Health factors as potential mediators of the longitudinal effect of loneliness on general cognitive ability

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Abstract

OBJECTIVE: Higher levels of loneliness in older adulthood predict cognitive decline, but research on mediating mechanisms is sparse. We examine multisystemic physiological risk, functional ability, self-rated health, depressive symptoms, and social participation as mediating processes for the association between loneliness and general cognitive ability over a 10-year follow-up in an older adult sample.

METHODS: Three waves of data from 3,005 individuals (mean intake age: 69.30 (SD: 7.85) years; female = 51.61%) recruited during Wave 1 of the National Social Life, Health, and Aging Project were used to test whether hypothesized mediators collected at the 5-year follow-up explained effects of baseline loneliness on 10-year general cognitive ability.

RESULTS: The relationship between baseline loneliness and 10-year general cognitive ability was not mediated by multisystemic physiological risk. Functional ability ($\beta = -0.24$, $SE = 0.05$, $p < .001$), self-rated health ($\beta = -0.08$, $SE = 0.02$, $p < .001$), depressive symptoms ($\beta = -0.20$, $SE = 0.05$, $p < .001$), and social participation ($\beta = -0.03$, $SE = 0.01$, $p = .016$) significantly mediated effects. Indirect effects remained significant after adjusting for demographic covariates and 5-year general cognitive ability, except social participation.

DISCUSSION: Loneliness may influence cognitive ability indirectly, signaling waning physical and psychiatric health more proximally correlated with cognitive ability. These mechanisms may serve as targets of intervention for cognitive maintenance in lonely older adults. (217/250)

Keywords: loneliness, cognition, mediation

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Significant effects of loneliness, conceptualized as perceived social isolation, on general cognitive ability (hereafter, cognition) are sometimes observed [1, 2] but not always [3-6].

Further, reported associations are largely descriptive, as studies rarely examine the physiological, psychological, or social pathways that might mediate longitudinal effects of loneliness on cognition [7]. The inclusion of health mediators may clarify null findings; effect sizes between processes that are more causally distal tend to be small or nonsignificant because effects are transmitted through intermediary links in the causal chain [8]. Clarifying the mechanisms underlying longitudinal associations between loneliness and cognition may explain inconsistent findings in the literature. Further, these mechanisms may inform late-life interventions that promote cognitive health. We examined whether temporal mediation through five health factors partially or fully explains the effect of loneliness on cognition over ten years.

Mechanisms Linking Loneliness and Cognition

Cross-sectionally, loneliness predicts diminished performance across several cognitive domains [9-11], including global cognition, executive functioning, memory recall, visuospatial ability, and processing speed [1]. Longitudinally, baseline loneliness correlates with decline in global cognition, memory, crystallized ability, processing speed, visuospatial ability, and minimal status exam scores [2, 12].

More recent research suggests less reliable associations. Loneliness was uncorrelated with global cognition after adjusting for effects of age, sex, depression, and family and friend social ties [3]. Further, null longitudinal correlations [4] or reverse causation [6] also have been found. Finally, cortisol mediated an otherwise null effect of loneliness on cognition [5].

Physiological dysregulation has been proposed as one mechanism underlying associations between loneliness and cognition [1, 13-15]. Greater loneliness correlates with worse functioning of numerous physiological systems, particularly the hypothalamus-pituitary-adrenal axis and inflammation [16, 17]. Loneliness is also associated with poorer cardiovascular [18, 19], immune [20], and metabolic function [21]. Physiological dysregulation also correlates with lower cognition [22-26], suggesting a potential mediating pathway. As an example, loneliness differentially predicts pro-inflammatory responses [17] that can lead to chronic stress and worsening cognition [1]. We, thus, take a multi-systems approach through which physiological dysfunction may link loneliness to cognition in older adults [27-30].

Other measures of physical health may also serve as mediators. Functional ability, which indexes people's ability to perform instrumental activities of daily living [31], negatively correlates with loneliness [32] and positively correlates with cognitive function [33, 34]. Lonely middle-aged adults tend to have insufficient physical activity levels [35] and are two times more likely to experience difficulty with activities of daily living compared to their nonlonely counterparts [36]. Further, loneliness may causally predict functional decline and frailty, as two prospective studies find that loneliness temporally precedes functional deficits [37, 38], possibly due to lonely people's greater tendency to be inactive. Loneliness may dampen motivation to engage in the kinds of activities that allow people to take care of themselves, like housework, chores, grocery shopping, and cooking. Cognitive dysfunction may be one consequence of loneliness that subsequently has an impact on the ability to accomplish functional activities.

