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CHAPTER

16 Biopsychosocial Patterning of Multimorbidity and Its Consequences

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Abstract

By many estimates the majority of adults over age 65 have two or more chronic medical conditions (multimorbidity) and are consequently at increased risk of adverse functional outcomes. Nonetheless, many older adults with multimorbidity are able to maintain high levels of function and retain good quality of life. Research presented here is designed to understand the influences that help ensure better functional outcomes in these older adults. This chapter presents findings that draw on data from the Midlife in the United States study. The independent and interactive contributions of diverse factors to multimorbidity and changes in multimorbidity over time are reviewed. The degree that multimorbidity increases risk of cognitive impairment and disability is examined. The role of inflammation as a mediator is considered. Multimorbidity is increasingly the norm for older adults, so better understanding of factors contributing to variability in multimorbidity-related outcomes can lead to improved quality of life.

Keywords: [multimorbidity](#), [older adults](#), [MIDUS study](#), [cognitive impairment](#), [cognitive disability](#), [inflammation](#), [chronic disease](#), [health](#)

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Introduction

This chapter reviews our ongoing work on the ways in which social, psychological, and biological processes affect multimorbidity and related adverse outcomes. We begin with a consideration of empirical and theoretical material that informs the research followed by a brief discussion of earlier work that laid the foundation for this line of inquiry. We then discuss a series of studies using Midlife in the United States (MIDUS) data that examine (a) diverse factors that are associated with risk for multimorbidity and (b) adverse outcomes related to multimorbidity, notably disability, cognitive impairment, and mortality, as well as the extent to which these outcomes are mitigated by psychosocial resources and mediated by a health-related biological factor, inflammation. Finally, we consider a number of themes that have emerged from this work and ways in which we plan to pursue them in the future.

Overview and Conceptual Framework

Marked gains in life expectancy over the course of the last century mean that the average person in the United States now lives long enough to be diagnosed with at least one chronic medical condition, and the majority of adults over age 65 have two or more (multimorbidity; Agborsangaya, Lau, Lahtinen, Cooke, & Johnson, 2012; Anderson & Horvath, 2004; Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005). Multimorbidity is thus the norm for older adults, the fastest growing segment of the population. The bulk of research on multimorbidity focuses on the substantial challenges it presents for optimal coordination of patient care (Wolff, Starfield, & Anderson, 2002), especially given the prevailing single-disease focus of the US healthcare system (Institute of Medicine, 2012; Parekh & Barton, 2010). Far less attention has been devoted to the diverse factors, particularly nonmedical ones, that may affect the likelihood of multimorbidity and influence outcomes related to multimorbidity.

p. 222 One aim of our research program is a better understanding of the determinants of multimorbidity, including demographic, socioeconomic, and psychosocial factors. Relatively few studies have examined the social distribution of multimorbidity in the United States, although those that have suggest women have higher rates than men (DuGoff, Canudas-Romo, Buttorff, Leff, & Anderson, 2014). Results from studies in multiple countries showed higher rates of multimorbidity in women and in those with less education (Marengoni et al., 2011). While racial and ethnic differences regarding multimorbidity have not been widely examined, a recent study of over 1.3 million Medicare beneficiaries showed that whites had higher rates than blacks (DuGoff et al., 2014). Finally, virtually no research has examined the contribution of psychosocial factors to multimorbidity, although depression is considered a chronic condition in some conceptions of multimorbidity (Institute of Medicine, 2012). Among patients in a set of Dutch family practice clinics, multimorbidity was more common in those who reported smaller social networks and less social support (Van den Akker, Buntinx, Metsemakers, & Knottnerus, 2000), but there are no similar studies involving population samples.

A second aim of our program is to examine the relationships between multimorbidity and adverse outcomes, specifically disability, cognitive impairment, and mortality. Multimorbidity is known to increase risk of functional impairment (Marengoni, von Strauss, Rizzuto, Winblad, & Fratiglioni, 2009), and the relationship appears to be nonlinear. One report using data from the Medicare Beneficiary Study estimated that while the new onset of a single chronic condition doubled subsequent risk of functional limitations, the new onset of two or more conditions more than quadrupled the risk; onset of three or more new conditions increased the risk 13-fold (Wolff, Boult, Boyd, & Anderson, 2005). Research on links between multimorbidity and cognitive function, more limited than the work related to disability, has shown poorer performance on tasks related to verbal and episodic memory, psychomotor speed, numerical ability,

reasoning, and mental status in those with multiple chronic conditions (Aarts et al., 2010; Blaum, Ofstedal, & Liang, 2002; Lyketsos et al., 2005; Zelinski, Crimmins, Reynolds, & Seeman, 1998).

Mortality rates also tend to be substantially higher in people with multimorbidity than in those who have single conditions or are condition free (Marengoni et al., 2011), although there is some suggestion that this greater mortality risk is largely due to related disability (Landi et al., 2010; Marengoni et al., 2009; St. John, Tyas, Menec, & Tate, 2014). Finally, multimorbidity is associated with impairments in some forms of well-being, including greater negative affect, lower levels of life satisfaction, and increased feelings of depression and anxiety (Aarts et al., 2012; Friedman & Ryff, 2012b; Marengoni et al., 2011). In contrast, we have observed no associations between multimorbidity and measures of eudaimonic well-being, such as purpose in life and positive relations with others (Friedman & Ryff, 2012a).

