Not Seeing Double: Discordance in Disease, Function, and Their Longitudinal Associations in Monozygotic Twins

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ABSTRACT

Objective: Prior research on the causality and directionality between disease and functional limitations is ambiguous. The current study used longitudinal monozygotic twin data to test both directions linking disease burden and functional limitations in middle-aged and older adults, controlling for genetic and familial factors. We also examined potential moderation by psychological well-being.

Methods: The twin subsample from the first two waves of the longitudinal Midlife in the United States (MIDUS) study was used (wave 1, 1995–1996; wave 2, 2004–2006). Only monozygotic twins (n = 713) were included in analyses. In separate multilevel models, we examined disease burden at MIDUS 2 predicted by functional limitations at MIDUS 1 and MIDUS 2 functional limitations predicted by disease burden at MIDUS 1.

Results: Disease burden and functional limitations at MIDUS 2 varied substantially within families. There was no within-family association of earlier functional limitations with change in later disease burden (b = 0.40, p = .39), but there was a within-family association such that the twin with higher baseline disease burden had a greater increase in functional limitations than his/her co-twin (b = 0.06, p = .02). Well-being was not a moderator in either model.

Conclusions: We found support for a potentially causal association between earlier disease burden and later increases in functional limitations, consistent with the Disablement Process Model. Sensitivity analyses confirm the detected within-family effect. Possible mechanisms linking disease burden and functional limitations are discussed as potential targets for future research.

Key words: disease burden, functional limitations, causality, twin studies, well-being.

INTRODUCTION

Chronic conditions and functional limitations are common in midlife and later life and have broad implications for mortality and quality of life. Older adults are disproportionately burdened by multiple chronic conditions, or multimorbidity. Sixty-two percent of Americans older than 65 years have more than one chronic condition (1), and the absolute number of people with multimorbidity is predicted to double by 2035 (2). Likewise, the proportion of people with functional limitations has steadily increased since 1995 across all age groups (3). Chronic conditions and functional limitations are often associated in middle adult and elderly populations (4), and these associations are often treated as causal. Typically, and consistent with the Disablement Process Model (5), multimorbidity is thought to precede and result in functional impairment, although much of the prior work reporting these associations is correlational (6,7). In contrast, some research supports a progression from functional limitations to chronic conditions (8), whereas other studies have suggested that multimorbidity and functional limitations may exacerbate each other bidirectionally (9). Given this lack of certainty surrounding causality and directionality related to chronic conditions and functional limitations, the present study uses longitudinal monozygotic (MZ) twin data to test both directions linking disease burden and functional limitations, controlling for genetic and familial influences that may contribute to both outcomes.

Direction of Effects

The Disablement Process Model describes how both chronic and acute medical conditions affect functioning of specific body systems, which in turn can lead to functional limitations and ultimately disability. For example, an estimated 121.5 million American adults (48%) have one or more types of cardiovascular disease (10), and cardiovascular disease is known to be an important determinant of disability among those 65 years and older (11). In previously healthy adults, risk of functional dependency was shown to increase exponentially with each newly diagnosed chronic condition in a 3-year cohort study (12), and faster rates of multimorbidity development are linked to a higher risk of developing new activity impairments compared with those who accumulated diseases slower over time (13).

MZ = monozygotic, **MIDUS** = Midlife in the United States, **MWI** = multimorbidity weighted index

SDC Supplemental Digital Content

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It is also possible that functional limitations could lead to chronic conditions. Findings from the Irish Longitudinal Study on Ageing showed that slower gait speed and lower grip strength were longitudinally associated with developing multimorbidity and with accruing new diseases (8). In addition, low grip strength and slow gait speed are linked to lower levels of physical activity (14); low physical activity, in turn, is a risk factor for many chronic conditions (e.g., cardiovascular disease (15)). Low grip strength has also been linked to higher levels of inflammation (16), which contributes to the development and progression of numerous chronic diseases and conditions (17). Thus, there is existing empirical support for the possibility that functional limitations, either directly or through other processes or behaviors, can lead to disease.

Overall, research supports both the Disablement Process Model (i.e., chronic conditions leading to functional limitations) and a model that flows from functional limitations to chronic conditions. Calderón-Larrañaga and colleagues (9) suggested a multimorbidity-functional limitations circle to be more appropriate, which supports the possibility of bidirectional effects. Methodologically, statistical evidence of bidirectional pathways could indicate real bidirectional modes of causality, but it could also be an artifact induced by inadequate control of stability or key predictors of both outcomes (i.e., an "omitted variable problem" (18)). Based on studies reviewed previously, genetic influences are a potential source of bias that, if unaccounted for, could inflate estimates of transactional processes between multimorbidity and functional limitations over time. Here we use an MZ discordant design to control for potential genetic and familial confounds that could contribute to both chronic conditions and functional limitations and thereby obtain more precise within-family estimates of key associations. In the context of longitudinal analyses, this design also provides more precise estimates of direction of influence between disease burden and functional limitations.