Self-rated health, a subjective measure that encompasses global perceptions of physical and psychological health ranging from chronic conditions to adverse psychosocial states including negative life events and stress, correlates with loneliness and cognition in cross-

sectional [39, 40] and longitudinal studies [41, 42]. Self-rated health is a good measure of health in the current study, as it has been found not only to be a reliable correlate of people's actual health condition, but also of loneliness [43] and cognitive ability [44]. Greater levels of loneliness augur low levels of self-rated health [43], possibly because of inactivity [35] or general malaise in response to upregulated stress response [17]. As loneliness precedes self-rated health and self-rated health precedes cognitive decline [44], self-rated health may mediate longitudinal effects of loneliness on cognition.

Depressive symptomatology also correlates with loneliness [45-47] and cognition [48]. Importantly, loneliness often precedes depressive symptomatology [45] and depressive symptomatology covaries with worse cognitive functioning in older adults [49]. As depressive symptoms increase among those reporting greater loneliness, for example, clouding of consciousness (or "brain fog") also increases, leading to lower cognitive functioning [50]. Although other studies have controlled for depressive symptoms [51], in examining associations between loneliness and cognition, we propose that depressive symptomatology may be a temporal mediator in their association.

Finally, social participation correlates with loneliness [3, 52, 53] and cognition [54, 55], making it a potential mediator of their longitudinal association. Several studies demonstrate the importance of social connection for prevention of cognitive decline [55-58]. In the current study, we consider the possibility that people who report higher loneliness are predicted to participate less in social activities, a hypothesis supported in prior research [59]. Social participation may engender demands that are protective and maintain cognition, thus, leaving lonely people vulnerable to worse cognition.

Taken together, we hypothesized that greater physiological dysfunction, lower functional ability, lower self-rated health, greater depressive symptoms, and lower social participation at least partially mediate effects of loneliness on cognition.

Clinical Relevance of Identifying Mechanisms Linking Loneliness and Cognition

Interventions for loneliness in older adult populations have downstream effects on healthy aging, including physical, cognitive, and longevity benefits [60, 61]. Interventions range from senior support centers, activity-based programs (e.g., horticultural therapy programs), and traditional manualized interventions. Cognitive behavioral therapy, for example, can adequately address maladaptive social cognitions (e.g., “No one will ever want to include me.”) in lonely patients to lower risk of poor physical and mental health outcomes [62]. Clarifying mediating mechanisms in the temporal association between loneliness on cognition can elucidate which health factors to include and emphasize in interventions that promote social connectedness to protect against cognitive decline.

Social connectedness is important for health, as prolonged loneliness leads to worse physical and psychiatric health [60]. Interventions for loneliness have downstream effects on preventing psychiatric conditions, like depressive symptomatology, even 1-2 years later [63]. Support for our general hypothesis that physical, mental, and social health outcomes mediate found effects of loneliness on cognition supports development of early assessment and informed intervention of loneliness in older adults. Such efforts will sustain physical and psychological health important for cognition.

Method

Participants

We used publicly available data from the National Social Life, Health, and Aging Project (NSHAP), a population-based longitudinal study of social, physical, and psychological health in U.S. citizens born between 1920 and 1965 [64]. NSHAP consists of three waves: Wave 1 (2005/2006); Wave 2 (2010/2011); and Wave 3 (2015/2016). For the present study, three waves of data from participants recruited during Wave 1 ($N = 3,005$; born 1920-1947) were used. Baseline, 5-year, and 10-year follow-up data were derived from Wave 1, 2, and 3, respectively. Participants were recruited from the community using a national area probability sampling strategy. African-American and Hispanic people were oversampled. Through national household screening, NSHAP selected one person per household who could provide informed consent.

Table 1 presents the means, standard deviations, and available sample sizes of all variables. The majority of the sample was white/Caucasian (76.37%), educated at the high school level or beyond (74.20%), and female (51.61%). Participants had a mean age of 69.30 years (range: 57-85 years). The mean household income at intake was \$51,264.35 (median = \$35,000). The current study was approved by the Institutional Review Board at the University of Southern California (ID: UP-17-00067).

[Table 1 goes about here.]

Measures

Cognitive ability. Five-year and 10-year follow-up cognitive ability were measured by the Chicago Cognitive Function Measure (CCFM), an adapted version of the Montreal Cognitive Assessment (MoCA) [65] that assesses multiple cognitive domains in the following order: executive function, visuo-construction skills, naming, immediate memory recall, attention, language, abstract thinking, short-delay memory recall, and orientation [66]. The assessment

takes 10-15 minutes to administer. CCFM items were summed to create a general measure of cognitive ability and converted to MoCA-equivalent scores [66]; higher scores indicate better cognition (range: 10.25 – 29.63).