Collectively, these lines of research suggest that, on average, multimorbidity takes a substantial toll on quality of life in aging adults. However, they also obscure substantial variance in these outcomes. Quantitative and qualitative studies of older adults suggest that the presence of multimorbidity does not inevitably result in substantial impairments or declines in quality of life (Poon et al., 1992; Reichstadt, Sengupta, Depp, Palinkas, & Jeste, 2010; Strawbridge, Wallhagen, & Cohen, 2002). The principal aim of our research program is to better understand the social, psychological, and biological factors that contribute both to risk of multimorbidity and to heterogeneity of outcomes related to multimorbidity; particular attention is paid to psychosocial resources that may act as protective factors. The diverse assessments of physical and mental well-being in MIDUS offer the opportunity to make substantial progress in understanding the factors that promote or protect against multimorbidity as well as those that may exacerbate or buffer against multimorbidity-related impairments and mortality.

This work is informed by three intersecting theoretical perspectives. First, where the focus of the biomedical model is the identification of pathological processes that are unique to each disease and the design of precisely targeted treatments, fundamental social cause theory (Link & Phelan, 1995; Phelan, Link, & Tehranifar, 2010) points to broader social factors that increase risk for disease generally. For example, higher standing in society—typically indexed by socioeconomic status (SES) indicators such as education, income, or occupational status—is argued to provide a set of resources that can be used to promote health no matter the circumstances or specific disease conditions. It should therefore be possible to discern processes—biological, behavioral, or social—that contribute generally to poor health in socioeconomically disadvantaged populations.

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Applying this perspective to multimorbidity, it may be that two conditions co-occur because they have a specific pathology in common. Diabetes, for example, raises the risk of heart disease in part because both conditions involve damage to heart muscle (Grundey et al., 1999). However, it is also true that both diabetes and heart disease are more likely to occur (and perhaps co-occur) in individuals with lower social status (Adler et al., 1994; Marmot & Wilkinson, 1999). It should therefore be possible to identify disease-relevant social, psychological, or biological processes that make both diabetes and heart disease more likely to co-occur in disadvantaged groups. Because the focus is on processes that are not unique to any particular condition, research on multimorbidity promises to illuminate potential mechanisms underlying the fundamental social causes of disease.

Second, the Disablement Process Model predicts that chronic medical conditions substantially increase the risk of functional impairment, but it also makes allowances for exacerbation or mitigation of that risk by diverse factors that are both external (e.g., medical care, environmental hazards) and internal (e.g., positive affect, health behaviors) to the individual (Verbrugge & Jette, 1994). Consistent with this model, we examine the ways in which psychosocial factors moderate the extent to which multimorbidity results in disability. In particular, while the bulk of health-related psychosocial research focuses on factors that increase risk of

disability, we examine the unique role of psychosocial resources in reducing disability risk and in buffering the negative effects of challenging life circumstance, such as low social status.

We focus principally on social relationships and psychological well-being because of their robust associations with diverse health outcomes (Cohen, 2004; Pressman & Cohen, 2005; Ryff et al., 2012), although we consider other resources, such as sense of control, that have also been linked to health (Taylor & Seeman, 1999). Strong social ties are seen as critical for optimal health (Cohen, 2004). For example, individuals in happy marriages tend to live longer and in better health than those who are single or in unhappy marriages (Robles, Slatcher, Trombello, & McGinn, 2014). Positive affect and greater life satisfaction, two indices of hedonic well-being, have also been shown to predict better health (Pressman & Cohen, 2005; Steptoe, Deaton, & Stone, 2015). Purpose in life, a domain of eudaimonic well-being, has been shown to reduce the risk of declines in health and cognitive function in aging adults (Boyle, Barnes, Buchman, & Bennett, 2009; Boyle, Buchman, Barnes, & Bennett, 2010; Boyle, Buchman, & Bennett, 2010; Hill & Turiano, 2014; Kim, Sun, Park, Kubzansky, & Peterson, 2013).

Finally, our research is guided by a biopsychosocial perspective: Risk for chronic illness and subsequent outcomes is shaped by social, psychological, and biological processes interacting with one another within individuals and over time. In addition to SES and psychosocial resources, we focus on a biological factor, inflammation, an evolutionarily ancient component of host defense against injury or infection (Franceschi et al., 2007). Chronic circulating levels of inflammation have been implicated in a range of age-related diseases, including heart disease, cancer, and Alzheimer disease (Michaud et al., 2013), making inflammation an attractive target for research linking multimorbidity to a range of diseases and related adverse outcomes. Our ability to pursue research from this integrative perspective is only possible because of studies like MIDUS that collect data on physical and mental health, including laboratory measurement of health-related biomarkers, as well as diverse functional outcomes.

Key Prior Work

Our current research on biopsychosocial interactions in the context of multimorbidity is informed by earlier work examining the relationships among positive psychosocial functioning, health, and health-related biomarkers. In one of the first studies to link eudaimonic well-being and inflammation, we showed that positive social relationships were inversely associated with circulating levels of the inflammatory protein interleukin 6 (IL-6) and its soluble receptor (another marker of inflammation) in a sample of community-dwelling older women (Friedman, Hayney, Love, Singer, & Ryff, 2007). A second study using the same sample examined the extent to which social well-being would mitigate the pro-inflammatory effects of poor sleep. We found that circulating levels of IL-6 were highest in older women with both poor sleep quality and absence of strong social ties, but if these women had either good quality sleep or strong social relationships, their levels of IL-6 were comparable to those with both resources (Friedman et al., 2005). We later repeated these analyses using the much larger, nationally representative MIDUS sample and found the same compensatory relationship between sleep quality and social ties in their associations with IL-6 (Friedman, 2011).

