



Loneliness, social isolation, and all-cause mortality in the United States

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ABSTRACT

Social isolation and loneliness are both established risk factors for mortality, but it remains unclear how these two conditions interact with each other. We used data from 3975 adults aged 25–74 years who completed self-administered questionnaires (SAQs) for the Midlife in the United States (MIDUS) National Study Wave 2 (2004–2006). Loneliness was measured by asking participants how often they felt lonely. A shortened version of the Berkman-Syme Social Network Index that captured partnerships, friends/family, religious participation, and other forms of social connection was used to assess social isolation. Follow-up for all-cause mortality was censored at the end of 2016. We used progressively adjusted Cox proportional hazard models to examine the mortality risks of loneliness, social isolation, the components of social isolation, and combinations of loneliness and isolation. We adjusted for sociodemographic characteristics in our first models and then added health behaviors and physical and mental health conditions in subsequent models. In the minimally adjusted model, loneliness was associated with higher mortality risk (HR, 1.34; 95% CI, 1.22–1.47), but the association was not significant in the fully adjusted model. Social isolation was significantly associated with mortality in the minimally adjusted model (HR, 1.24; 95% CI, 1.15–1.34) and the fully adjusted model (HR, 1.13; 95% CI, 1.04–1.23). Having infrequent contact with family or friends was the component of isolation that had the strongest association with mortality. Contrary to prior literature, which has found either no interaction or a synergistic interaction between isolation and loneliness, we identified a significant, negative interaction between the two measures, indicating that loneliness and social isolation may partially substitute for one another as risk factors for mortality. Both are associated with a similar increased risk of mortality relative to those who express neither; we find no evidence that the combined effect is worse than experiencing either by itself.

1. Introduction

Prior studies suggest that social isolation and loneliness are negatively associated with a range of different health outcomes across the life course. In addition to affecting external causes of death, social isolation and loneliness are associated with cardiovascular disease, cognitive decline, depression, and premature mortality (Cacioppo et al., 2011; Kuiper et al., 2015; Martín-Maria et al., 2020; O'Suilleabháin et al., 2019; Steptoe, Shankar, Demakakos, & Wardle, 2013; Valtorta et al., 2016, 2018). Loneliness is an emotion that a person feels when they are isolated from people they can trust, interact with, and connect with (Cacioppo et al., 2015). While social isolation refers to an objective absence of social contact and relationships, a person can feel lonely even when surrounded by family and friends (Qualter et al., 2015). Loneliness can be a symptom of depression, but they are separate constructs (Domènech-Abella et al., 2017). More than 40% of adults over 60 years report that they experience

loneliness (Perissinotto et al., 2012). According to a 2020 National Academies of Science, Engineering, and Medicine (NASEM) report, social isolation and loneliness represent significant, under-appreciated public health problems (National Academies of Sciences and Medicine, 2020).

Social isolation and loneliness are both sources of chronic stress and implicit hypervigilance that lead to reduced sleep quality, physiological changes in cardiovascular health, impaired immune function, neuroendocrine effects, and elevated cortisol levels (Hawkey & Cacioppo, 2010). While social isolation refers to the quantity of social relationships a person has, loneliness can partially be viewed as a measure of the quality of social relationships in a person's life. Prior literature indicates that having few relationships is a source of stress as is having poor (low quality) relationships (Xia & Li, 2018). Thus, we hypothesize that the synergy of social isolation and loneliness poses additional stress compared to either of these factors individually, leading to increased health impacts.