Loneliness. Baseline loneliness (UCLA) was measured using the 3-item version of the UCLA Loneliness Scale [67]. Participants rated how often they felt they were left out, isolated, and lacking companionship on a 3-point Likert scale. Items were summed with higher scores indicating stronger loneliness (range: 0 – 6).

Multisystemic physiological risk. Multisystemic physiological risk (MSPR) was measured with eight variables. Measures used to assess cardiovascular functioning included systolic blood pressure, diastolic blood pressure, and pulse rate. C-reactive protein measured inflammatory functioning. Glycosylated hemoglobin assessed metabolic functioning. An index of Epstein-Barr Virus antibodies measured immune functioning. Dehydroepiandrosterone-sulphate was used as a neuroendocrine biomarker [28]. Body mass index was included as an anthropometric measure of health.

We used a group allostatic load index score to index multi-system physiological risk [28]. The score gives equal weight to each of the eight biomarkers available in NSHAP at 5-year follow-up. Scores were calculated by summing the number of biomarkers that exceed clinical cutoff values or lie above a percentile threshold if no clinical cutoff was available (**Appendix 1**). Higher scores indicate more risk (range: 0 – 6).

Functional ability. Functional ability (FA) was measured by eight items: one's degree of difficulty with preparing meals, taking medications, managing money such as writing checks and keeping track of bills, shopping for groceries, performing light housework such as dishes, light vacuuming, or dusting, using a telephone, driving a car during the day, and driving a car during

the night. Responses were given on a 4-point Likert scale. Composite scores consist of mean scores with higher scores indicating greater difficulty (range: 0 – 2.88)

Self-rated health. Self-rated health (SRH) was measured by a single item asking, “Would you say your health is excellent, very good, good, fair, or poor?” on a 5-point Likert scale. Higher scores indicate better health (range: 1 – 5).

Depressive symptoms. Depressive symptoms (CESD) were measured by ten items from the CES-D scale on a 4-point Likert scale. The CES-D loneliness item was excluded from this variable. Higher sum scores indicate stronger symptomatology [68] (range: 0 – 27).

Social participation. Social participation (SP) was measured by four items that assessed frequency of attending organized meetings, attending religious services, volunteering, and socializing with family and friends in the past year. Participants responded using a 7-point Likert scale. Higher mean scale scores indicate greater social participation (range: 0 – 6).

Covariates. Covariates in the fully adjusted models included sex, race/ethnicity, age, annual household income, and MoCA at 5-year follow-up. All demographic covariates were taken at baseline. *Sex* is a dichotomous variable. *Education level* is a 3-level nominal variable (less than high school, high school diploma, more than high school). *Race/ethnicity* is a 5-level nominal variable (American Indian/Alaskan Native, Asian/Pacific Islander, Black/African American, Caucasian/White, and Other/Not reported). *Age* is a continuous variable. *Annual household income* is a continuous variable measuring income in the last 12 months at time of intake. *Total MoCA* at 5-year follow-up is a continuous variable.

Data Analysis

Variables were examined to assess for assumptions of normality and log transformed when necessary. Categorical variables were dummy coded while continuous variables were centered on the sample mean.

[Figure 1 here]

Mediation models (**Figure 1**) were used to examine the possible mediating effects of five health factors in the association between baseline loneliness and 10-year follow-up cognitive ability:

$$Health_{i5YR} = i_{Health} + a*Loneliness_{iB} + e_{Health} \quad (1)$$

$$Cog_{i10YR} = i_{Cog} + c'*Loneliness_{iB} + b*Health_{i5YR} + d*W_{iB} + e_{Cog} \quad (2)$$

Equation 1 demonstrates effects of loneliness at baseline, a , on health factors at 5-year follow up. The parameters i_{Health} and e_{Health} represent the intercepts and residual variances of the health factors. Equation 2 specifies direct effects of loneliness, c' , health factors, b , and covariates (e.g., age, gender, household income), d , on cognitive ability at 10-year follow-up. The parameters i_{Cog} and e_{Cog} represent the intercepts and residual variances of cognitive ability. Indirect effects ($a*b$) indicate effects of loneliness on cognitive ability via health factors. Models were estimated in lavaan (version 0.6-5) [69] using full information maximum likelihood (FIML) with robust standard errors. Missing data were assumed to be missing at random (MAR), as group comparisons between those who completed follow-up assessments differed from those who did not on the following variables: age, race, education, and loneliness. FIML was used to handle missing data and is appropriate when data are MAR or even missing not at random.

[Figure 1 goes about here.]