Moderating Factors

Many older adults maintain high levels of functional capacity even in the context of disease, implying that there may be compensatory factors that can reduce the impact of disease burden. Similarly, not all adults with functional limitations develop chronic conditions. There is growing evidence that eudaimonic well-being (e.g., purpose in life, self-acceptance, personal growth) is a critical component of healthy aging (19). Prospective studies have shown that higher levels of purpose in life, for example, are associated with a reduced risk of future disability (20). Several studies have probed eudaimonic well-being as a moderator of various health-related associations. For example, in a prospective study of healthy 70-year-olds, those who reported higher baseline levels of purpose in life had better cognitive function than did those with comparable brain pathology but with lower levels of purpose in life (21). Similarly, among Midlife in the United States (MIDUS) participants, higher levels of eudaimonic well-being attenuated the association between low levels of education and higher circulating levels of the inflammatory protein interleukin 6. Moreover, and importantly for this study, eudaimonic well-being has also been found to moderate the relationship between multimorbidity and inflammation. Where more chronic conditions predicted higher levels of interleukin 6, those levels were lower in adults with higher levels of purpose in life and positive relations with others (22). Collectively, research underscores the importance of eudaimonic well-being as a potential protective resource in the context of age-related adversity generally and burden of chronic disease specifically. Thus, in the present study, we examined eudaimonic well-being as a moderating factor in the relationship between disease burden and functional limitations.

MZ Discordant Design

Sibling comparison designs are genetically informed studies that control for genetic and environmental factors shared by siblings raised in the same family (23–25). This approach tests whether siblings who are discordant for a hypothesized predictor are also discordant for an outcome. Because MZ twins share 100% of their genes, using MZ twins is the most stringent design for sibling comparison studies because it controls for a greater portion of genetic influences than using full siblings, who share an average of 50% of their genes (25). Thus, the use of the discordant-twin design is one of the most promising approaches to strengthen causal inferences in observational research (26). Within an MZ discordant design, a longitudinal approach is especially important to assess directionality.

MZ pairs have identical DNA but often display some level of phenotypic discordance, or differences in a characteristic or condition. By studying MZ twin pairs, the possible confounding factors (either genetic or shared familial) can be controlled. MZ twin analyses can therefore help strengthen theories of causality by identifying nonfamilial predictors that can explain discordant outcomes. In other words, within-family differences in outcomes for identical twins who are also discordant on a predictor lend support for a causal relationship between the predictor and outcome.

Prior studies have used MZ discordant designs to study several age-related conditions. MZ twins can be discordant on a disease when the disease is not 100% heritable or familial, which is true of most complex diseases such as cancer and dementia (27,28). Heritability of objective measures of physical function ranges from 30% to 60% in studies of older twins (29), and frailty has been shown to be 45% heritable (30). Specific to our measure of multimorbidity, significant effects of heritable factors ranged from 27% to 42% for colon, breast, and prostate cancers in a large study of twins (31). Collectively, longevity more generally is only moderately heritable, with genes accounting for about 25% of what determines longevity (32–34).

In the present study, we leverage MZ twin discordance on disease burden and functional limitations to determine whether the twin with more disease burden is also the twin with more functional limitations across time. The design of these studies can also suggest a noncausal association. Null findings for the within-twin pair associations, although possibly an indicator of a lack of power to detect a significant effect, can also rule out a potentially causal explanation, instead suggesting that genetic and/or family level influences explain the observed relationship. For example, one study examining the association between years of education and allostatic load found that discordance in allostatic load was entirely explained by familial influences shared between both MZ and dizygotic twin pairs, indicating the relationship between education and allostatic load is not likely to be causal (35). Because the within-pair effect on allostatic load was essentially zero for both MZ pairs and DZ pairs, the association between education and allostatic load is explained by familial influences shared between twins.