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Most prior studies on the association of social isolation and loneliness with health have treated each factor independently (Alcaraz et al., 2019; Henriksen et al., 2019; Laugesen et al., 2018; Luo, Hawkey, Waite, & Cacioppo, 2012; O'Suilleabhain et al., 2019; Rico-Uribe et al., 2018; TabueTeguo et al., 2016). Research examining the two factors in combination is limited, and the findings are inconsistent (Cornwell & Waite, 2009; Holwerda et al., 2012; Luo et al., 2012; Perissinotto et al., 2012). The 2020 NASEM report identifies only a handful of studies that examine both social isolation and loneliness, and it remains unclear whether these two factors have independent effects. A previous study using data from the English Longitudinal Study of Aging (Step toe et al., 2013), a prior analysis of UK Biobank data (Hakulinen et al., 2018), an investigation of patients with cardiovascular disease in Taiwan (Yu et al., 2020), and a past study using data from the Living Conditions Survey in Finland (Tanskanen & Anttila, 2016) all found no evidence of a statistical interaction between the effects of social isolation and loneliness on mortality. In contrast, in a nationally representative survey of older adults in Germany, Beller and Wagner did identify a synergistic interaction between social isolation and loneliness (Beller & Wagner, 2018). In their study, as social isolation increased, loneliness was found to have a greater effect on mortality and vice versa. However, the authors cautioned that the results may be dependent on the cultural context and sensitive to their approach of specifying loneliness and social isolation. Prior literature could also be subject to confounding by illness if the individuals under study developed social isolation or loneliness as a result of a pre-existing condition (Step toe et al., 2013).

In this study, we examine the separate and joint effects of social isolation and loneliness on all-cause mortality in a sample of adults in the United States. We also disaggregate the mortality risk of social isolation into its multiple components including the effects of marriage or partnership, relationships with family and friends, religious attendance, and other types of social participation. Finally, to help mitigate the potential for confounding by illness (i.e., both loneliness/isolation and premature death are the result of ill health), we also conduct sensitivity analyses that exclude deaths that occurred within four years after the measurement of loneliness and social isolation, and that exclude respondents who self-report their overall physical health to be "fair" or "poor".

2. Methods

We used data from Wave 2 of the Midlife in the United States (MIDUS) study. Initiated in 1995, the first wave of data collection was conducted among 7108 non-institutionalized, English-speaking adults aged 25–74 years in the contiguous United States. The main sample (N = 3487) and a sample of twins (N = 1914) were obtained through national random digit dialing with oversampling of older people and men; the study also included a random subsample of siblings of individuals in the main sample (N = 950) and oversamples from five metropolitan areas in the U.S. (N = 757) (Ryff et al., 2017). The response rate for the phone interview ranged from 60% for the twin subsample to 70% for the main sample. In 2004–2006, the MIDUS cohort was re-contacted. A total of 4963 (75% of survivors) completed a follow-up telephone interview and 4041 (81% of those who completed the phone interview) completed the self-administered questionnaire. We further excluded 66 respondents with missing information on loneliness and/or social isolation (Supplementary Fig. 1), resulting in an analysis sample of 3975 respondents (who represent about 40% of survivors from the original sample targeted at Wave 1).

2.1. Vital status ascertainment

Vital status was determined through multiple sources: 1) MIDUS Wave 3 tracing conducted before, during, and after fielding; 2) National Death Index (NDI) Plus search through the end of 2009 for all respondents, and through the end of 2016 for 713 respondents for whom there was no evidence that they were still alive (e.g., no recent contact,

invalid addresses, etc.) but MIDUS had sufficient identifiers for matching; 3) longitudinal sample maintenance (Ryff et al., 2020). Follow-up was censored on December 31, 2016. Because MIDUS provided only the month and year of death, we modeled survival in terms of months.

2.2. Loneliness and social isolation

Loneliness was assessed by a single item at Wave 2—"During the past 30 days, how much of the time did you feel lonely" (0 = none of the time, 1 = a little of the time, 2 = some of the time, 3 = most of the time, 4 = all of the time). This loneliness measure resembles an item included in the Center for Epidemiological Studies Depression Scale (CES-D). Similar single-item loneliness measurements have been shown in previous studies to be sensitive (Shiovitz-Ezra & Ayalon, 2012) and to correlate well with UCLA Loneliness Scale (Wilson & Moulton, 2010).

We used the Berkman-Syme Social Network Index to measure social isolation (Ford et al., 2006; LOUCKS et al., 2006). The components included the following: 1) respondent was married or lived with a partner/companion; 2) respondent had weekly contact with at least one non-resident family members and at least one friend/neighbor; 3) respondent attended church/temple at least sometimes/monthly; and 4) respondent participated in some other social group. The components were summed and reverse coded, with a score ranging from 0 to 4, with a higher score indicating higher level of isolation.