We estimated two models. In Model 1, we estimated a mediation model with only age included as a covariate (i.e., without d effects given in Equation 2). The focus of this model is whether the indirect effect ($a*b$) mediates effects of loneliness on cognition via health factors [70]. Full mediation occurs when c' is nonsignificant in the presence of $a*b$, otherwise partial mediation is assumed. Model 2 included all covariates and was used to test whether indirect effects were robust. The alpha level was set at .05; the alpha level adjusted for the False Discovery Rate (FDR) was .003.

Results

Descriptive Results

Mean MoCA scores at 5-year and 10-year follow-ups were below the normal range cutoff of 26 [65], although the large standard deviations reflect variability in cognitive ability. Baseline loneliness scores were low ($M = 1.04$). Mean multisystem physiological risk (MSPR; $M = 2.03$) suggests that the average participant in NSHAP had around two biomarkers with values that fall within the risk range.

Table 2 presents correlations among all key variables with bolded values indicating statistically significant correlations ($p < .05$). The correlation between loneliness and cognition was significant but small ($r = .08$); the magnitude of correlations between loneliness and all health variables were small (.06 - .35); and the correlations between health variables and cognition were small (.04 - .39).

[Table 2 goes about here.]

Mediation Results

Table 3 presents results of models examining if health factors at 5-year follow up mediate the association between baseline loneliness and cognition at 10-year follow-up. In unadjusted models, the regression coefficient (c) between loneliness_B and MoCA_{10YR} was

significant and negative. Loneliness_B predicted all health factors_{5YR} (*a*) and all health factors_{5YR} predicted MoCA_{10YR} (*b*). Indirect effects, however, varied by health factor.

[Table 3 goes about here.]

For multisystemic physiological risk, only the direct effect *c'* was significant ($\beta = -0.22$, $SE = 0.10$, $p = .032$), indicating no evidence for mediation through MSPR_{5YR}. Functional ability fully mediated effects of loneliness on 10-year cognition, as the indirect effect *a*b* was significant ($\beta = -0.24$, $SE = 0.05$, $p < .001$). Similarly, self-rated health fully mediated effects of loneliness on 10-year cognition ($\beta = -0.08$, $SE = 0.02$, $p < .001$). Depressive symptomatology also fully mediated effects of loneliness on 10-year cognition ($\beta = -0.20$, $SE = 0.05$, $p < .001$). Finally, social participation partially mediated effects of loneliness on 10-year cognition, as the adjusted direct effect *c'* was significant ($\beta = -0.20$, $SE = 0.10$, $p = .048$) as was the indirect effect ($\beta = -0.03$, $SE = 0.01$, $p = .016$). Effect sizes of the direct and indirect associations between loneliness and cognition were small (**Table 4**).

[Table 4 goes about here.]

In models adjusted for all covariates, all indirect effects remained significant but were attenuated, except for social participation, which was nonsignificant (**Table 3**). Post-hoc probing indicated that including MoCA_{5YR} and education level in the model explained the mediating effect of social participation.

At the FDR-adjusted alpha cutoff, the mediating effect of functional ability, self-rated health, and depressive symptoms were significant in the unadjusted models while only functional ability was significant in the adjusted models.

Discussion

Health factors possibly play a crucial role in the causal chain between loneliness and cognition. Based on current findings, loneliness may serve as a harbinger of physical and psychiatric decline more proximally associated with cognition. Such an interpretation is consistent with previous studies reporting only an indirect relationship between loneliness and cognition [3-5]. While biological dysregulation is considered to be the leading hypothesized mediating mechanism [1] in the correlation between loneliness and cognition, null findings in the present study provide little support for this pathway. Other health factors should not be overlooked as important mediating mechanisms in the temporal correlation between loneliness and cognition.

Importance of Health Factors in the Temporal Correlation of Loneliness and Cognition

The finding that functional ability mediates the temporal relationship between loneliness and cognition has several possible implications. For one, diminished functional ability may indicate the effects of an underlying disease process exacerbated or induced by loneliness that eventually leads to worse cognition. Loneliness may also decrease the motivation necessary to effectively care for oneself, leading to downstream effects on cognition. A general sense of disconnection from one's social relationships may precipitate declines in actual and perceived health functioning, both of which augur worse cognitive functioning in older adulthood [34, 40, 53, 54].

Self-rated health might be a proxy for unhealthy lifestyles that explain the longitudinal effect of loneliness on cognition. While the validity of SRH is supported primarily by its correlation with mortality [71, 72], there is no common definition of what constitutes "good" and "poor" health. Lonely people might feel as though they have worse health despite being as objectively healthy as nonlonely people. Yet, feeling worse about one's health without having

treatable medical conditions may increase worry and anxiety about possible health issues and decrease motivation to tend to basic needs. Prolonged worry and physical inactivity, thus, may be the subcomponents of SRH that mediate long-term effects of loneliness on cognition [41, 43].