The Present Study

We operationalized chronic conditions as disease burden using a recently developed multimorbidity index that assigns weights to each condition based on each condition's propensity to be disabling (36). In the present longitudinal study, we examined within-family associations of disease burden with later functional limitations and within-family associations of functional limitations with later disease burden in a sample of MZ twins. We used a multilevel model with a random intercept, which has previously been well described (25,26,37). We expected that the results would support one of three perspectives. Greater disease burden being associated with larger increases in later functional limitations would support the Disablement Process Model. Greater functional limitations being associated with later increases in disease burden would support a potential causal relationship between functional impairment and chronic disease. Evidence for both of these longitudinal patterns would support bidirectional, potentially causal influences between functional limitations and disease burden. Finally, we tested the moderation of the longitudinal associations of functional limitations and disease burden by psychological well-being.

METHODS

Sample

The twin subsample from the longitudinal MIDUS survey was the source of the data for the current study. Begun in 1995 to 1996, MIDUS recruited 1914 MZ and dizygotic twins from a national twin registry, including 894 twin pairs. A follow-up study was completed in 2004 to 2006 (MIDUS 2). Participants completed a telephone interview and self-administered questionnaires at both waves. Data for the current study included only MZ twins from the MIDUS twin sample (n = 713 individual twins). Mortality-adjusted retention for the twin sample was 81% between MIDUS 1 and MIDUS 2. Participant characteristics are presented in Table 1.

TABLE 1. Participant Characteristics (n = 713)

	MZ Twins	Discordance, %
Age, y	44.08 (11.83)	—
Sex (female), %	45	—
Education, %		29
High school/GED or less	250	
Some college	218	
College or more	202	
Smoking status, %		28
Never smoker	369	
Ex-smoker	160	
Current smoker	141	
Meets PA guidelines		34
Does meet PA guidelines	507	
Does not meet PA guidelines	163	
Well-being MIDUS 1 (1–7)[a]	16.89 (2.56)	31
Well-being MIDUS 2 (1–7)[a]	16.84 (2.62)	50
Disease burden MIDUS 1[a]	1.51 (2.56)	28
Disease burden MIDUS 2[a]	1.71 (2.90)	38
Functional limitations MIDUS 1 (1–4)[a]	1.27 (0.53)	27
Functional limitations MIDUS 2 (1–4)[a]	1.47 (0.70)	48

Values are mean (standard deviation) unless otherwise specified.

MZ = monozygotic; GED = General Education Diploma; PA = physical activity; MIDUS = Midlife in the United States.

[a] Higher values indicate greater well-being, greater disease burden, and greater functional limitations, and discordance for these variables is defined as a difference of greater than or equal to half a standard deviation between twin scores.

Disease Burden

Because of the heterogeneity in the impact of chronic conditions on functional capacity, simple disease count variables commonly used in many prior studies may not adequately capture the burden of multiple diseases. We therefore assessed disease burden using a multimorbidity weighted index as developed and described by Wei and colleagues (36). In brief, weights were established for 81 clinician-diagnosed conditions based on cross-sectional associations with physical functioning items on the Short Form-36. Absolute values of the chronic condition weights are equivalent to the decline in physical functioning units.

In the current study, absolute values of the chronic condition weights were matched with corresponding conditions available in MIDUS from the phone survey and self-administered questionnaire. Individual multimorbidity weighted index scores reflect the summed weighted values of all chronic conditions the participant reported, and disease burden varied widely depending on condition. Individual chronic condition weights ranged from −0.068 for skin cancer to 10.6 for multiple sclerosis, where higher scores indicated higher propensity for reduced physical functioning. See Table 1 for average disease burden and twin discordance. A full list of the 26 chronic conditions and weights that were matched in MIDUS is available in Appendix A (Supplemental Digital Content, http://links.lww.com/PSYMED/A760).

Functional Limitations

Self-administered questionnaire items assessed functional limitations. Respondents were asked how much (1 = not at all to 4 = a lot) health limited their ability to lift or carry groceries; climb one flight of stairs; climb several flights of stairs; bend, kneel, or stoop; walk more than a mile; walk several blocks; and walk one block. Responses were averaged to generate an overall limitations score (range = 1–4), which was continuous and not rounded to the nearest integer.

Eudaimonic Well-Being

Eudaimonic well-being was measured with six scales (38): autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, and self-acceptance. These items were included in the self-administered questionnaire. Each scale consisted of seven items, with a mix of positive and negative items. Respondents indicated the extent (1 = strongly agree to 7 = strongly disagree) to which the statements described them. Negative items were reverse coded so that higher scores reflected more positive appraisals. Internal consistency for these scales at MIDUS 2 ranged from 0.67 to 0.83 (compared with 0.70–0.84 for the full MIDUS sample).