Using MIDUS data, we further probed the potential for psychosocial resources to buffer the impact of life adversities, including low SES and chronic illness. Like many others (Gruenewald, Cohen, Matthews, Tracy, & Seeman, 2009; Jousilahti, Salomaa, Rasi, Vahtera, & Palosuo, 2003; Lubbock, Goh, Ali, Ritchie, & Whooley, 2005), we have found that low SES is inversely associated with inflammation (Friedman & Herd, 2010; Herd, Karraker, & Friedman, 2012). However, low SES MIDUS participants who also reported high levels of well-being had IL-6 levels that were comparable to those found in college graduates (Morozink, Friedman, Coe, & Ryff, 2010), suggesting that the inflammatory effects of low educational attainment can be mitigated by

strong psychosocial resources. In the context of chronic illness, circulating levels of inflammation are strongly, linearly associated with numbers of chronic medical conditions, but the relationship between numbers of conditions and inflammation is markedly weaker in those with stronger social relationships and a greater sense of purpose in life (Friedman & Ryff, 2012a), suggesting that well-being may buffer against the pro-inflammatory effects of chronic illness.

These lines of work suggesting that psychosocial resources predict favorable profiles of biological risk and that they may buffer against the pro-inflammatory impact of various forms of adversity supported the development of broader theoretical perspectives on positive psychosocial functioning in health and disease-related biological processes in aging adults (Friedman, 2012; Friedman & Ryff, 2012b). They have also provided the empirical and conceptual foundations for a series of research questions about how these processes may function in adults with multimorbidity. Specifically, do sociodemographic factors and psychosocial resources directly and interactively predict risk of multimorbidity? Do these factors directly and interactively predict adverse outcomes related to multimorbidity? Does inflammation mediate the relationship between multimorbidity and adverse outcomes? After a brief description of measures that we commonly use in our work, this chapter details a number of lines of research that we are pursuing to address these questions.

Measures of Key Constructs

Multimorbidity

The multimorbidity variable consists of 13 self-reported conditions: cancer, heart problems, high cholesterol, hypertension, arthritis, AIDS/HIV, asthma/bronchitis/emphysema, diabetes, obesity, neurological problems, tuberculosis, stroke, and ulcers. The selection of these specific conditions was based in part on their likelihood of resulting in adverse health outcomes (Charlson, Pompei, Ales, & MacKenzie, 1987). They are also among the most commonly used in different formulations of multimorbidity (Anderson & Horvath, 2004; Diederichs, Berger, & Bartels, 2011; Fortin, Hudon, Haggerty, Akker, & Almirall, 2010; Rothrock et al., 2010; Schneider, O'Donnell, & Dean, 2009; Thacker et al., 2006; Tinetti et al., 2011; Verbrugge & Patrick, 1995; Wolff et al., 2002). Finally, many of these conditions were also listed by the Institute of Medicine in their recent call for increased attention to multimorbidity as a public health concern (Institute of Medicine, 2012). We use both continuous (number of conditions) and dichotomous (0–1 vs. 2 or more conditions) in our analyses.

Psychosocial Resources

Psychological Well-Being

We bring two distinct domains of psychological well-being—hedonic and eudaimonic (Ryan & Deci, 2001; Waterman, 1993)—to this work. Hedonic well-being is associated with pleasure, contentment, and the avoidance of physical and psychic discomfort. It is typically assessed using the frequency and intensity of positive and negative mood and ratings of life satisfaction (Diener, 1984; Ryan & Deci, 2001). In this research, we use ratings of life satisfaction and positive and negative affect. In contrast, eudaimonic well-being stems from the Aristotelian ideal of the pursuit of personal excellence (Ryan & Deci, 2001; Waterman, 1993) and is operationalized here with Ryff's Psychological Well-Being (PWB) scales (Ryff, 1989; Ryff & Keyes, 1995).

Social Relationships

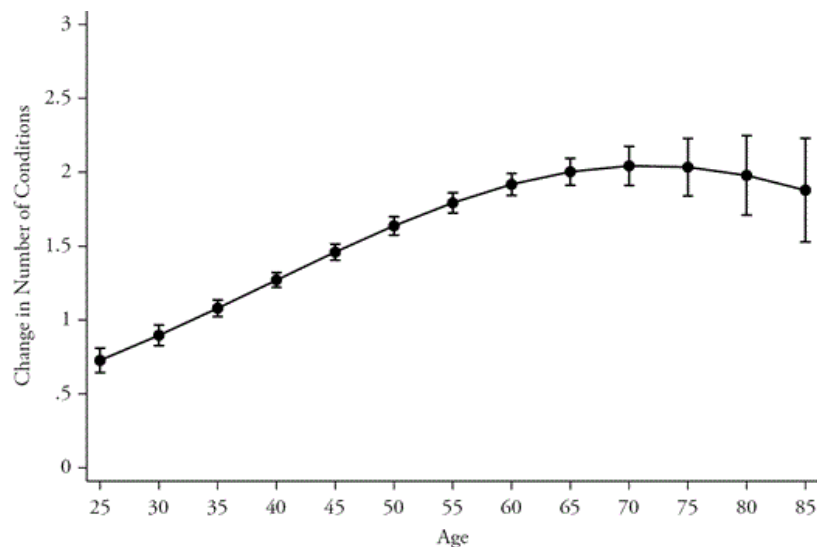
p. 225 The social relationships domain is assessed in a number of ways, including marital status (married vs. unmarried) and quality of relationships with family, friends, and spouse. MIDUS includes questions about social support (e.g., “Not including your spouse or partner, how much do members of your family really care about you?”) and social strain (e.g., “Not including your spouse or partner, how often do members of your family make too many demands on you?”); similar questions are used for each type of social relationship. Frequency of contact with friends and family is also used to measure social connectedness.