To examine the interaction between loneliness and isolation, we collapsed the measures to ensure sufficient numbers of respondents and deaths in each combination. Specifically, we combined those who reported feeling lonely "some of the time" with "most of the time" and "all of the time", and dichotomized isolation as "high" (scoring 2–4 on the social isolation index) vs "low" isolation (scoring 0 or 1 on the index).

2.3. Covariates

Covariates—informed by current literature—were selected to mitigate confounding and/or improve precision (Beller & Wagner, 2018; Brooks et al., 2014; Gleib et al., 2012; Step toe et al., 2013). All covariates in the analysis were assessed at Wave 2. Sociodemographic controls included sex (male, female), race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic other, Hispanic), education (some grade school, high school, some college, graduated college), and household income from all sources (continuous, log transformed).

Smoking status (never smoker, ex-smoker, current smoker) and physical exercise were included. Physical activity was measured by frequency of vigorous leisure physical activity, using a scale ranging from 1 (never) to 6 (several times a week or more), averaged across summer and winter. We also included four dichotomous indicators for major chronic conditions (i.e., diabetes, hypertension, heart disease, cancer) that the respondent reported experiencing or being treated for in the 12 months prior to survey. We measured physical limitations based on 8 tasks (e.g., lifting/carrying groceries, bathing or dressing, and climbing several flights of stairs), each of which was coded 0 = not at all, 1 = a little, 2 = some, 3 = a lot. Following the recommendations of Long and Pavalko (Long & Pavalko, 2004), we summed the 8 items (potential range 0–24), added a constant of 0.5, and applied a log-transformation. We also included self-rated physical health status (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent).

Personality traits were assessed by self-administered measures of the Big Five (extraversion, openness, conscientiousness, agreeableness, and neuroticism) (Prenda & Lachman, 2001). On a scale ranging from 1 (not at all) to 4 (a lot), respondents were asked how well each of 25 adjectives described themselves. The adjectives were: outgoing, friendly, lively, active, and talkative (extraversion); creative, imaginative, intelligent, curious, broad minded, sophisticated, and adventurous (openness); organized, responsible, hardworking, and careless (conscientiousness); helpful, warm, caring, softhearted, and sympathetic (agreeableness); and moody, worrying, nervous, and calm (neuroticism). After reverse-coding

calm and *careless*, the scores for each personality trait were derived as the mean across relevant items. The Cronbach's alpha was 0.76 for extraversion, 0.77 for openness, 0.68 for conscientiousness, 0.80 for agreeableness, and 0.74 for neuroticism.

Mental and behavioral conditions were assessed by 5 summary measures: 1) the Composite International Diagnostic Interview short-form (CIDI-SF) subscale for generalized anxiety disorder (Kessler et al., 1998) (dichotomized at 3 out of 10), 2) the CIDI-SF subscale for major depression (Kessler et al., 1998) (dichotomized at 4 out of 7) or anhedonia (dichotomized at 4 out of 6), 3) psychological distress measured by the Kessler (K-6) scale (Kessler et al., 2010) 4) drug misuse (yes, no), and 5) alcohol problems based on 6 items from the CIDI-SF subscale for alcohol dependence. More details about the constructs for mental/behavioral problems are available in [Supplementary Table 1](#).

2.4. Statistical analysis

We defined baseline as the time when participants completed the Wave 2 phone interview. Cox proportional hazards regression models predicting all-cause mortality were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) associated with loneliness and social isolation. Respondent's age was used as the underlying time scale. Using age as the underlying time-scale allows a fully nonparametric adjustment for the most important risk factor for mortality, and has been shown to be superior in providing robust estimations than using time since the baseline survey as the time-scale (Kom et al., 1997; Thiébaud & Bénichou, 2004).

