How Loneliness Gets Under the Skin: Inflammation Mediates the Relationship Between Loneliness and Gait Speed

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ABSTRACT

Objective: Loneliness is linked to interleukin 6 (IL-6), a marker of systemic inflammation, which chronically has deleterious effects on physical and mental health across the adult life span. This study investigated cross-sectional relationships among loneliness, IL-6, demographics, multimorbidity, depression, obesity, friendship quantity, and slowed gait.

Methods: Data from the Midlife Development in the United States Biomarker Project, a national adult sample (N = 822; age range, 26–78 years) was used for this study. The PROCESS macro tested the hypothesis that IL-6 would mediate the relationship between loneliness and gait, after adjusting for demographic and health risk factors.

Results: Age ($\beta = 0.292$, $p < .001$), sex ($\beta = 0.197$, $p < .001$), body mass index (BMI, $\beta = 0.374$, $p < .001$), waist-hip ratio ($\beta = 0.242$, $p < .001$), and loneliness ($\beta = 0.089$, $p = .025$) but not multimorbidity ($\beta = 0.043$, $p = .20$), depression history ($\beta = 0.022$, $p = .47$), depression symptoms ($\beta = 0.036$, $p = .28$), and number of friends ($\beta = 0.022$, $p = .46$) contributed to the variance in IL-6. Serial mediation analyses supported the chained effect of loneliness on walking time through BMI and IL-6. Results also showed specific indirect effects of BMI and IL-6 on walking time, suggesting more than one pathway by which loneliness influences health.

Conclusions: These results suggest that loneliness may increase the risk of systemic inflammation, leading to slowed gait and adverse health outcomes. Psychosocial interventions that address loneliness may provide an optimal treatment target for reducing inflammation and preventing declines in health.

Key words: social self-preservation theory, loneliness, obesity, inflammation, depression, gait speed.

INTRODUCTION

Systemic inflammation is a major public health concern that has been recognized as a key driver of age-related diseases and dementia (1). Extensive research has investigated circulating levels of proinflammatory cytokines, particularly interleukin 6 (IL-6), in health and aging, given their crucial role in initiating inflammatory responses (2,3). Furthermore, considerable evidence has linked elevated IL-6 levels to several prevalent chronic diseases and disorders, including depression, cardiovascular disease, diabetes, and Alzheimer's disease (4,5). However, intervention efforts to manage systemic inflammation and its consequences have had limited success. Consequently, although attention has focused on directly modifying disease risk or targeting inflammation, emerging evidence suggests that focusing on emotional health and perceptions of social connectedness may hold the key to prevention.

There is a wealth of evidence supporting the association between negative emotional states and systemic inflammation. Studies have fairly consistently shown that peripheral levels of IL-6 are reliably elevated in response to negative affect induced by psychosocial stress (6–8). In particular, situations that threaten one's social self and/or that lead to appraisals of social rejection can preferentially elicit physiological responses (e.g., cortisol and IL-6), as proposed by the Social-Self Preservation (SSP) theory (9,10). It is worth noting that the heightened stress responses observed in these situations are not attributed to increased cognitive load or task difficulty (11). Instead, the perceived rejection or lack of social acceptance plays a significant role in eliciting these stress responses.

The impact of psychosocial stress on inflammatory markers, particularly IL-6, underscores the intricate relationship between the social self, negative emotional states, and systemic inflammation. Consequently, loneliness, a negative emotional state related to perceptions of social isolation and/or exclusion, may play a crucial role in increasing inflammatory responses owing to its social relevance and self-evaluative nature. The SSP theory posits that maintaining social acceptance is evolutionarily important to self-preservation, and as a result, perceived social isolation elicits autonomic, endocrine, and immune system responses (12). Layden and colleagues'

BMI = body mass index, **CES-D** = Center for Epidemiologic Studies Depression, **IL-6** = interleukin 6, **MASQ** = Mood and Anxiety Symptom Questionnaire, **MIDUS** = Midlife Development in the United States, **SSP** = Social-Self Preservation, **WHR** = waist-hip ratio