Disability

Information on limitations in activities of daily living (ADL) comes from the Functional Status Questionnaire (Jette & Cleary, 1987). Respondents were asked how much health limited their ability to do a number of activities, such as “bathing or dressing yourself” and “lifting or carrying groceries.” Responses ranged from 1 = Not at all to 4 = A lot. To determine the number of activities for which respondents reported at least some degree of limitation, responses of “Some” or “A lot” of limitation were scored 1 and other responses 0. Responses were then summed, with possible scores of 0–9.

Other measures are discussed in the following material in relation to specific analyses.

Figure 16.1



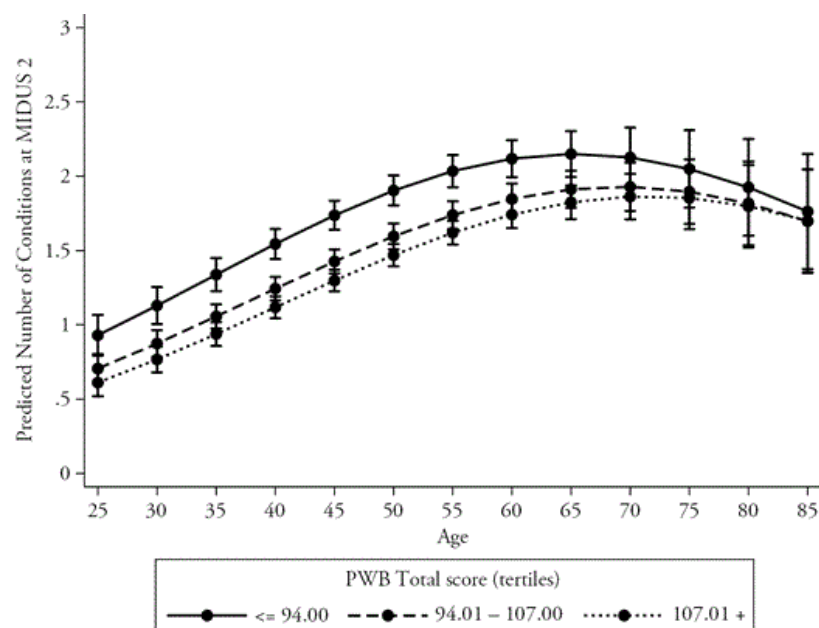
Change in number of chronic conditions between MIDUS 1 and MIDUS 2. Number of conditions increased at each age, but rate of increase was highest between 55 and 85. As suggested by a significant coefficient for age squared, however, past age 70 the rate of increase stabilized (although the oldest adults still had the greatest absolute numbers of conditions).

Key Findings: Patterning of Multimorbidity

As noted, relatively few studies have estimated the distribution of multimorbidity within the general population, particularly in the United States. Fewer still have examined the extent to which psychosocial factors are related to multimorbidity. As an initial step in addressing this gap in the literature, we examined diverse predictors of cross-sectional prevalence of and longitudinal increases in multimorbidity between the first two waves of the MIDUS study. At MIDUS 1, the average respondent had 1.0 chronic conditions; this rate increased to 1.7 conditions by the time of MIDUS 2 follow-up. Poisson regression models showed that at MIDUS 1, numbers of chronic conditions were higher among older adults, those with less than a college education, those with less income, those with relatively lower levels of psychological well-being, and those who had Composite International Diagnostic Interview Short Form (CIDI-SF) scores that suggested possible depression (Friedman & Wehrspann, 2014). Longitudinal models estimating change in chronic conditions over time showed that the rate of increase in conditions rose through midlife and then tapered off in older adults (statistically significant effects for both age and age squared; Figure 16.1). The rate of increase was also higher in women, African Americans, and those with less than a college education, less income, and CIDI-SF scores indicating possible depression. Higher scores on the PWB scales were associated with less of an increase. Importantly, most of these factors interacted with age to predict fewer differences in the rate of increase in conditions over time. For example, among those over age 60, the rate of increase in chronic conditions was similar across all education categories. The one exception to this was PWB: Increases in chronic conditions over time were greatest in those with the lowest scores on the PWB scales, even among older adults (Figure 16.2; (Friedman & Wehrspann, 2014)).

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Figure 16.2



Change in chronic conditions between MIDUS 1 and MIDUS 2 across tertiles of psychological well-being. As shown in the figure, those in the lowest tertile of scores on PWB at MIDUS 1 added more chronic conditions over time than those in the upper two tertiles. There was no PWB-times-age interaction, suggesting that the disadvantages associated with low well-being persist across middle and later life.