The finding that depressive symptoms serve as a temporal mediator for the loneliness-cognition relationship is consistent with studies suggesting that loneliness predicts depressive symptomatology at follow-up [45, 73] and findings that depressive symptoms are a risk factor for worse cognitive ability [48]. Increased loneliness leads to behavioral changes like less exercising and difficulty sleeping [35] – changes that overlap with depressive symptoms – which in turn can disrupt cognitive functioning. Loneliness is a correlate of depressive symptomatology [68] and found to be a precursor of depressive symptomatology [45, 74]. Further, early intervention of loneliness has an impact on depressive symptomatology [63], which suggests that increasing social connectedness may sustain cognition by preventing downstream depressive symptoms.

Although initially considered to be a mediating mechanism, social participation appears to be confounded with longitudinal effects of cognition. When controlling for concurrent cognitive ability at 5-year follow-up, social participation no longer was a significant mediator. Good cognitive functioning might be a precondition for social participation [56], such that differences in social participation might be a proxy for differences in complex cognitive processes required for social interaction [75]. Effects of social participation on cognitive ability at 10-year follow-up, particularly weak effects like those observed here, may not account for additional variance above and beyond effects of concurrent cognitive ability.

Effect sizes between loneliness and cognition are worthy of comment, particularly given theoretical interest in the mechanisms that explain their association [1]. Effects of loneliness on

cognition, both direct and indirect, are small, ranging from .005 – .015 in the current study (**Table 4**). These values are consistent with *R*-squared values of .002 – .05 reported in previous studies using datasets comparable to the NSHAP sample [11, 15]. This is not to say that the correlation between loneliness and cognition or the health factors that mediate the correlation are not interesting; indeed, they are. But such small effects must be contextualized, as many older adults do not feel lonely [76]. The present study further suggests that older adults who report feeling lonely may not be as beset with worse physical and psychological health as is assumed sometimes nor at increased risk for cognitive decline and impairment.

Clinical Implications

A loneliness-health-cognition model may inform the conceptualization of targets for cognition-promoting interventions. Current behavior interventions for loneliness and social connection rarely consider downstream consequences for cognition, but rather focus on increasing social connectedness to reduce depression and anxiety [63]. Yet, our results support the idea that implementing these very interventions not only for the purposes of decreasing emotional distress, like depressive symptoms, but also for galvanizing motivation to engage in health-promoting behaviors, can ultimately bolster cognition [60, 61].

Behavioral activation [77], for example, is an intervention designed to impart active coping strategies (e.g., maintaining a daily schedule, calling a family member even when you do not feel up to it) that may remediate loneliness and reinforce healthy behaviors that maintain cognitive functioning [78]. Of those who are lonely, for example, few might be expected to experience functional decline, but those who do will may experience high risk of lower cognition. Cognitive and behavioral interventions for loneliness may lower the chances of becoming depressed or functionally impaired, thereby weakening the likelihood of lower

cognition. We recommend that when health providers assess for cognitive functioning, they too assess for loneliness in their review, as increasing social connection may also improve cognition.

Limitations

One limitation of this study is that NSHAP is a nonexperimental research design, so strict causal conclusions cannot be inferred despite the longitudinal approach. Although we established temporal precedence in our study design, reverse causation is a plausible rival hypothesis. As an example, declines in functional ability may antecede loneliness in the causal chain [79]. This does not necessarily diminish causal conclusions in the current study but admonishes future research to consider that the evaluated pathways are not the *only* causal pathways that may be important for understanding the temporal correlation between loneliness, health factors, and cognition. Second, changes in loneliness over time may confound the mediating role of health factors. However, previous research shows that loneliness scores are relatively constant across late adulthood in NSHAP [46, 80], which supports selection of the temporal order among loneliness, health factors, and cognition in the current study. Third, the cognitive screening measure employed may be a more valid measure of distinguishing normal cognitive functioning from impaired functioning versus evaluating general cognitive ability [65].

Conclusion

Little support was found to conclude that baseline loneliness predicts cognitive ability over 10-year follow-up after accounting for mediating processes and covariates. The current study, thus, emphasizes the importance of considering mediating mechanisms of the temporal association between baseline loneliness and general cognitive ability.

Author Contributions

Alice J. Kim contributed to the analysis, interpretation of data, drafting of the work, and final revisions.

Christopher R. Beam contributed to the conception of the study, analysis, interpretation of data, drafting of the work, and final revisions.

Nicole Greenberg contributed to the analysis, drafting of the work, and final revisions.

Shanna L. Burke contributed to the conception of the study, drafting of the work, and final revisions.