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(13) evolutionary model further suggests that loneliness activates opposing long-term and short-term motivations to promote self-preservation. Indeed, evidence suggests that loneliness heightens alertness for social threats and elicits activation of the hypothalamic-pituitary-adrenocortical axis as a means to promote short-term survival (13). Studies using data from the Midlife Development in the United States (MIDUS) Biomarker Project have also shown that loneliness is associated with elevated inflammatory markers, including IL-6, fibrinogen, and C-reactive protein, among adults aged 35 to 64 years (14). In addition, loneliness has predicted elevated IL-6 levels among Americans; however, this relationship was not observed in the Japanese sample in the MIDUS study (15). Longitudinal data from the National Social Life, Health, and Aging Project have also demonstrated that lonely older adults are more likely to exhibit increases in inflammatory and metabolic markers during a 5-year period, even after adjusting for relevant covariates (16).

Loneliness is associated not only with inflammation but also with declines in physical health, such as slowed gait. Research indicates that individuals reporting higher levels of loneliness exhibit poorer physical performance, such as slower gait speed (17). Among older adults with type 2 diabetes, McCaffery and colleagues (18) found that higher ratings of loneliness were associated with slower gait and more severe disability. In addition, loneliness across development has been associated with various psychological and physical consequences, including poor bone density (19). These findings highlight the wide-ranging impact of loneliness on both mental and physical well-being.

The present study focuses on gait speed, as an indicator of physical health and functional status, because of its established longitudinal associations with life expectancy, depression, multimorbidity, and mortality (20–23). Higher levels of loneliness independent of levels of social isolation have been longitudinally associated with a decline in gait speed in older adults (17). Although the exact mechanisms underlying this association are unclear, several studies have suggested a causal role of IL-6 on gait speed. For instance, longitudinal research has shown that higher IL-6 levels are associated with an annual decrease of 0.98 cm/s in gait velocity in older adults (24), and there is a moderate effect size between the trajectories of IL-6 and slowed gait in those with depression, suggesting that inflammation contributes to declines in gait speed over time (25). Here, the bidirectional relationships between obesity, IL-6, and depression should be noted, as each of these factors is associated with slowed gait. Specifically, there is robust longitudinal evidence of a bidirectional relationship between obesity and depression (26). These findings indicate that adipose tissue in obese individuals both produces and releases higher amounts of IL-6. In turn, this can result in increased inflammation as well as production of stress hormones like cortisol, which, when chronically elevated, can contribute to depressive symptoms (26,27).

Present Study

Overall, the data suggest that loneliness, inflammation (IL-6), depression, and gait velocity are interconnected factors that can influence an individual's health, functional abilities, and mortality risk. Although loneliness is often associated with depression (28), emerging evidence suggests that loneliness has unique detrimental effects on physical health, potentially through increased inflammation. In addition, it is possible that prior research that has used the Center for Epidemiologic Studies Depression (CES-D; (29)) scale may partly reflect the influence of social isolation and loneliness on IL-6, as many items measure socially relevant (e.g., "people were unfriendly," "I felt that people disliked me," "I felt that I was just as good as other people") as well as subjective experiences of loneliness (e.g., "I felt lonely"). Hence, this study uses the Mood and Anxiety Symptom Questionnaire (MASQ; (30–32)), which focuses on core symptoms of depression and does not include social content, to help disentangle loneliness from the measurement of depression.