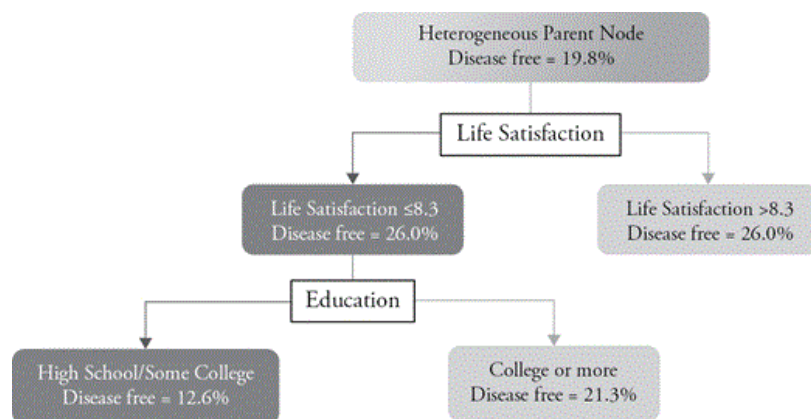
These initial results raised an interesting issue. If the norm for aging adults is multimorbidity, what are the characteristics of those who avoid multimorbidity as they age? To address this question, a second set of analyses examined the ways in which diverse demographic, socioeconomic, psychological, and health

behavior factors interact to predict better health (specifically, remaining free of chronic conditions) over time. To do this, we used an analytical technique—recursive partitioning (also called regression trees)—that is designed to take a heterogeneous sample and divide it into subsamples that are increasingly homogeneous based on an outcome of interest (in this instance, being free of chronic conditions vs. not). Predictor and outcome variables can be either continuous or categorical (Zhang & Singer, 1999). The end result is a tree structure, the branches of which consist of increasingly homogeneous subgroups. Recursive partitioning may not be as familiar as standard regression, so we now devote particular attention to this analysis.

A representative tree from a single recursive partitioning analysis of MIDUS participants 41–47 years old is shown in Figure 16.3. A heterogeneous sample (parent node) was partitioned into groups that were increasingly homogeneous on disease status. The lighter pathway to the right represents groups that are increasingly homogeneous in being disease free, while the darker pathway on the left represents groups that are increasingly homogeneous in having one or more chronic conditions. In this analysis, life satisfaction generated the best initial split into the most homogeneous subgroups. While 19% of the parent node was disease free, 26% of the subgroup with life satisfaction scores above 8.3 (out of 10) was disease free, while only 16.3% the group with lower life satisfaction scores was disease free. The next variable that yielded the most homogeneous subgroups was education. In the lower life satisfaction subgroup, those with less than a college degree were less likely to remain disease free over time (12.6%) than those with a college education or more (21.3%). Interestingly, education only improved homogeneity for the branch with low life satisfaction scores; homogeneity in the higher life satisfaction group could not be improved. Thus, while relatively lower levels of life satisfaction generally decrease the chances of remaining disease free over time, chances are improved in people who also have more education.

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Figure 16.3



Output from a single recursive partitioning analysis of MIDUS participants 41–47 years old. While 19% of the parent node were disease free, 26.8% of the subgroup with life satisfaction scores above 8.3 (out of 10) were disease free compared to 16.3% of the group with lower life satisfaction scores. Further, among those with low life satisfaction scores and less than a college degree, only 12.6% were free of any conditions compared to 21.3% of those with a college degree or more.

This relatively simple tree represents a two-way interaction between life satisfaction and education, a result that would have been possible to predict and test in a standard linear regression model. The analyses described in the material that follows included a large set of demographic (age, sex, race); socioeconomic (educational attainment); behavioral (smoking, alcohol use, physical activity); and psychosocial (personality, depression, control beliefs, well-being) variables with the potential for much larger more complex trees. A signature strength of the recursive partitioning approach is the ability to interpret complex trees with many splits—higher order interactions that would be challenging to interpret let alone predict in a regression framework—quite easily. Moreover, the factors that best partition a subsample may be

different in different branches of the tree (i.e., nonlinear associations between one factor and different levels of another), as seen in the previous example. Such nonlinear relationships are generally masked in linear regression models.

The full recursive partitioning analysis proceeded in two steps. First, because age is such a robust predictor of chronic illness, we preliminarily identified age cut points that partitioned the sample into groups that were maximally homogeneous for presence or absence of chronic conditions; the age groups were ≤ 30 , 31–40, 41–47, and >47 . We then stratified the full sample by these age ranges. Second, we split each age-stratified subsample into training samples used to generate trees and testing samples used to validate these trees. We generated forests of 50 trees for each age group, pruned trees that were statistically unreliable, and examined the resulting pathways.

The results supported two general conclusions. First, forests were smaller and less diverse for the youngest (≤ 30 years) and oldest (>47 years) samples: Each of these forests contained only five unique trees. In contrast, forests for respondents in their 30s and 40s were larger and more diverse, with 16 unique trees for those in the 31- to 40-year-old group and 13 trees in the 41- to 47-year-old group. These results suggest that the youngest and oldest groups were already relatively homogeneous—the youngest being disease free while the oldest mostly had at least one condition—and it was not possible to make them more homogeneous. Second, and perhaps more interestingly, the factors and combinations of factors that were most common in a forest varied across the different age groups, suggesting that different risk and protective factors may contribute to sustained health at different points in the adult years. For example, among the 31- to 40-year-olds, low levels of negative affect (<1.6 on a 1–5 scale), engaging in moderate or vigorous physical activity at least once a week and low levels of neuroticism (<2.5 on a 1–4 scale) appeared in a majority of the trees. In the 41- to 47-year-old group, being male and having relatively higher levels of positive affect (>3.0 on a 1–5 scale) appeared in many of the trees. In the group older than 47 years, having relatively lower scores on the personality trait of agreeableness (≤ 3.8 on a 1–5 scale) was a component of every tree.