Covariates

To control for potential confounds, age, sex, and educational attainment were included in the models as covariates; smoking status and physical activity were also included as life-style covariates owing to their associations with both functional limitations and disease (39–42). A continuous variable was used for age, and a dichotomous variable was used for sex (1 = female): these did not vary across twins. Respondents indicated their highest level of educational attainment using 12 categories ranging from "no school/some grade school" to "PhD, MD, JD, or other professional degree." Responses were combined into three categories: high school degree or General Education Diploma, some college, and college degree or more. Participants indicated the

frequency of moderate and vigorous physical activity during the summer and winter (1 = never; 6 = several times a week). As done in prior work (43), responses to these items were used as indicators for a continuous latent physical activity variable, and this variable was included in all models. Participants were also asked about history of cigarette smoking, and a three-level categorical variable indicating smoking status (current smoker, ex-smoker, nonsmoker) was created. Education, smoking status, and physical activity could vary across twins.

Analytic Strategy

Our hypotheses were centered on understanding whether there are longitudinal, within-family associations between chronic conditions and functional limitations to strengthen theories of directionality and causality. Therefore, we used sibling comparison models to test hypotheses. The use of MZ twins in these models allows us to a) control for genetic and shared familial factors and b) examine within-family associations over time to identify nonfamilial predictors that can explain discordant outcomes.

In the first step of the sibling comparison approach, "family average" and "twin-specific relative to family average" variables were created for all predictors, the education and smoking covariates, and the moderator (well-being). We did not create twin-specific variables for age and sex because the twins were identical and thus could not differ on these variables. Family average scores are the average of twin 1 and twin 2 on that variable and index the between-family portion of the association. Because only two individuals are represented for each family, the family average variables were included as covariates indexing familial levels of predictors, but not interpreted, as they are presumed not to be reliable (25). The twin-specific relative to family average variables are each twin's score centered within family. In other words, these scores are the result of subtracting the family average score from each twins' score. Twins who are concordant would each have a score of 0 on the twin-specific variables.

After creating these scores, we conducted two series of multilevel models in M*plus* v.8 using full-information maximum likelihood estimation wherein twins (level 1) are nested in twin pairs (level 2). In the first series, we examined disease burden reported at MIDUS 2 as the outcome predicted by functional limitations at MIDUS 1; in the second series, we examined MIDUS 2 functional limitations as the outcome predicted by disease burden at MIDUS 1. Both series consisted of the following model-building steps: In step 1, an unconditional model with no predictors was estimated to determine the distribution of within- versus between-family variation in the outcome. In step 2, we added earlier disease burden at MIDUS 1 in series 1 (predicting disease burden) and earlier functional limitations at MIDUS 1 in series 2 (predicting functional limitations) to the model from step 1 to control for prior levels of the outcome in addition to the covariates (age, sex, and twin-specific and family average indices of smoking, education, and physical activity from MIDUS 1). In step 3, we added the twin-specific and family average indices of functional limitations in series 1 (predicting disease burden) and disease burden in series 2 (predicting functional limitations) to the models. In step 4, we added the twin-specific and family average indices of well-being and the within-family interaction of well-being with functional limitations in series 1 (predicting disease burden) and disease burden in series 2 (predicting functional limitations) to the models. Percent reduction in error (pseudo-R^2 change) values were computed for steps 2, 3, and 4 to obtain a measure of effect size for the inclusion of the covariates, twin-specific and family average indices of focal predictors, and moderators, respectively.

RESULTS

Twins averaged disease burden scores of 1.51 (standard deviation [SD] = 2.56, range = −0.07 to 15.28) at MIDUS 1 and 1.70 (SD = 2.90, range = −0.07 to 32.61) at MIDUS 2. For functional limitations, twins averaged scores of 1.27 (SD = 0.53) at MIDUS 1 and 1.47 (SD = 0.70) at MIDUS 2. Twins had average well-being scores of 16.89 (SD = 2.56) and 16.84 (SD = 2.62) at MIDUS 1 and 2, respectively. The increase in functional limitations ($p < .001$) and the decline in well-being ($p = .05$) over time were both statistically significant. Means and SDs for all key study variables are presented in Table 1. Because we used a latent physical activity variable, which is not inherently meaningful, we present frequency data based on how many participants met physical activity guidelines (i.e., moderate or vigorous activity several times per week, with no seasonal distinction).