Loneliness has been linked to negative health outcomes, including slowed gait, depression, and elevated IL-6 levels. As per SSP theory, loneliness may trigger psychosocial stress that activates inflammatory pathways and the release of IL-6. In this context, loneliness has the capacity to lead to cytokine dysregulation, which in turn negatively impacts gait speed. Although these factors have been studied individually, this model remains to be tested. To our knowledge, the present study is the first to investigate inflammation's role in the relationship between loneliness and gait speed. The primary aim of this study was to test a cross-sectional mechanistic model. We hypothesized that the relationship between loneliness and gait speed would be mediated by IL-6, even after adjusting for relevant covariates in the model. We also aimed to determine the relative contributions of demographic factors, markers of adiposity (body mass index [BMI] and waist-hip ratio [WHR]), depression, multimorbidity, and friendship quantity to IL-6 and whether loneliness contributed to the variance in IL-6 beyond these established risk factors. Correlational analyses were conducted to better characterize the relationships among age, inflammation (IL-6), depression, loneliness, friendship quantity, and gait. One-way analysis of variance examined sex-related differences in means on the primary variables. Finally, because obesity can increase adipose tissue–derived IL-6 and lead to higher circulating levels of IL-6 (26,33–35), we were interested in statistically testing the sequential process of whether loneliness influenced BMI, which successively influenced IL-6 levels, which culminated in slower walking time. Post hoc analyses thus explored a serial multiple mediator model that investigated the direct and indirect effect(s) of loneliness (X) on walking time (Y) sequentially through BMI (M1) and IL-6 (M2).

METHODS

Participants

This study used data from the MIDUS Biomarker Project. The MIDUS is an interdisciplinary study that investigates behavioral, psychological, and social factors contributing to health and well-being in a nationally representative sample of Americans (36). Recruitment and study procedures are described in detail elsewhere (see Ref. (37)) and are available at www.midus.wisc.edu. Briefly, data used for this study were collected from October 2012 to March 2016 at the following academic medical center sites: University of Wisconsin (n = 334), University of California at Los Angeles (n = 294), and Georgetown (n = 235; total N = 863) (37). The present study included 822 adults aged 26 to 78 years who had valid IL-6 data. Those needing an assistive device to walk or missing gait data were excluded from the study. The University of Wisconsin at Madison Institutional Review Board approved the MIDUS procedures, and the respective institutional review boards for the Biomarker

Project collection sites approved the respective substudy procedures. All participants provided written informed consent. The data used for this study are publicly available through the ICPSR data repository (https://www.icpsr.umich.edu/), and the database's variable names for this study are provided in List S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A984.

Measures

Clinical Characteristics

Structured clinical interviews were used to collect survey information on the participants' health history and demographics. The presence of physician diagnosed medical conditions (heart disease, hypertension, diabetes, hypercholesterolemia, transient ischemic attack or stroke, thyroid disease, and depression) was coded as being present or absent (38). The total number of conditions excluding depression was summed to form the summary health variable of multimorbidity (see List S1 for further details, Supplemental Digital Content, http://links.lww.com/PSYMED/A984). Self-reported history of depression served as a categorical variable.

Inflammatory Cytokine

IL-6 levels were measured using the Quantikine High-sensitivity enzyme-linked immunosorbent ELISA assay (kit no. HS600B; R & D Systems, Minneapolis, Minnesota). Cytokine collection procedures included a fasting blood draw conducted in the morning with instructions to not engage in any intense physical activity (e.g., exercising) before the visit. Further details are reported in Weinstein et al. (39).

Gait Speed

Gait speed was measured via walking time. Participants were instructed to walk "at your usual speed, just as if you were walking down the street to go to the store." Time in seconds to walk 25 ft was collected for two trials via stopwatch (40). Participants are positioned at floor markers that delineate the start-stop points but are blinded to the timed walkway points. The examiners walked behind patients out of their field of vision to avoid influencing their pace. The present study used the second trial as the first walking trial is more impacted by whether the participant understood the walking instructions. Longer walking times reflect worse function.

Socioemotional Scales

Feelings of loneliness and social isolation were measured by seven items from the UCLA Loneliness Scale (41). Participants are asked to rate each item on a scale from 1 (never) to 4 (often). Cronbach α coefficient suggested adequate internal item consistency for the UCLA Loneliness Scale within the total sample (α = .871, n = 863) (42). The MASQ's 12-item General Distress-Depressive Symptom, which demonstrated good internal item consistency within this sample (α = .891, n = 863) (42), evaluated depressive symptoms. The Social Support scale measured friendship quantity on an interval scale of 1 (0–5 friends), 2 (6–10 friends), 3 (11–20 friends), 4 (21–50 friends), and 5 (51 or more friends; see Ref. (42)). The distribution of the number of friends was negatively skewed with 59.8% of the participants endorsing 0 to 10 friends (median range = 6–10).