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These analyses suggest that once large age differences are accounted for through sample stratification, the most common predictors of sustained health over time in midlife may be behavioral and psychosocial factors. It is notable that some of the variables that we expected to exert a consistent influence on remaining free of conditions over time, such as education, smoking, and depression, did not appear as frequently as variables related to personality and well-being. That said, interpretation of these results must be tempered by the relatively limited set of variables used. Future analyses along these lines can, for example, take advantage of the biomarkers available from MIDUS 2 as well as the third wave of MIDUS data collection to expand the number and type of health-related variables that could be considered.

Key Findings: Psychological Impact of Multimorbidity

Multimorbidity itself constitutes a significant threat to psychological well-being, but there may be psychosocial resources that can reduce the negative impact. One psychosocial resource that has been shown to help individuals cope with diverse challenges is beliefs about control over life circumstances. Briefly, control beliefs represent a set of psychological resources that enable individuals to better manage stress and the demands of daily life (Lachman, 1986; Lachman, Neupert, & Agrigoroaei, 2011). Greater feelings of control have previously been linked to better self-rated health, fewer health symptoms, shorter recovery time from illness or surgery, greater likelihood of engaging in positive health behaviors, and greater adherence to treatment (Lachman, 2006; Lachman & Weaver, 1998; Mirowsky, 1995; Pudrovska, 2010).

Using MIDUS data from the first two waves of the study, we tested the hypothesis that multimorbidity and change in multimorbidity would impair later psychological well-being, but control beliefs would help

preserve well-being. These analyses involved three measures of hedonic well-being (life satisfaction, positive affect, and negative affect) and four measures of eudaimonic well-being (personal growth, purpose in life, self-acceptance, and positive relations with others). We first examined links between multimorbidity at MIDUS 1 and psychological well-being at MIDUS 2 (adjusted for MIDUS 1 well-being), as well as the extent to which those associations were moderated by age or control beliefs. Results indicated that multimorbidity at MIDUS 1 predicted lower levels of MIDUS 2 life satisfaction and positive affect and higher levels of negative affect. In contrast, and consistent with previous research, multimorbidity was unrelated to eudaimonic well-being. Interaction analyses showed that, in individuals with multimorbidity, those who also felt greater control showed no increases in negative affect compared to individuals with less control. In summary, more chronic conditions predicted decreases in hedonic well-being over the 9- to 10-year follow-up, but only in those with poor feelings of control over their lives.

We next determined whether changes in multimorbidity status between MIDUS 1 and MIDUS 2 might also impair psychological well-being; to the best of our knowledge, these are among the first studies to focus on dynamic changes in multimorbidity as independent predictors of quality of life. These analyses involved a person-centered approach. Using the same multimorbidity index as the first study, participants were categorized into one of five groups ranging from consistently healthy (zero chronic conditions at both time points) to consistent multimorbidity (two or more chronic conditions at both time points). Results indicated that the continuous multimorbidity group and those who became multimorbid over time showed the greatest decreases in life satisfaction and positive affect as well as the greatest increases in negative affect. In contrast, there was again no relationship between longitudinal profiles of multimorbidity status and changes in eudaimonic well-being. Interaction analyses showed that individuals with consistent multimorbidity or onset of multimorbidity between MIDUS 1 and MIDUS 2 who also had greater control beliefs showed smaller increases in negative affect over time compared to those with lower control belief scores.

These analyses showed overall that multimorbidity and onset of multimorbidity predicted lower levels of and longitudinal decreases in positive dimensions of hedonic well-being—positive affect and life satisfaction—along with higher levels of and increases in negative affect. In contrast, eudaimonic aspects of well-being are robust to multimorbidity and onset of multimorbidity over time. The extent to which individuals feel a sense of general control over their lives may act as a buffer in these associations, protecting against longitudinal declines in positive affect and life satisfaction and increases in negative affect associated with multimorbidity. Collectively, these analyses add to existing research suggesting that diverse psychosocial resources may protect against the adverse effects of poor health. They further suggest that hedonic aspects of well-being are influenced by health to a greater extent than eudaimonic dimensions of well-being, a topic that merits further exploration.

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Key Findings: Outcomes Related to Multimorbidity

A principal focus of our research is the extent to which psychosocial resources may help aging adults with multimorbidity avoid related adverse consequences, such as functional and cognitive decline and mortality. The work is guided by two central hypotheses: (a) Psychosocial resources (e.g., social relationships, purpose in life) will reduce the extent to which multimorbidity results in adverse outcomes; and (b) inflammation will partially mediate the association of multimorbidity with these adverse outcomes. Research along these lines is ongoing, but next we present some relevant findings.

Disability

We took advantage of MIDUS 3 data to determine the extent to which multimorbidity at MIDUS 1 predicted disability almost two decades later. Adjusted for a set of demographic and socioeconomic covariates and for baseline disability, respondents who had two or more chronic conditions at MIDUS 1 had a 68% greater increase in number of functional limitations by MIDUS 3 compared to those with 0–1 conditions. Importantly, though, among those with multimorbidity, higher PWB scores significantly reduced disability rates. Being 1 standard deviation (*SD*) above the mean on overall PWB at MIDUS 1 meant that the risk of becoming more disabled over the subsequent 17–18 years was cut almost in half compared to being 1 *SD* below the mean. These results suggest that psychological well-being acts as a buffer against the disability that typically results from multimorbidity, and that protective effects of well-being can be observed over large stretches of time (Friedman, unpublished data).