Although twin discordance is operationalized continuously in analyses, we quantified twin discordance on key study variables as an initial description to aid in interpretation. Twin discordance was computed as 0 if twins had equivalent scores and 1 if they had differing scores for level of education attained and smoking status (categorical measures). For disease burden, functional limitations, and well-being, twin discordance was computed as 0 if the difference between twin scores was within half an SD and 1 if the difference was greater than or equal to half an SD. This cutoff for amount of discordance is consistent with other analyses using MIDUS data (44). Based on this criterion, 28% of twins (95 pairs) were discordant for disease burden at MIDUS 1 and 38% (115 pairs) at MIDUS 2. For functional limitations, 27% of twins (97 pairs) were discordant at MIDUS 1 and 48% (177 pairs) were discordant at MIDUS 2. For well-being, 31% of twins (114 pairs) were discordant at MIDUS 1 and 50% (182 pairs) at MIDUS 2. Discordance rates for all key study variables are shown in Table 1. Based on rates of discordance in prior studies (44,45), we observe sufficient discordance here for the current analysis. Furthermore, within-family differences in disease burden, functional limitations, and well-being increased over time. Finally, nominal discordance rates were higher (54%–91%), and between 40%–80% of all nominal discordance on the continuous variables fell outside of the +0.5 SD cutoff, indicating that much of the variance in discordance indicates moderately sized differences between twins and supports the meaningfulness of within-family effects in the present study.

Before the main analysis, bivariate correlations between all key study variables were examined separately by twin. As shown in Table 2, disease burden at MIDUS 1 positively correlated with disease burden at MIDUS 2 for both twins ($r = 0.28$ [$p < .001$] and $r = 0.42$ [$p < .001$], respectively). Functional limitations at MIDUS 1 positively correlated with functional limitations at MIDUS 2 for both twins ($r = 0.40$ [$p < .001$] and $r = 0.56$ [$p < .001$], respectively). Functional limitations at MIDUS 1 correlated positively with disease burden at MIDUS 2 ($r = 0.27$, $p < .001$) for both twins, and disease burden at MIDUS 1 correlated positively with functional limitations at MIDUS 2 for both twins ($r = 0.35$ [$p < .001$] and $r = 0.39$ [$p < .001$], respectively). In addition, well-being at MIDUS 1 correlated negatively with disease burden at MIDUS 1 for twin 1 ($r = −0.17$, $p = .002$) but not twin 2. Well-being at MIDUS 1 correlated negatively with functional limitations at MIDUS 1 for both twins ($r = −0.11$ [$p = .04$] and $r = −22$ [$p < .001$], respectively). Finally, well-being at MIDUS 1 was correlated negatively with functional limitations at MIDUS 2 for twin 2 only ($r = −0.18$, $p = .01$).

A table of cross-twin cross-trait correlations is provided in supplementary materials (Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A760). Overall, we found relatively low indication of familial influence for the main variables, with well-being being the highest correlated ($r = 0.52$, $p < .001$). This is consistent with the amount of discordance we demonstrated, meaning there is

TABLE 2. Phenotypic Correlations Separately by Twin

	M1 DB	M2 DB	M1 FL	M2 FL	M1 WB	M2 WB	M1 PA	M1 Age	M1 Educ	M1 Smoke
M1 DB		0.42***	0.36***	0.39***	−0.08	−0.03	−0.16**	0.17**	−0.05	0.10
M2 DB	0.28***		0.27***	0.44***	−0.08	−0.03	−0.05	0.21***	−0.13*	0.14*
M1 FL	0.49***	0.27***		0.40***	−0.22***	−0.15*	−0.30***	0.18***	−0.15**	0.09
M2 FL	0.35***	0.38***	0.56***		−0.18*	−0.10	−0.18**	0.33***	−0.23***	0.19**
M1 WB	−0.17**	−0.08	−0.11*	−0.12		0.62***	0.19***	0.03	0.14**	−0.08
M2 WB	−0.22***	−0.08	−0.13	−0.24***	0.74***		0.13	0.18**	0.02	−0.10
M1 PA	−0.26***	−0.14*	−0.34***	−0.24***	0.14**	0.15*		−0.14*	0.13*	−0.12*
M1 Age	0.16**	0.17**	0.26***	0.23***	0.04	0.16*	−0.19***		−0.14*	0.01
M1 Educ	−0.13*	−0.19**	−0.22***	−0.31***	0.17**	0.19**	0.18**	−0.17**		−0.23***
M1 Smoke	0.24***	0.13*	0.12	0.21**	−0.14*	−0.13*	−0.14**	0.07	−0.22***	

Twin 1 and twin 2 correlations are displayed below and above the diagonal, respectively.