Analyses

Preliminary analyses examined variable distributions and sample characteristics to make sure assumptions were met. Highly skewed data were log-transformed to approximate a normal distribution when appropriate, which included IL-6, walking time, BMI, and WHR. Descriptive statistics were generated, and potential group-related differences were evaluated using univariate analyses. Spearman rank correlation analyses investigated the simple associations among the study variables. The mediation models were tested using the SPSS PROCESS macro (version 4, 43). The PROCESS approach is a regression-based method that simultaneously evaluates the direct and indirect effects and provides bootstrapped 95% confidence intervals (CIs) for these estimates, which may serve as measures of effect size (43). Scores were centered at their mean to aid in their interpretation. Hierarchical multiple regression analyses investigated contributors to IL-6. Listwise deletion was used for missing data for the health variables. The Durbin-Watson test indicated sufficient independence of residual terms, and collinearity diagnostics (Tolerance and Variance Inflation Factor) indicated that assumptions of independence were met for the study variables included in the regression models (44). Statistical analyses were performed via SPSS (version 28), and all tests of significance were two-tailed.

RESULTS

Sample Characteristics

The mean (standard deviation [SD]) age for the study sample was approximately 52 years (M [SD] = 52.53 [13.46] years), with 51.0% being women. Table 1 presents descriptive statistics for the study sample and the Spearman ρ correlation coefficients for the simple associations among all of the study variables. As hypothesized, the predictor variable, loneliness, was statistically associated with greater IL-6 levels (in picrograms per milliliter), walking times, MASQ depression symptoms, BMI, and negatively associated with friendship quantity. The mediator variable, IL-6, was also statistically associated with greater age, slower walking time, multimorbidity, and obesity. In addition to being associated with loneliness and IL-6, the outcome variable of slower gait speed was associated with older age, sex, multimorbidity, obesity (BMI and WHR), and friendship quantity.

One-way analyses of variance examining sex-related differences in means on the primary variables found that women were younger, had slower walking times, and reported more depressive symptoms than men. Men were higher in vascular risk factors than women, whereas women were more likely to have a diagnosis of depression or thyroid disease. Relevantly, men and women did not significantly differ in inflammatory markers or subjective ratings of loneliness. Those with a self-reported history of depression (n = 280: M [SD] = 21.86 [7.82]) reported significantly higher depression symptoms on the MASC as compared with those without a history of depression (n = 530: M [SD] = 16.95 [4.56]; Welch $F(1, 380.50) = 94.08$, $p < .001$).

Further descriptive statistics for the study sample by sex are presented in Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A984.

Regression Analysis of Contributors to IL-6

Hierarchical regression analysis investigated the relative contributions of demographics (age and sex), obesity (BMI and WHR),

TABLE 1. Participant Characteristics

Variables	M (SD)	1	2	3	4	5	6	7	8	9
1. Age, y	52.5 (13.46)	—								
2. % Female	52.6	−0.122**	—							
3. IL-6, pg/ml	2.68 (2.01)	0.351**	0.024	—						
4. Loneliness	12.67 (4.52)	−0.056	−0.065	0.117**	—					
5. Walking time	13.42 (2.80)	0.152**	0.104*	0.338**	0.120**	—				
6. MASQ scores	18.63 (6.32)	−0.204**	0.115**	0.015	0.411**	0.029	—			
7. Multimorbidity	1.16 (1.17)	0.460**	−0.051	0.331**	0.036	0.255*	0.071*	—		
8. WHR	0.90 (0.10)	0.300**	−0.615**	0.315**	0.050	0.121**	−0.115*	0.310	—	
9. BMI, kg/m^2	30.24 (7.49)	0.023	−0.010	0.458**	0.089*	0.290**	0.015	0.261**	0.325**	—
10. Friends	2.35 (1.18)	0.070*	−0.052	−0.039	−0.272**	−0.112*	−0.110*	0.002	−0.003	−0.041