In a second set of studies, we tested the hypothesis that higher circulating levels of inflammatory proteins in those with multimorbidity would increase the risk or rate of disability. Initial cross-sectional analysis using data from MIDUS 2 showed direct associations between multimorbidity and ADL disability as well as indirect associations mediated by inflammation. Inflammation was indicated by circulating levels of IL-6, C-reactive protein (CRP), and fibrinogen. In keeping with the conceptual idea that these different proteins have in common a nonspecific and negative influence on diverse disease processes, we modeled this shared influence in the form of a latent factor for which each protein was an indicator. The latent variable showed a good fit with the data. The results of these analyses confirmed that multimorbidity was significantly and positively associated with both disability and the latent inflammation factor. Inflammation was also positively associated with disability.

The key indirect effects analyses—tested using a structural equation model—showed that inflammation significantly mediated the association of multimorbidity and disability. The effect was relatively small, suggesting partial mediation (Friedman, Christ, & Mroczek, 2015). For comparison purposes, though, the effect size for this indirect pathway was the largest of any of the indirect effects in the model (age, sex, race, education). The main limitation of this study was the cross-sectional nature of the analyses. However, we recently examined the mediating role for inflammation in the longitudinal association of multimorbidity and MIDUS 2 and disability at MIDUS 3, and the results confirmed a mediating role for inflammation. These results are currently under review for publication.

Cognitive Function

Cognitive function and the prospect of age-related declines in cognitive abilities are substantial concerns for aging adults, in part because marked declines are the norm (Institute of Medicine, 2014). As noted, the research on the cognitive impact of multimorbidity is relatively limited—there is stronger evidence (not presented in this chapter) documenting the cognitive impact of single chronic conditions—but it suggests that cognitive function is generally impaired in adults with multimorbidity. Because chronic conditions typically increase as we age (Ward, Schiller, & Goodman, 2014), however, it is also important to consider the impact of change in disease burden over time. As was the case for the impact of change in multimorbidity on psychological well-being discussed previously, to the best of our knowledge no previous research has examined how longitudinal change in numbers of chronic conditions is associated with cognitive function.

To address this issue, we examined change in multimorbidity between Waves 1 and 2 of MIDUS as a predictor of performance on the Brief Test of Adult Cognition by Telephone (BTACTION; Tun & Lachman, 2006).

p. 230 This test separately assesses short-term episodic memory via word list recall and executive functioning via assorted measures of attentional control, response inhibition, and cognitive flexibility (Lachman, Agrigoroaei, Tun, & Weaver, 2014). Analyses adjusted for a large set of demographic, socioeconomic, and

psychosocial covariates, including age, sex, education, depression (via the CIDI-SF), physical activity, cigarette smoking, and number of chronic conditions at MIDUS 1 (to adjust for baseline differences). We also examined moderation by age, sex, and education for both cognition outcomes.

Results from linear regression models showed that number of chronic conditions at MIDUS 1 and longitudinal increases in number of chronic conditions between MIDUS 1 and MIDUS 2 independently predicted worse executive functioning. Interaction analyses showed this association was not moderated by age, sex, or education. Episodic memory performance at MIDUS 2 was significantly predicted by number of chronic conditions at MIDUS 1, but change in chronic conditions over time was only marginally related to memory. However, interaction analyses showed that the cognitive impact of increases in chronic conditions was significantly moderated by education. Specifically, greater educational attainment appeared to buffer against the impact of longitudinal increases in chronic conditions on episodic memory performance at MIDUS 2.

These results support earlier research linking cognitive performance to burden of chronic illness in midlife and older adults. They further suggest that, independently of how many conditions a participant had at the first wave of MIDUS, accumulating new conditions in the 9–10 years between MIDUS 1 and MIDUS 2 was associated with worse cognitive function. These results held after adjustment for a diverse set of demographic, socioeconomic, psychosocial, and behavioral covariates. The impact of increasing disease burden on cognition was more robust for executive function than for episodic memory, with effects on episodic memory dependent on the education of participants. Although past research showed that episodic memory and executive functioning typically decline at similar rates (Buckner, 2004), some lines of research have demonstrated that constructs similar to episodic memory (e.g., semantic memory, verbal recall) remain intact longer (Gunstad et al., 2006; Institute of Medicine, 2014; Nilsson et al., 1997; Simen, Bordner, Martin, Moy, & Barry, 2011). Overall, these findings highlight the importance of accumulation of chronic conditions throughout the life span and their potential influence on cognition for aging adults.

Mortality

We recently began work on the third major focus of this line of research: the impact of multimorbidity on mortality. Initial analyses showed that the likelihood of mortality in respondents with two or more chronic conditions at MIDUS 1 was twice that of respondents with a single or no condition. We then examined the potential protective effects of psychological well-being and social relationships (in this instance, marital status) on mortality. Results showed that respondents who were married at MIDUS 1 had lower mortality rates than those who were not. Moreover, those with higher aggregate scores on the PWB scales at MIDUS 1 had lower mortality rates than those with lower scores. Importantly, the protective effects of well-being and marital status were also present in those with multimorbidity, although the protective effects were smaller than those among respondents without multimorbidity (Franks, Friedman, Thomas, Gotschall, & Moench, 2016). These results suggest a robust protective effect of marriage and higher levels of eudaimonic well-being that is reduced, but not eliminated, in the presence of multiple chronic conditions.

Key Themes and Future Directions

In this final section, we distill out general themes from our research to date and consider future research efforts to examine them further.