We began by assessing mortality risk associated with an ordinal specification of loneliness and social isolation separately. Covariates were added progressively. Model 1 included sex and race/ethnicity; education and household income were added in Model 2; smoking and physical activity were added in Model 3; physical health conditions were added in Model 4; we added personality traits in Model 5; and finally, Model 6 further included mental/behavioral problems. We then examined the joint effect of social isolation and loneliness, assessing the interaction between the two factors. We assessed the mortality risks associated with each component of social isolation. We also explored the mortality risks associated with different combinations of the social connections ([Supplementary Fig. 2](#)). Finally, we assessed cause-specific mortality associated with loneliness/isolation. Because of the limited number of deaths, we were unable to assess suicide or drug overdose; we disaggregated deaths into three groups: cardiovascular diseases ($N = 174$), cancer ($N = 153$), and other causes ($N = 220$).

The proportional hazards assumption was tested with Schoenfeld residuals (Schoenfeld, 1982), and no significant deviation from proportionality in hazards over time was detected. We used multiple imputation by chained equations (20 imputations) to account for missing data in covariates. Our investigation relied on de-identified publicly available data and was exempted from review by the Boston University Medical Center institutional review board. STATA 16 (StataCorp) was used for all analyses. Statistical significance was determined by a 2-sided $p < 0.05$.

We tested the sensitivity of the results to confounding by illness by repeating the analyses after excluding deaths that occurred within 4 years of baseline and among a subgroup of healthy respondents, defined as those who self-reported overall physical health condition as "good", "very good", and "excellent". We also re-estimated the models restricting analyses to individuals without missing data (i.e., listwise deletion).

3. Results

Of the 3975 respondents included in the analysis, 547 died over follow-up (mean length of time from baseline to death (converted to years) was 11.8 (SD 2.4); range: 0.1–13.0). On average, deceased participants were older, more likely to be male, less educated, more likely to smoke, less likely to exercise, more likely to exhibit physical health problems, and more likely to experience loneliness and isolation

compared to individuals who survived ([Table 1](#)). In the analytic sample, 35.2% of respondents experienced at least a little loneliness and 54.6% had a score of at least 2 on the social integration index (high isolation).

3.1. Association of loneliness, isolation with mortality risk

[Table 2](#) presents the progressively adjusted models evaluating the association of loneliness with all-cause mortality. In the minimally adjusted model (model 1), a one unit increase in loneliness was associated with significantly higher mortality risk (HR, 1.34; 95% CI, 1.22–1.47). The association attenuated gradually as more covariates were introduced in Models 2–6. The association was not significant in the fully adjusted model (model 6).

Mortality risks increased with higher levels of social isolation ([Table 3](#)). Each one unit increase in social isolation was associated with 24% (HR, 1.24; 95% CI, 1.15–1.34) higher mortality risk, adjusting for sex and race/ethnicity only (model 1). Social isolation remained a significant predictor of mortality (HR, 1.13; 95% CI, 1.04–1.23) when all covariates were included in model 6, although the magnitude of the association attenuated as more covariates were introduced.

With respect to the specific components of social isolation ([Table 4](#)), the strongest association was with weekly contact with family or friend. To simplify the presentation, we included only results from Models 1 and 6. In the fully adjusted model (model 6), having infrequent contact with family or friend was associated with 22% higher mortality risk (HR, 1.22; 95% CI, 1.02–1.45) relative to those who had weekly contact with family or friend.

The results from exploratory analyses with different combinations of social connections ([Supplementary Fig. 2](#)) were largely consistent with findings presented in [Tables 3 and 4](#). The most isolated participants had the highest mortality risk. Cause-specific mortality results were presented in [Supplementary Fig. 3](#). The associations with loneliness and isolation do not appear to differ significantly across these three groups of causes.

Finally, [Table 5](#) and [Supplementary Fig. 4](#) show results based on models that include interactions between loneliness and isolation. In [Table 5](#), the main effects for loneliness represents the effects for someone who reports low social isolation. Model 6 indicates that, relative to no loneliness, mortality risk increased by 55% (HR 1.55; 95% CI, 1.11–2.17) for "a little loneliness" and 47% (HR 1.47; 95% CI, 0.91–2.37) for "some or more loneliness". The main effect of isolation in Model 6 indicates that, for someone who reports no loneliness, high isolation was associated with 59% (HR 1.59; 95% CI, 1.26–2.01) higher mortality rates. Overall, the interaction terms between loneliness and isolation were negative and jointly significant ($p \sim 0.032$ in Model 6). [Supplementary Fig. 4](#) shows the HRs associated with different combinations of loneliness and isolation. The mortality risks were elevated at higher levels of loneliness and/or higher isolation, but the magnitude of the associations based on Model 6 were similar across different combinations. That is, there is no indication that the mortality rate for those expressing *both* isolation and some loneliness (HR = 1.43, 95% CI 1.02–2.01) is any higher than the rates for someone who is isolated but not lonely (HR = 1.59, 95% CI 1.26–2.01) or for someone who reports some loneliness but low isolation (HR = 1.47, 95% CI 0.91–2.37).