M (SD) = mean (standard deviation); IL-6 = interleukin 6; Loneliness = UCLA Loneliness Scale; Greater walking time (in seconds) reflects worse function; MASQ = Mood and Anxiety Symptom Questionnaire Distress—depressive symptoms; WHR = waist-hip ratio; BMI = body mass index; Friends = number of friends reflects ranked values on a scale 1 to 5, with approximately 68% of scores falling between 0 and 50 friends.

* $p < .05$ (two-tailed).

** $p \leq .001$ (two-tailed).

multimorbidity, depression history, depression symptoms (continuous), number of friends, and loneliness to IL-6. The first model indicated that age, sex, BMI, and WHR but not depression status, depression symptoms, multimorbidity, or number of friends contributed to the variance in IL-6 levels (model 1 summary: adjusted $R^2 = 0.370$, $F\Delta = 58.12$ (8, 769), $p < .001$). The fully adjusted model with age ($\beta = 0.299$, $p < .001$), sex ($\beta = 0.186$, $p < .001$), BMI ($\beta = 0.374$, $p < .001$), WHR ($\beta = 0.236$, $p < .001$), multimorbidity ($\beta = -.041$, $p = .20$), depression history ($\beta = 0.023$, $p = .46$), depression symptoms ($\beta = 0.041$, $p = .23$), and number of friends ($\beta = 0.011$, $p = .72$) found that the addition of loneliness contributed to 8.7% of the variance in IL-6 ($\beta = 0.087$, $p = .010$) beyond these established risk factors in the model (model 2 summary: adjusted $R^2 = 0.375$, $F\Delta = 6.62$ (1, 768), $p = .010$). Examination of the standardized coefficients suggests that BMI, age, and WHR made the largest contributions to IL-6, followed by sex and loneliness. Multimorbidity, depression, and number of friends did not make an appreciable contribution to inflammation when these other risk factors are accounted for in the model.

Inflammation Mediates the Relationship Between Loneliness and Walking Time

Our primary aim was to evaluate whether the observed relationship between loneliness (*X*) and slowed gait (*Y*) was mediated by IL-6 levels (*M*). For this analysis, age, sex, BMI, WHR, and depressive symptoms (MASQ scores) served as covariates in the model. Table 2 presents the descriptive summary statistics for the PROCESS Model ($N = 818$). Results from this model found evidence of significant direct and indirect effects. As Table 2 shows, the covariates of age, sex, BMI, WHR, and loneliness but not depression symptoms were significantly associated with IL-6. For interpretation purposes, the coefficients were exponentiated as the outcome variables of IL-6 and walking time were log-transformed. Adjusting for age, sex, age, BMI, and WHR, the total effect indicated that

TABLE 2. PROCESS Model Summary for the Mediating Role of Inflammation Between Loneliness and Gait While Adjusting for Age, Sex, Obesity, and Depression Symptoms

$N = 818$		Inflammation (IL-6)				Walking Time (Time in Seconds)		
Variable		Coefficient	SE	*P*		Coefficient	SE	*P*
Constant	i_M	−2.287	0.1631	<.001	i_y	0.7817	0.0500	<.001
Loneliness	*a*	0.0058	0.0024	.016	*c′*	0.0011	0.0007	.10
IL-6		—	—	—	*b*	0.0403	0.0097	<.001
Age	cov	0.0082	0.0008	<.001	*cov*	0.0006	0.0002	.037
Sex	cov	0.1145	0.0246	<.001	*cov*	0.0286	0.0068	<.001
BMI	cov	1.322	0.1041	<.001	*cov*	0.1601	0.0314	<.001
WHR	cov	1.521	0.2627	<.001	*cov*	0.1425	0.0737	.053
MASQ	*cov*	0.0022	0.0017	.20	*cov*	0.0005	0.0005	.27
Summary:		$R = 0.614$; $R^2 = 0.378$, $p < .001$				$R = 0.415$; $R^2 = 0.172$, $p < .001$		

IL-6 = interleukin 6; Loneliness = UCLA Loneliness Scale; cov = covariate; Sex reflects 1 = male and 2 = female; BMI = body mass index; WHR = waist-hip ratio; MASQ = Mood and Anxiety Symptom Questionnaire Distress—depressive scale.