Biopsychosocial Integration

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The overarching perspective guiding this research is that multimorbidity and related adverse outcomes are determined in part by the direct and interactive effects of processes acting on social, psychological, and biological levels. It is worth noting that these studies are among the first to focus explicitly on social and psychological predictors of multimorbidity and related outcomes. Consistent with the fundamental social causes perspective, and perhaps not surprisingly given the social patterning of health generally, multimorbidity tends to be more common and to increase more rapidly over time in adults who were less educated as well as those older, female, and nonwhite. The apparent protective role of positive psychosocial functioning, on the other hand, is more novel. Well-being (broadly construed) predicted greater likelihood of remaining free of chronic conditions over time and reduced the risk of adding new chronic conditions even in those who already had multimorbidity. Interestingly, the results from the recursive partitioning analyses suggest moderation of low social status by psychosocial resources, an observation that merits further examination in future work.

Future work will gradually build toward a fully integrative model. Specifically, we will test the hypothesis that the links between multimorbidity and disability, cognitive, and mortality outcomes are simultaneously moderated by psychosocial resources and mediated by inflammation. We will also examine potential moderation by SES. In addition to standard parametric tests of key association, this work will also incorporate methods such as recursive partitioning that are expressly designed to illuminate complex, nonlinear associations among diverse variables.

Multimorbidity—Specific Conditions Versus Overall Burden

Another important future step in this line of inquiry is to examine more closely the role of specific conditions in the associations we have observed to date. The multimorbidity measure includes conditions that are common (e.g., hypertension) and rare (e.g., HIV), that range in severity (Charlson et al., 1987), and that are symptomatic (e.g., arthritis) and asymptomatic (e.g., high cholesterol). Despite this diversity, we have not found that any particular condition drives key effects. For example, in our examination of links between multimorbidity and cognitive function, we ran models excluding single conditions from the index multimorbidity variable (see Fabbri et al., 2015, for a similar approach). In each of the models, the relationships between multimorbidity and longitudinal change in multimorbidity and the two cognitive outcomes were unchanged. Thus, the impact on cognition was not linked to any particular condition, but rather appeared to be a consequence of becoming less healthy over time. Nonetheless, given relatively undeveloped literature on social and psychological determinants of multimorbidity and its outcomes, it will be important to examine more closely patterns of co-occurring conditions, whether those patterns vary with SES or psychosocial resources, and whether different combinations of conditions are more or less likely to result in adverse outcomes over time.

Protective Effects of Positive Psychosocial Resources

We observed seemingly protective effects of psychosocial resources in their associations with both multimorbidity and related outcomes, including disability and mortality. This work fits into the broader and growing literature on links between positive psychological functioning and health, but it is the first to document protective influences in the context of multimorbidity. There are a number of ways in which we plan to extend this line of research. First, while high scores on well-being may indeed be protective, an alternative possibility is that low scores may be influenced by as-yet-undiagnosed disease processes. The diverse data in MIDUS will be helpful in further illuminating these associations.

For example, biomarkers collected at MIDUS 2 and planned for the MIDUS 3 follow-up—as well as data from the refresher cohort—can be used to provide information about nascent disease risk. Protective influences of well-being can be demonstrated if two people matched on disease risk but diverged in well-being prove to have different multimorbidity outcomes. In addition, it will be important to expand the number and type of psychosocial resources examined to establish which are most robustly linked to multimorbidity and its outcomes and therefore potential targets of intervention. Marriage, for example, appears to be protective against mortality in those with multimorbidity; this work can be extended by inclusion of assessments of marital quality. Other social relationships—friends, family—along with feelings of social connectedness are also available in MIDUS and can be considered in order to provide a detailed picture of each person's social environment.

Dynamic Processes

Many of the key variables in our studies—number of chronic conditions, psychosocial resources, disability, cognitive function—are likely to change over time, and a full explication of our research questions must account not only for how these variables interact but also how change in one affects change in the others. While some analyses have assessed these dynamic processes (the examination of change in multimorbidity as a unique predictor of later cognitive function, for example), we are beginning to consider the relationships among time-varying variables more explicitly using a variety of techniques, including person-centered approaches such as latent trajectory models designed to identify subgroups of people with similar patterns of change over time. Underlying these approaches is the notion that how these processes change over time is an important determinant of health and quality of life in aging adults independent of the absolute number of medical conditions or levels of functional and cognitive impairment.

Life Course Perspective

Finally, the recursive partitioning analyses showed that SES and psychosocial resources were most likely to influence likelihood of remaining healthy in midlife adults. This observation is one example of the importance of approaching this work with a life course perspective in mind. That is, the factors that make individuals more or less vulnerable to multimorbidity and to related outcomes may differ by age. For example, the psychosocial resources that predict better health and that buffer against the adverse effects of multimorbidity may be different or may function differently in midlife than in later life. Relatedly, to this point we have focused on the original MIDUS cohort, but in the 20 years since the study's inception, there have been marked declines in disease-related mortality and disability. The MIDUS refresher cohort offers the opportunity to determine the extent to which our observations to date are unique to the original cohort or more universal.

Conclusion

Multimorbidity is increasingly the norm for aging adults, and while prevention of disease in the first place is a critical long-term goal, the short-term reality is that older adults will need to adapt to living with multiple chronic conditions. This research suggests that more attention should be paid to social and psychological factors as important determinants of multimorbidity and related consequences and to the development of interventions that can help adults with multimorbidity maintain a high quality of life.

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