3.2. Sensitivity analyses

Sensitivity checks for confounding by illness and the use of listwise deletion yielded similar patterns of association ([Supplementary Fig. 5](#)). Confidence intervals were wider due to the smaller sample sizes.

4. Discussion and conclusion

The current study adds to the literature describing the relationship between social isolation, loneliness and mortality. Our findings suggest that loneliness and social isolation are each associated with increased all-

Table 1
Descriptive statistics of variables used in the analyses (n = 3975) ^a

Variables ^b	Analytic Sample		Survival over follow-up			
			Alive		Deceased	
Number of participants	3975	(100.0)	3428	(86.2)	547	(13.8)
Loneliness						
None of the time	2576	(64.8)	2258	(65.9)	318	(58.1)
A little of the time	889	(22.4)	751	(21.9)	138	(25.2)
Some of the time	373	(9.4)	305	(8.9)	68	(12.4)
Most of the time	104	(2.6)	88	(2.6)	16	(2.9)
All the time	33	(0.8)	26	(0.8)	7	(1.3)
Isolation						
0 (very low isolation)	609	(15.3)	541	(15.8)	68	(12.4)
1	1200	(30.2)	1070	(31.2)	130	(23.8)
2	1239	(31.2)	1046	(30.5)	193	(35.3)
3	762	(19.2)	641	(18.7)	121	(22.2)
4 (very high isolation)	165	(4.2)	130	(3.8)	35	(6.4)
Loneliness by Isolation category ^c						
No loneliness + low isolation	1307	(32.9)	1182	(34.5)	125	(22.9)
No loneliness + high isolation	1269	(31.9)	1076	(31.4)	193	(35.3)
A little loneliness + low isolation	353	(8.9)	302	(8.8)	51	(9.3)
A little loneliness + high isolation	536	(13.5)	449	(13.1)	87	(15.9)
Some or more loneliness + low isolation	149	(3.8)	127	(3.7)	22	(4.0)
Some or more loneliness + high isolation	361	(9.1)	292	(8.5)	69	(12.6)
Age, mean (sd)	56.1	(12.3)	54.0	(11.3)	68.9	(10.3)
Sex						
Female	2195	(55.2)	1941	(56.6)	254	(46.4)
Male	1780	(44.8)	1487	(43.4)	293	(53.6)
Race/ethnicity						
Non-Hispanic White	3592	(90.6)	3099	(90.6)	493	(90.5)
Non-Hispanic Black	140	(3.5)	121	(3.5)	19	(3.5)
Non-Hispanic other	120	(3.0)	96	(2.8)	24	(4.4)
Hispanic	112	(2.8)	103	(3.0)	9	(1.7)
Education						
1. Some grade school	310	(7.8)	242	(7.1)	68	(12.5)
2. High school	1065	(26.8)	895	(26.2)	170	(31.1)
3. Some college	1158	(29.2)	995	(29.1)	163	(29.9)
4. Graduated college	1435	(36.2)	1290	(37.7)	145	(26.6)
Household income (log), mean (sd)	10.3	(2.6)	10.5	(2.5)	9.5	(3.2)
Smoking						
1. Never smoker	2048	(51.5)	1837	(53.6)	211	(38.6)
2. Former smoker	1347	(33.9)	1102	(32.2)	245	(44.8)
3. Current smoker	580	(14.6)	489	(14.3)	91	(16.6)
Exercise, mean (sd)	2.3	(1.9)	2.4	(1.9)	1.5	(1.7)
Physical health indicators						
Diabetes	402	(10.1)	275	(8.0)	127	(23.2)
Hypertension	1202	(30.2)	924	(27.0)	278	(50.8)
Heart diseases	128	(3.2)	61	(1.8)	67	(12.3)
Cancer	550	(13.9)	154	(28.2)	396	(11.6)
Physical limitations index, mean (sd)	0.8	(1.3)	0.6	(1.3)	1.7	(1.2)
Self-rated health, mean (sd)	3.6	(1.0)	3.7	(1.0)	2.9	(1.1)
Big five personality traits						
Openness, mean (sd)	2.9	(0.5)	2.9	(0.5)	2.9	(0.6)
Conscientiousness, mean (sd)	3.4	(0.5)	3.4	(0.5)	3.3	(0.5)
Extroversion, mean (sd)	3.1	(0.6)	3.1	(0.6)	3.1	(0.6)
Agreeableness, mean (sd)	3.4	(0.5)	3.4	(0.5)	3.5	(0.5)
Neuroticism, mean (sd)	2.1	(0.6)	2.1	(0.6)	2.0	(0.6)
Mental/behavioral problems						
Depression/anhedonia	411	(10.3)	355	(10.4)	56	(10.2)
Generalized anxiety disorders	72	(1.8)	65	(1.9)	7	(1.3)
K-6 psychological distress, mean (sd)	1.5	(0.6)	1.5	(0.6)	1.6	(0.6)