Values for IL-6, BMI, WHR, and walking time are based on log transformation data and bootstrap estimates.

those with a 1-unit increase in loneliness are expected to be 1.001 units slower in walking time. In addition, these findings indicated that, for every 1-unit increase in loneliness, there was expected to be a 1.006-unit increase in IL-6. The significant indirect effect of loneliness on walking time through IL-6 (0.0002, 95% CI = 0.0015–0.0280) accounted for 1.3% of the variance in walking time.

Exploratory Analyses

Given the robust relationship between BMI with IL-6 in the greater literature and evidence of relationships among BMI, IL-6, and walking time within the present study, a serial multiple mediator model investigated the direct and indirect effect(s) of loneliness (*X*) on walking time (*Y*) through BMI (M1) and IL-6 (M2) sequentially, while adjusting for age and sex in the model. Figure 1 presents the conceptual serial mediation model with the standardized coefficients for the parameter estimates. Results from this model found evidence of significant direct (0.0024, $t = 3.82$, $p < .001$) and indirect effects (0.0014, $t = 2.38$, $p = .017$). There were specific indirect effects of loneliness on slowed gait through BMI ($a_1b_1 = 0.0005$, 95% CI = 0.0002–0.0080) and IL-6 ($a_2b_2 = 0.0003$, 95% CI = 0.0001–0.0006), as indicated by the CIs that did not contain zero. There was also evidence of a specific indirect effect of loneliness sequentially through BMI and IL-6 ($a_2d_{21}b_2 = 0.0003$, 95% CI = 0.0001–0.0003). As Figure 1 shows, these latter results show that those who were lonelier had higher BMI, which was sequentially associated with higher IL-6 levels. In turn, this greater IL-6 was linked to slower walking times.

DISCUSSION

This study extends previous work by providing a mechanistic model by which loneliness impacts walking time through IL-6 across a wide age range of adults. In all, this study's findings are consistent with literature that proposes that loneliness predicts functional health outcomes beyond obesity, depression, and medical risk factors through physiological mechanisms, particularly IL-6. Consistent with our hypotheses, statistical analyses supported that the relationship between loneliness and walking time was mediated by inflammation, even after adjusting for relevant risk factors. Furthermore, regression models showed that, in addition to demographic, physical, and emotional health factors, loneliness accounted for approximately 9% of the variance in IL-6. As expected, interrelationships among loneliness, inflammation, walking time, demographic factors, multimorbidity, obesity, depressive symptoms, and friendship quantity were found. However, only the findings central to understanding the relationships between loneliness and inflammation on gait are presented in detail.

Loneliness is a complex negative emotion, encompassing perceived isolation that may have evolved to promote survival as maintaining social connections was necessary for protection and resources (12,13,45). Accordingly, loneliness has been shown to elicit hormonal and immunity responses to motivate social connections. For example, loneliness may increase the production of oxytocin, to promote bonding and social connection (45). However, there are also maladaptive consequences of loneliness, with a growing body of evidence that links loneliness to mental and physical health problems via dysregulation of immune and stress responses (12,16). Most notably emotional and physical health declines are suggested as mechanisms through which loneliness leads to increases in mortality risk, with cross-lagged models suggesting that lonely adults are 1.96 times more likely to die within 6 years (46).