DB = disease burden; FL = functional limitations; WB = well-being; PA = physical activity; Educ = education achievement category; Smoke = smoking status.

* $p \leq .05$.

** $p \leq .01$.

*** $p \leq .001$.

room for nonshared influences on the discordance. Also shown in this table, familial contributions to stability in disease burden ($r = 0.21$, $p < .001$) and functional limitations ($r = 0.23$, $p < .001$) over time are both relatively small, indicating mostly nonshared influences contribute to differences from MIDUS 1 to MIDUS 2. The familial contributions to concurrent associations among disease burden and functional limitations at MIDUS 1 ($r = 0.19$, $p < .001$) and MIDUS 2 ($r = 0.16$, $p < .01$) are also small. Similarly, familial contributions to longitudinal associations among MIDUS 1 disease burden and MIDUS 2 functional limitations ($r = 0.14$, $p < .01$) and MIDUS 1 functional limitations and MIDUS 2 disease burden ($r = 0.19$, $p < .001$) are minor.

Disease Burden as Outcome

Disease burden at MIDUS 2 varied substantially within families: 72% of the variance in disease burden was attributable to differences between twins within families, whereas 28% of the variance in disease burden was attributable to between-family differences. Covariates explained 6.60% of the within-family variation of disease burden in the second step, driven by stability in within and between family disease burden over time ($b = 0.21$ [SE = 0.07, $p = .005$[and $b = 46$ [SE = 0.08, $p < .001$], respectively. The inclusion of twin-specific and family average functional limitations in the third step accounted for no additional variance in later disease burden; there was no within-family association of earlier functional limitations with later disease burden ($b = 0.40$, SE = 0.39, $p = .305$). Finally, the inclusion of well-being as a predictor and moderator of the effect of earlier functional limitations explained an additional 2.08% of the variance in disease burden. Contrary to hypotheses, well-being was not a moderator of the within-family association of earlier functional limitations with later disease burden ($b = -0.40$, SE = 0.34, $p = .247$). Estimates for the final disease burden model are presented in Table 3.

Functional Limitations as Outcome

Functional limitations at MIDUS 2 varied substantially within families: 74% of the variance in functional limitations was attributable to differences between twins within families, whereas 26% of the variance in functional limitations was attributable to between-family differences. Covariates explained 18.26% of the within-family variation of functional limitations in the second step, driven by within- and between-family stability in functional limitations over time ($b = 0.41$, SE = 0.10, $p < .001$; $b = 0.67$, SE = 0.08, $p < .000$). The inclusion of disease burden in the third step accounted for an additional 3.67% of the variance in later functional limitations. There was a within-family association such that the twin with higher baseline disease burden also had a greater increase in functional limitations than his/her co-twin ($b = 0.06$, SE = 0.02, $p = .009$). Finally, the inclusion of well-being as a predictor and moderator of the effect of earlier disease burden explained only 0.694% additional variance in later functional limitations. Contrary to hypotheses, well-being was not a moderator of the within-family association of earlier functional limitations with later disease burden ($b = 0.02$, SE = 0.02, $p = .237$). Estimates for the final functional limitations model are presented in Table 3.

Sensitivity Analyses

We ran a series of sensitivity analyses to better contextualize our main analyses. First, we added a fifth step for each model, which stripped the model back to only the within-family estimate without any covariates or between-family variables. In addition, past sibling comparison studies have examined a "standard" model, which simply assesses, for example, whether adults who have greater multimorbidity also have more functional limitations later. We ran the same standard models with a clustering variable to adjust standard errors to account for individuals nested within families. We used this approach in the same sample used in the main analyses.

Results from these sensitivity analyses can be found in supplementary materials (Table S2, Supplemental Digital Content, http://links.lww.com/PSYMED/A760). We provide unstandardized coefficients and standardized coefficients to allow for comparisons across models. Earlier functional limitations did not significantly predict later disease burden in any of the models. With functional limitations as an outcome, earlier disease burden was a significant

TABLE 3. Unstandardized Model Estimates for Disease Burden as Outcome and Functional Limitations as Outcome