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Table 1. *Descriptive Statistics of Sample*

	<i>M (%)</i>	<i>SD</i>	<i>n</i>
Total MoCA _{10YR}	23.23	3.84	1249
UCLA Loneliness _B	1.04	1.41	2385
Health Mediators			
Multisystem Physiological Risk _{5YR}	2.03	1.21	1589
Functional Ability _{5YR}	0.25	0.45	1971
Self-Rated Health _{5YR}	3.20	1.06	2258
Depressive Symptoms _{5YR}	4.18	4.24	2040
Social Participation _{5YR}	3.11	1.43	1914
Covariates			
Age _B	69.30	7.85	3005
Sex (Female)	51.61%		3005
Education			
< HS	25.81%		3003
HS	36.80%		3003
> HS	37.40%		3003
Race/Ethnicity			
American Indian or Alaskan Native	0.73%		3005
Asian/Pacific Islander	1.20%		3005
Black/African American	16.94%		3005
Other/Not reported	4.76%		3005
White/Caucasian	76.37%		3005
Household Income _B	51264.35	76559.34	2124
Total MoCA _{5YR}	23.14	3.85	1807

Note. B = Baseline. 5YR = 5-Year Follow-Up. 10YR = 10-Year Follow-Up. MoCA refers to MoCA-equivalent scores derived from the Chicago Cognitive Function Measures (Shega et al., 2014) and assesses multiple cognitive domains in the following order: executive function (Trails b), visuo-construction skills (cube and clock), naming (animal recognition), immediate memory recall (five words), attention (forward/backward digit span, vigilance task, serial 7s), language (sentence repetition and verbal fluency), abstract thinking (item similarity), short-delay memory recall (same five words), and orientation. Loneliness was measured with three items from the UCLA Loneliness Scale [67] with higher scores indicating greater loneliness (range: 0-6). All

health mediators were taken at 5-year follow-up. Multisystems physiological risk is the sum of eight physiological measures that exceed clinical cutoff values or lie above a percentile threshold (Appendix 1) with higher scores indicating worse health (range: 0-6). Functional ability is the mean of eight instrumental activities of daily living in which participants self-reported the level of difficulty they had with each activity from no difficulty unable to do (range: 0-2.88). Self-rated health is a single item that reports the subjective rating of participants' health from poor to excellent (range: 1-5). Depressive symptoms is the sum of 10 items from the Center for Epidemiological Depression Scale, excluding the loneliness item, in which higher scores indicate greater symptomatology (range: 0-27). Social participation is the mean of four items in which participants self-reported social involvement in a variety of social activities on a 7-point scale with higher scores indicating greater participation (range: 0-6). Covariates in the fully adjusted models included sex, race/ethnicity, age, annual household income, and MoCA at 5-year follow-up. All demographic covariates were taken at baseline. *Sex* is a dichotomous variable, *education level* is a 3-level nominal variable (0 = less than high school, 1 = high school, 2 = greater than high school), *race/ethnicity* is a 5-level nominal variable, *age* is a continuous variable, *annual household income* is a continuous variable measuring income (USD in 2005/2006) in the last 12 months at time of intake. *Total MoCA* at 5-year follow-up is a continuous variable.

Table 2. *Intercorrelations of All Key Variables*

	UCLA_B	MoCA_{10YR}	MSPR_{5YR}	FA_{5YR}	SRH_{5YR}	CESD_{5YR}	SP_{5YR}
UCLA_B	1						
MoCA_{10YR}	-.08	1					
MSPR_{5YR}	.06	-.07	1				
FA_{5YR}	.16	-.23	.10	1			
SRH_{5YR}	-.14	.20	-.12	-.39	1		
CESD_{5YR}	.35	-.17	.04	.30	-.35	1	
SP_{5YR}	-.10	.10	-.02	-.19	.20	-.15	1

Note. Bolded values indicate statistically significant correlations ($p < .05$). UCLA_B = loneliness.

MoCA_{10YR} = cognition. MSPR_{5YR} = multisystemic physiological risk. FA_{5YR} = functional ability.

SRH_{5YR} = self-rated health. SP_{5YR} = social participation.