An increasing body of evidence suggests that, although correlated with other risk factors, loneliness exerts unique and shared effects on health outcomes. Within the present study, we found that global (BMI) and central markers of obesity (WHR) were associated with higher inflammation and slower gait. Relevantly, the effect of loneliness remained statistically significant after these as well as other health risk factors were held constant in the models. The results from our exploratory serial mediation analyses are consistent with literature suggesting that loneliness is associated with obesity, which may give rise to IL-6, leading to negative health outcomes, such as slowed gait. Our findings provide evidence that those higher in loneliness had slower walking times as a result of IL-6 that was beyond the contribution of global obesity, as well as evidence of a unique relationship between loneliness and global obesity on walking time.

Obesity can lead to increased inflammation and increases the risk of metabolic and cardiovascular health issues, as well as there are psychosocial effects of obesity that impact self-esteem that can contribute to depression, leading to the "obesity-inflammation-depression

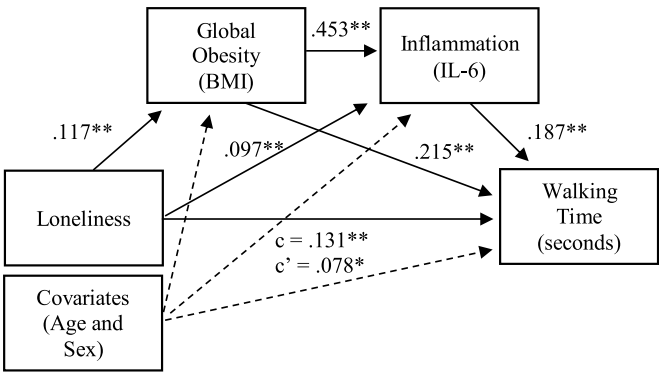

FIGURE 1. Markers of global obesity and inflammation mediates the relationship between loneliness and walking time. Note. Serial multiple mediator model of the direct and indirect effect(s) of loneliness on walking time through BMI and IL-6 with age and sex as covariates. The statistical diagram depicts the standardized coefficients for the mediation model. Age and sex served as covariates in the model, but individual parameters are not shown for simplicity. * $p < .01$, ** $p < .001$. BMI = body mass index; IL-6 = interleukin 6; Loneliness = UCLA Loneliness Scale.

cycle" (26). Notably, however, there is also evidence that the health behaviors of physical exercise, sleep, and smoking do not explain loneliness-related differences in mortality (46). Consequently, an alternative explanation is that loneliness may increase depression and lead to unhealthy behaviors, such as cigarette smoking (47) and alcohol consumption (48), out of a desire for increased social connection and peer acceptance in lonely adults. Collectively, these findings suggest that there is more than one pathway by which loneliness influences health.

Like past work, depression symptoms were linked to slower gait speed and greater loneliness, but we did not find a direct connection between depression symptoms with IL-6. It is interesting that this study that purposefully used the MASQ, which is not laden with social content or the measurement of loneliness, was not associated with IL-6. Here, it is worth noting that loneliness has been shown to longitudinally predict depressive symptoms using the CES-D minus the loneliness item (CESDML) but not vice versa; further, this relationship did not seem to be due to affective traits, social factors, or demographic factors (49). Further support for this notion is demonstrated by a meta-analysis that found that loneliness at baseline predicted the new onset of depression (odds ratio = 2.33) (50). Another explanation for this finding, which is not mutually exclusive with the aforementioned findings, is that the relationship between depression and IL-6 varies by clinical severity (51,52), with a meta-analysis suggesting that there is a stronger relationship between depression and IL-6 in patient populations than in community studies (52). This meta-analysis also found that the presence of comorbid conditions contributed to the high heterogeneity within the study, suggesting that the relationship between cytokines and depression is obscured in the presence of comorbid conditions that are associated with inflammation, particularly cardiovascular disease (52).

The relationship between loneliness and demographic factors is mixed and likely reflects the multifactorial and diverse sociocultural influences on loneliness (46,49,53–59). Although loneliness and social isolation have been stereotyped as a problem of old age, the present study did not find an association between older age and loneliness. These findings highlight that loneliness affects people of all ages. Furthermore, although women had a slower walking speed and experienced more depressive symptoms than men, we did not find sex-related differences in loneliness. Lastly, although friendship quantity was associated with less loneliness, having more friends was not linked to lower levels of inflammation. Collectively, these findings highlight that perceptions of having meaningful social connections are a critical aspect of the human experience that withstands throughout development and the experience and influence of loneliness on inflammation and health outcomes across the life span is not sex-specific or entirely explained by social integration.