	MIDUS 2 Disease Burden		MIDUS 2 Functional Limitations	
	Est.	(SE)	Est.	(SE)
Intercept	1.55	(0.12)	1.47	(0.03)
Within-family effects				
M1 Functional limitations	0.40	(0.39)	0.33	(0.10)**
M1 Disease burden	.16	(0.08)*	0.06	(0.02)**
M1 Well-being	−0.18	(0.09)	0.02	(0.03)
M1 Functional limitations by well-being	−0.40	(0.34)	—	—
M1 Disease burden by well-being	—	—	0.02	(0.02)
Covariates (within-family)				
M1 Twin-specific smoking	0.15	(0.29)	0.06	(0.07)
M1 Twin-specific education	0.18	(0.28)	−0.02	(0.08)
M1 Twin-specific physical activity	−0.26	(0.38)	−0.11	(0.07)
Covariates (between-family)				
M1 Family average functional limitations	0.94	(0.43)*	0.54	(0.09)***
M1 Family average disease burden	0.39	(0.09)***	0.05	(0.02)*
M1 Family average well-being	0.05	(0.07)	−0.02	(0.02)
M1 Family average smoking	0.15	(0.20)	0.10	(0.05)
M1 Family average education	−0.33	(0.20)	−0.13	(0.04)**
M1 Family average physical activity	0.19	(0.20)	0.05	(0.07)
M1 Age	0.03	(0.01)**	0.01	(0.00)***
M1 Female	−0.15	(0.27)	−0.04	(0.06)

MIDUS = Midlife in the United States.

* $p \leq .05$.

** $p \leq .01$.

*** $p \leq .001$.

predictor in the standard approach as well as in the model that did not control for twin-specific and family-average covariates (step 5). Furthermore, the effect was only reduced slightly when specifying a within-family effect and controlling for covariates (from 0.13 to 0.09).

DISCUSSION

The purpose of this study was threefold. First, we examined potential causal associations between disease burden and functional limitations over time. Second, to assess directionality of the association, we tested two longitudinal models, one predicting later functional limitations based on initial disease burden and one predicting later disease burden based on initial functional limitations. Third, we sought to determine the potential moderating role of well-being, or its contribution to discordance within MZ twin pairs on disease burden, functional limitations, and their longitudinal associations. Overall, results support substantial heterogeneity in disease burden and functional capacity within MZ twin pairs at baseline and over time. Directionally, results favor the Disablement Process Model, or disease burden leading to increases in functional limitations. Results did not support a moderating role for well-being.

Prior research has supported two directions linking disease burden and functional limitations, and it has recently been posited that the effects may actually be bidirectional (9). Thus, in the present study, we tested both directions linking disease burden and functional limitations. We found general support for the Disablement Process Model only. In other words, baseline disease burden was more strongly linked to increases in functional limitations over time than baseline functional limitations were to change in disease burden. The use of MZ twin data controlled for genetic and familial confounds that could contribute to both disease burden and functional limitations, strengthening this interpretation. The longitudinal within-family effect of earlier disease burden with increases in functional limitations remained in the final model, and it was observed after controlling for familial confounds by nature of the design as well as key covariates. The results bolster the support for a potentially causal association between disease burden and functional limitations and sharpen the spotlight on nonfamilial influences on functional limitations as a result of multimorbidity.

The results from the sensitivity analyses confirm that the effect we detected between earlier disease burden and later functional limitations was purely a within-family effect. The effect of earlier disease burden on later functional limitations was only slightly reduced (0.13–0.09) when specified to be a within-family effect, and this reduction is primarily explained by the covariates; thus, the majority of the standard approach effect detected in MZ twins is driven by within-family variability.

As proposed by the Disablement Process Model, there are extraindividual and intraindividual factors that mediate the link between disease and functional limitations. Possible direct mechanisms include physiological risk factors, such as inflammation. Arthritis, a contributor to disease burden and the most prevalent

condition in our multimorbidity index, involves chronic inflammation of one or more joints and is one of the leading risk factors for functional limitations among adults. One prospective study showed that people who had arthritis at the age of 50 to 62 years had a higher risk of developing mobility limitations over a 10-year follow-up compared with those who did not have arthritis (46). In a longitudinal sample, inflammation partly explained the link between multimorbidity and onset of functional limitations (47). Therefore, inflammation is a good candidate for future research investigating the mechanisms of the disablement process. Additional physiological mechanisms could include cardiovascular pathways, based on evidence that cardiovascular biomarkers (e.g., blood pressure and serum lipids) are linked to functional ability (48).

Potential indirect mechanisms facilitating the disablement process could include behavioral factors. For example, chronic diseases often result in reduced physical activity at a time when physical activity is already declining with advancing age (49). Reduced physical activity could lead to declines in physical functioning. This possibility is bolstered by prospective studies showing that higher levels of physical activity from midlife onward decrease the risk of functional limitations in older age (50).