Table 3. *Mediation Model Results*

Multisystemic Physiological Risk (MSPR)								
Unadjusted for covariates (N = 3005)					Adjusted for covariates (N = 3005)			
Effect	b	SE	95% CI	p	Effect	b	SE	95% CI
a. UCLA _B → MSPR _{5YR}	0.06	0.03	[0.01, 0.11]	.017	a. UCLA _B → MSPR _{5YR}	0.06	0.03	[0.01, 0.11]
b. MSPR _{5YR} → MOCA _{10YR}	-0.23	0.12	[-0.46, -0.001]	.049	b. MSPR _{5YR} → MOCA _{10YR}	-0.14	0.08	[-0.29, 0.02]
c'. UCLA _B → MOCA _{10YR}	-0.22	0.10	[-0.42, -0.02]	.032	c'. UCLA _B → MOCA _{10YR}	-0.11	0.08	[-0.26, 0.04]
a*b. UCLA _B → MSPR _{5YR} → MOCA _{10YR}	-0.01	0.01	[-0.03, 0.004]	.130	a*b. UCLA _B → MSPR _{5YR} → MOCA _{10YR}	-0.001	0.01	[-0.02, 0.004]
c. UCLA _B → MOCA _{10YR}	-0.23	0.10	[-0.43, -0.03]	.022	c. UCLA _B → MOCA _{10YR}	-0.12	0.08	[-0.27, 0.03]
Functional Ability (FA)								
Unadjusted for covariates (N = 3005)					Adjusted for covariates (N = 3005)			
Effect	b	SE	95% CI	p	Effect	b	SE	95% CI
a. UCLA _B → FA _{5YR}	0.06	0.01	[0.04, 0.08]	<.001	a. UCLA _B → FA _{5YR}	0.06	0.01	[0.04, 0.08]
b. FA _{5YR} → MOCA _{10YR}	-4.11	0.47	[-5.04, -3.18]	<.001	b. FA _{5YR} → MOCA _{10YR}	-1.49	0.46	[-2.38, -0.60]
c'. UCLA _B → MOCA _{10YR}	-0.08	0.10	[-0.27, 0.12]	.433	c'. UCLA _B → MOCA _{10YR}	-0.07	0.08	[-0.23, 0.08]
a*b. UCLA_B → FA_{5YR} → MOCA_{10YR} **	-0.24	0.05	[-0.34, -0.14]	<.001	a*b. UCLA_B → FA_{5YR} → MOCA_{10YR} **	-0.09	0.03	[-0.15, -0.03]
c. UCLA _B → MOCA _{10YR}	-0.32	0.10	[-0.52, -0.12]	.002	c. UCLA _B → MOCA _{10YR}	-0.16	0.08	[-0.32, -0.01]
Self-Rated Health (SRH)								
Unadjusted for covariates (N = 3005)					Adjusted for covariates (N = 3005)			
Effect	b	SE	95% CI	p	Effect	b	SE	95% CI
a. UCLA _B → SRH _{5YR}	-0.11	0.02	[-0.15, -0.08]	<.001	a. UCLA _B → SRH _{5YR}	-0.11	0.02	[-0.15, -0.08]
b. SRH _{5YR} → MOCA _{10YR}	0.75	0.11	[0.53, 0.96]	<.001	b. SRH _{5YR} → MOCA _{10YR}	0.20	0.09	[0.03, 0.37]
c'. UCLA _B → MOCA _{10YR}	-0.15	0.10	[-0.35, 0.05]	.132	c'. UCLA _B → MOCA _{10YR}	-0.11	0.08	[-0.26, 0.05]
a*b. UCLA_B → SRH_{5YR} → MOCA_{10YR} **	-0.08	0.02	[-0.12, -0.05]	<.001	a*b. UCLA_B → SRH_{5YR} → MOCA_{10YR} **	-0.02	0.01	[-0.04, -0.002]
c. UCLA _B → MOCA _{10YR}	-0.24	0.10	[-0.43, -0.04]	.02	c. UCLA _B → MOCA _{10YR}	-0.13	0.08	[-0.28, 0.02]
Depressive Symptoms (CESD)								
Unadjusted for covariates (N = 3005)					Adjusted for covariates (N = 3005)			
Effect	b	SE	95% CI	p	Effect	b	SE	95% CI
a. UCLA _B → CESD _{5YR}	1.14	0.08	[0.98, 1.31]	<.001	a. UCLA _B → CESD _{5YR}	1.14	0.08	[0.98, 1.31]
b. CESD _{5YR} → MOCA _{10YR}	-0.18	0.04	[-0.25, -0.11]	<.001	b. CESD _{5YR} → MOCA _{10YR}	-0.06	0.03	[-0.11, -0.01]
c'. UCLA _B → MOCA _{10YR}	-0.05	0.11	[-0.26, 0.17]	.661	c'. UCLA _B → MOCA _{10YR}	-0.08	0.08	[-0.24, 0.08]
a*b. UCLA_B → CESD_{5YR} → MOCA_{10YR} **	-0.20	0.05	[-0.29, -0.11]	<.001	a*b. UCLA_B → CESD_{5YR} → MOCA_{10YR} **	-0.07	0.03	[-0.13, -0.01]
c. UCLA _B → MOCA _{10YR}	-0.25	0.10	[-0.44, -0.05]	.012	c. UCLA _B → MOCA _{10YR}	-0.15	0.08	[-0.30, 0.002]
Social Participation (SP)								
Unadjusted for covariates (N = 3005)					Adjusted for covariates (N = 3005)			
Effect	b	SE	95% CI	p	Effect	b	SE	95% CI
a. UCLA _B → SP _{5YR}	-0.11	0.03	[-0.16, -0.06]	<.001	a. UCLA _B → SP _{5YR}	-0.11	0.03	[-0.16, -0.06]
b. SP _{5YR} → MOCA _{10YR}	0.26	0.09	[0.09, 0.43]	.003	b. SP _{5YR} → MOCA _{10YR}	0.01	0.07	[-0.13, 0.14]
c'. UCLA _B → MOCA _{10YR}	-0.20	0.10	[-0.40, -0.002]	.048	c'. UCLA _B → MOCA _{10YR}	-0.12	0.08	[-0.28, 0.03]
a*b. UCLA_B → SP_{5YR} → MOCA_{10YR} *	-0.03	0.01	[-0.05, -0.01]	.016	a*b. UCLA_B → SP_{5YR} → MOCA_{10YR} *	-0.001	0.01	[-0.01, 0.01]
c. UCLA _B → MOCA _{10YR}	-0.23	0.10	[-0.43, -0.03]	.024	c. UCLA _B → MOCA _{10YR}	-0.12	0.08	[-0.28, 0.03]