Despite significant interest in interventions aimed at reducing or blocking systemic inflammation, current findings on anti-inflammatory pharmacological treatments have yielded inconsistent and, at times, iatrogenic effects (1,45,49). Consequently, there is a critical need for multimodal interventions to mitigate the impact of inflammation on health and well-being. Loneliness is a modifiable behavioral target with substantial evidence linking it to multisystemic disease risk and inflammation. Given the robust relationship between loneliness and health outcomes, routine screening for loneliness and contentment with social relationships may prove beneficial in preventing psychological distress and reducing disease risk. There are evidence-based psychosocial therapies, including modeling, enhancing communication skills, and cognitive restructuring techniques, that may be used to address what contributes to low satisfaction with relationships and loneliness (60) to prevent loneliness from "getting under the skin."

The current study has several limitations as well as strengths. First, although this cross-sectional study is beneficial in characterizing relationships among the study variables, it is important to acknowledge the criticisms surrounding cross-sectional mediation analyses. Namely, the interpretation and generalizability of the effects of such models are dependent on the stability, stationarity, and equilibrium hold (61). Hence, the degree to which there are changes within individual differences in a variable, the posited causal structure, and covariances can lead to biased estimates. However, longitudinal designs are also not without limitations and can also produce unstable models. In addition, depression is a complex construct. This study focused on the main symptoms of depression and did not investigate other features of depression, such as somatic and neurovegetative symptoms that have strong associations with cytokines (27). Notably, although it has been asserted within the literature that there are independent effects, in health research, it is often difficult to establish temporality and independence given bidirectional relationships and diverse influences. For instance, cyclical patterns may occur as cytokines can induce sickness behaviors that promote social withdrawal (27), which then can lead to increased loneliness and depression. Consequently, more research is needed to examine other facets to confidently determine that there is true independence of these factors. In this respect, having a strong theory based on prior evidence to inform the research question is crucial; in which, this study builds on prior evidence to provide a model for future longitudinal and experimental studies that manipulate feelings of loneliness (e.g., social exclusion tasks) so that we continue to improve our understanding of the relationship between loneliness and variation in IL-6 levels over time.

Strengths of this study include a relatively large sample that adjusted for multiple relevant risk factors and the use of a composite measure focused on core features of depression (e.g., feeling sad, depressed, and hopeless) that did not include items that tapped loneliness and interpersonal perceptions of social status to reduce measurement overlap with depression. Hence, regardless of directionality, these findings highlight important intersections among the social self, health behaviors, and inflammation across the life span, as combining these factors can have a potentiating impact on gait speed and global health.

Summary

In all, increasing evidence suggests that loneliness can contribute to and/or exacerbate depression symptoms and may increase the risk for unhealthy behaviors. Loneliness is an increasing public health concern. Findings from the American Perspectives Survey show a remarkable decrease in satisfaction with relationship quality (62). From an intervention standpoint, multimodal interventions that include psychosocial therapies that reduce loneliness by promoting skills that facilitate social connectedness and reduce maladaptive relational schemas may help to reduce disease risk. Our findings indicate that loneliness has both unique and shared effects on physical health (as indexed by slowed gait). In addition, loneliness was positively associated with greater depressive symptoms even in those

without depression; these findings add to the literature that suggests that feelings of loneliness may contribute to future mental health issues. Although there are several routes by which loneliness can influence inflammation and health, increasing evidence suggests that loneliness may be a driving factor in the stress-inflammation relationship, potentially due to the innate need for social self-preservation and connection. Collectively, these findings emphasize the importance of addressing loneliness and inflammation potentially through interventions that promote meaningful interpersonal connections.

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