Based on recent research supporting the unique role of positive influences, such as positive psychological well-being, on a variety of health outcomes (20–22), eudaimonic well-being was included as a moderator in the present study. Contrary to hypotheses, well-being was not a moderator in either of the directions tested. One possible explanation could be that eudaimonic well-being is directly related to chronic conditions or functional limitations but does not act as a moderator in the disablement process. Some previous work has found no direct association between well-being and multimorbidity in the MIDUS sample (22), although functional limitations have been cross-sectionally linked to lower well-being (51). Importantly, some of these prior findings involved different conceptualizations of well-being, such as positive affect and self-efficacy. Thus, eudaimonic well-being specifically may not act as a moderator in this context, but other domains of well-being (e.g., subjective well-being) may, and the latter can be the focus of future studies. In addition, Choi and colleagues (52) recently found longitudinal associations between eudaimonic well-being and functional limitations using the MIDUS sample. Specifically, findings showed that functional limitations negatively predicted well-being. Thus, instead of a moderator, lower eudaimonic well-being may be a more distal outcome of the disablement process.

Another possibility is that well-being is related to disease burden and functional limitations, but those associations are accounted for by within-family factors. Genetic effects on well-being have been frequently supported, with meta-analyses documenting a weighted average heritability in the range of 32% to 41% (53). However, most twin and family studies of well-being have focused on subjective well-being, hedonic well-being, and life satisfaction; few have examined the role of genetic factors in eudaimonic well-being. A genome-wide association study on hedonic and eudaimonic well-being found a large overlap in the genes influencing these two forms of well-being (54), but other studies suggest divergence. For example, Thege and colleagues (55) found a heritability estimate of less than 10% for meaning in life and 52% for sense of coherence (two eudaimonic well-being indicators), whereas heritability for life satisfaction was 67%. Future work should use MZ twin studies to further our understanding of how genetic factors influence eudaimonic well-being in particular and potential overlap in heritable aspects of well-being and disease burden.

LIMITATIONS, STRENGTHS, AND CONCLUSIONS

Although there are many strengths in the present study, some limitations warrant caution in interpretation. First, the sample used was mostly homogenous and lacked racial diversity (about 94% identified as White), which limits generalizability. Second, disease burden and functional limitations were measured using a self-reported assessment, which is not always the most reliable. That said, self-reports of chronic conditions do seem to be reasonably accurate (56). Nonetheless, the current results would be bolstered by analyses involving objective assessments of disease burden and functional capacity. Third, as noted previously, we assessed potential moderation by one domain of psychological well-being—eudaimonic. Other domains, such as hedonic well-being, and other aspects of psychosocial functioning, including depression, social connections, and self-efficacy, could contribute to discrepant associations between chronic disease and functional impairments in aging MZ twins. Contextual factors, such as socioeconomic status and access to health care, could also serve as potential moderators. Furthermore, there was asymmetry in the measures we used for disease burden and functional limitations. The disease burden measure was calculated based on a weighted index that accounted for each disease's propensity to lead to functional decline. However, we did not have a similar propensity score for functional limitations' ability to predict disease burden, making these models not completely comparable.

In a large sample of twins 75 years and older, older women (≥80 years) exhibited greater rates of heritability (34%–47%) for functional ability compared with women 75–79 years old (15%–34%; (57)). Thus, for older samples than the one used in the present study, the discordance in functional limitations may be smaller and within-twin effects of M1 disease burden on M2 functional limitations (for which we found support) may be harder to detect. However, among studies that use samples of the same age (i.e., MIDUS data; (35,58)), standardized within-family and between-family effects (e.g., −0.002 to −0.066) and variance explained (0.3%–18%) were very similar to our results.

Although the models used in this study accounted for both directions linking disease burden and functional limitations and included well-being as a moderator, we did not index the entire pathway. In other words, we did not include possible intermediaries or mechanisms that could influence the progression from disease burden to functional limitations, and vice versa. Future research should explore potential processes involved in the pathway, including some of the direct and indirect mechanisms mentioned previously.

Despite the limitations, there are many strengths of this study. By using longitudinal MZ twin data and testing two models for bidirectional effects, we were able to address the gaps of causality and directionality related to disease burden and functional limitations. We found support for a potentially causal mechanism by which earlier disease burden predicts later increases in functional limitations, controlling for unmeasured familial confounds including genetics. Although we did not find evidence for well-being as a moderator of this relationship, our results provide strong support of the direction of effects moving from disease burden to functional limitations, consistent with the Disablement Process Model.

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