Note. *Partial mediation: strength of mediation for social participation ($P_M = (a*b)/c = .13$).

**Full mediation: functional ability (Unadjusted = .75, Adjusted = .56); self-rated health (Unadjusted = .33, Adjusted = .15); depressive symptoms (Unadjusted = .80, Adjusted = .47).

Bolded = $p < .05$. UCLA = 3-item UCLA loneliness scale; MSPR = 8-item multisystem physiological risk score; FA = 8-item functional ability scale; SRH = 1-item self-rated health score; CESD = 10-item Center for Epidemiological Depression Scale score; SP = 3-item social participation scale score. Unadjusted models include only UCLA, MoCA, and health factor

scores. Adjusted models include the following covariates: sex, race/ethnicity, age, annual household income, and MoCA at 5-year follow-up.

Table 4. *Effect Sizes of Direct and Indirect Effects of Loneliness and Health Factors*

Multisystemic Physiological Risk (MSPR)	
Effect	R^2
a. UCLA _B → MSPR _{5YR}	.005
b. MSPR _{5YR} → MOCA _{10YR}	.006
c. UCLA _B → MOCA _{10YR}	.008
a*b. UCLA _B → MSPR _{5YR} → MOCA _{10YR}	.002
Functional Ability (FA)	
Effect	R^2
a. UCLA _B → FA _{5YR}	.033
b. FA _{5YR} → MOCA _{10YR}	.210
c. UCLA _B → MOCA _{10YR}	.008
a*b. UCLA _B → FA _{5YR} → MOCA _{10YR}	.013
Self-Rated Health (SRH)	
Effect	R^2
a. UCLA _B → SRH _{5YR}	.022
b. SRH _{5YR} → MOCA _{10YR}	.046
c. UCLA _B → MOCA _{10YR}	.008
a*b. UCLA _B → SRH _{5YR} → MOCA _{10YR}	.008
Depressive Symptoms (CESD)	
Effect	R^2
a. UCLA _B → CESD _{5YR}	.141
b. CESD _{5YR} → MOCA _{10YR}	.040
c. UCLA _B → MOCA _{10YR}	.008
a*b. UCLA _B → CESD _{5YR} → MOCA _{10YR}	.011
Social Participation (SP)	
Effect	R^2
a. UCLA _B → SP _{5YR}	.011
b. SP _{5YR} → MOCA _{10YR}	.011
c. UCLA _B → MOCA _{10YR}	.008
a*b. UCLA _B → SP _{5YR} → MOCA _{10YR}	.004

Note. UCLA = 3-item UCLA loneliness scale; MSPR = 8-item multisystem physiological risk score; FA = 8-item functional ability scale; SRH = 1-item self-rated health score; CESD = 10-

item Center for Epidemiological Depression Scale score; SP = 3-item social participation scale score.

Figure 1. Hypothesized Mediating Process.

Note. a = direct effect of loneliness at baseline on 5-year mediating health factor (e.g., multisystemic physiological risk, functional ability, self-rated health, depressive symptomatology, and social participation); b = direct effect of mediating health factor on 10-year cognition; c = total (unadjusted) direct effect of loneliness at baseline on 10-year cognition; c' = direct effect of loneliness at baseline on 10-year cognition, adjusting for indirect effect of mediating pathway ($a*b$).