and purpose in life) are positively ↳ associated with greater lumbar spine BMD and greater femoral neck bone strength, as assessed by composite indices that combine femoral neck BMD, femoral neck size, and body size (Karlamangla et al., 2012).

In sum, this body of new data from MIDUS on psychosocial factors and bone health demonstrate the importance of taking a life history approach to understanding the impact of the psychosocial environment on bone health, and the need to go beyond simple assessments of bone mass in order to gauge bone strength.

The Role of Physiological Dysregulation in Bone Fragility

The physiological systems that are affected by psychosocial stresses are also implicated in osteoporosis; hence, several authors have suggested that dysregulation of these systems likely represents the major biological pathways by which psychosocial stresses affect bone strength (Ilias, Alesci, Gold, & Chrousos, 2006; Mezuk, Eaton, & Golden, 2008). Studies in both animal models and humans supported this contention. In mice, bone loss triggered by chronic mild stress was associated with substantial increase in bone norepinephrine levels (Yirmiya et al., 2006), suggesting a role for the sympathetic system in the stress–bone connection. In one small cross-sectional study, depressed women (compared to nondepressed women) showed smaller increases in salivary cortisol during the anticipation period before a standardized laboratory challenge, consistent with burnout, and the anticipatory changes in cortisol explained 51–67% of the depression–BMD association (Furlan et al., 2005).

In this section, we discuss MIDUS evidence of links between physiological dysregulation and low bone strength.

Glucose Dysregulation and Bone Strength

Diabetics have repeatedly shown higher BMD than nondiabetics, which is in contrast to the increased fracture rates in diabetics (De Liefde et al., 2005; Vestergaard, 2007). MIDUS data demonstrated that femoral neck strength relative to load is actually lower in diabetic women than in nondiabetic women, and that there is a strong dose response between high insulin resistance and low bone strength. That is, adjusted for age, gender, race/ethnicity, menopausal transition stage (in women), and study site, every doubling of the insulin resistance measure, HOMA-IR (homeostatic model assessment for insulin resistance), was associated with 0.34- to 0.40-*SD* decrement in the femoral neck composite strength indices ($p < .001$). This finding is in sharp contrast to the association between insulin resistance and BMD: Consistent with prior evidence of higher BMD in diabetics compared to nondiabetics, BMD in the femoral neck increased with increases in HOMA-IR (Srikanthan et al., 2014). This MIDUS finding of an inverse association between insulin resistance and bone strength, in contrast to the oft-demonstrated positive association between diabetes and BMD, helps explain, at least partly, the diabetes–fracture paradox of increased fracture risk in diabetics despite their increased BMD.

The Role of Multisystem Dysregulation

It is unlikely that physiological systems act in isolation and more likely that multiple systems are simultaneously affected by psychosocial factors and crosstalk (Besedovsky & del Rey, 1996; Maes et al., 1998; Maier, 2003; McEwen, 2000) and jointly influence bone strength. The effects of co-dysregulation of multiple systems may exceed the sum of their individual effects. Synergistic effects between physiological systems is seen in the development of other physical health outcomes; for instance, the co-occurrence of diabetes and hypertension has also been associated with significantly greater atrophy of the cerebral cortex (Schmidt et al., 2004). Dysregulation in multiple systems of the stress response network, or allostatic load, has been shown to predict a variety of adverse health outcomes (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997) but had not been examined with respect to bone health. For the first time, MIDUS data showed that allostatic load is in fact associated with low BMD and low bone strength relative to load. Adjusted for age, gender, race/ethnicity, body mass index, menopausal transition stage, childhood SES, adult finances, education level, and study site, each *SD* increment in allostatic load score was associated with between 0.10- and 0.11-*SD* decrements in lumbar spine BMD and each of the three indices of femoral neck composite strength (all p values < .05) (Mori et al., 2014), adding to the accumulating evidence that multiple physiological systems play a role in mediating the link between the psychosocial environment and health.

Conclusion and Future Directions

p. 245 Osteoporosis-related fractures are a growing public health burden with huge economic costs ↳ and substantial morbidity in older adults. Their behavioral risk factors were well described, but little was known about the role of the psychosocial environment in the development of osteoporosis. Capitalizing on repeated assessments of rich socioeconomic, behavioral, and psychosocial predictor data in MIDUS, we presented evidence that psychosocial life histories are tightly linked to osteoporosis risk and on the importance of psychological well-being to offset these risks.

Much work remains to be done, including (a) determining the role of current stressors in longitudinal declines in bone strength; (b) establishing causality in the associations of psychosocial histories with adult bone strength; (c) quantifying the role of health behaviors as mediators and moderators of psychosocial factors; (d) delineating nonbone pathways from psychosocial life histories to low-trauma fracture (e.g., muscle strength, gait, and balance, which affect the risk of falling and the ability to reduce the impact of a fall); and (e) identifying resilience factors that buffer the impact of life stresses on bone health and, ultimately, fracture risk. The rich MIDUS data on several psychosocial domains, coping behaviors, and health behaviors, repeated over multiple waves of data collection and from multiple life stages, lend themselves well to addressing many, if not most, of these issues. The third wave of MIDUS, for instance, includes, in addition to repeat measurements of bone turnover, bone density and bone strength indices; measurement of muscle mass by DXA and bioelectrical impedance; innovative objective assessments of balance and gait, of bone microarchitecture integrity by trabecular bone score, and of vertebral fractures (compression deformities) by vertebral morphometry, which can all be leveraged in future work to answer these open questions.

Although causality in the MIDUS-documented associations needs to be confirmed, the findings described in this chapter provide initial evidence for the importance of assessing psychosocial life histories. Patients and providers benefit from recognizing that a range of psychosocial vulnerabilities over the life course are associated with low bone strength and increased risk of low-trauma fracture in older ages. Motivated by the evidence from MIDUS for bone health consequences of life stresses in childhood and young adulthood and by the twenty-first-century realities of economic inequities and population upheavals, osteoporosis researchers and public health officials need to urgently develop and test interventions that ameliorate the deleterious effects of life stresses.

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