Table 1 (continued)

Variables ^b	Analytic Sample		Survival over follow-up			
			Alive		Deceased	
Any drug abuse	476	(12.1)	417	(12.3)	59	(11.1)
No. of alcohol problems, mean (sd)	0.3	(0.7)	0.3	(0.7)	0.2	(0.7)

^a n and column % are reported, unless indicated otherwise.

^b The number of participants with missing values are 11 for race/ethnicity, 7 for education, 172 for household income, 40 for physical activity, 15 for functional limitation, 5 for cancer, 1 for self-rated health, 82 for alcohol problem, 92 for psychological distress, and 49 for drug abuse. Missing data for these variables were imputed using multiple imputation.

^c High isolation was defined as scoring 2–4 on the social integration index, while low isolation had a score of 0/1 on the index.

cause mortality. However, while the association remained robust for isolation even after full covariate adjustment, the association of loneliness with mortality was no longer significant in the fully adjusted model. Contrary to previous studies, we found a significant negative interaction between these two factors in relation to mortality risk. Indeed, we find no evidence that the combination of loneliness and isolation is significantly worse than either factor alone.

Most prior studies have found no evidence of interdependence between social isolation and loneliness and the risk of all-cause mortality (Hakulinen et al., 2018; Steptoe et al., 2013; Yu et al., 2020). However, a recent analysis by Beller and Wagner using data from the German Ageing Survey identified a significant positive (or synergistic) interaction between these two constructs (Beller & Wagner, 2018), indicating a stronger association between loneliness and mortality at higher levels of social isolation, and a stronger association for social isolation at higher levels of loneliness. In contrast, we found a significant negative interaction between social isolation and loneliness. This result indicates a stronger association between loneliness and mortality at lower levels of isolation, and a stronger association between isolation and mortality at lower levels of loneliness. Our finding is consistent with a recent study conducted in Ireland which indicates a similar negative interaction, finding a similar magnitude of association for respondents with high loneliness and isolation as compared to those with high isolation but low loneliness (Ward et al., 2021). While much remains to be clarified, the discrepancies between the present study and Beller & Wagner might be partially attributable to cultural differences. Loneliness may have less effect on health in individualistic countries such as the US (Beller et al., 2020). Differences in how the study defined loneliness could also be a factor.

Although the effects of loneliness and social isolation on the risk of death have yet to be fully described, multiple socio-biological pathways could be involved. Loneliness has been associated routinely with biomarkers of systemic inflammation (interleukin-6, fibrinogen and C-reactive protein) (Nersesian et al., 1982; Vingeliene et al., 2019). Chronic inflammation plays an important role in the development of cardiovascular disease and other chronic conditions, and is associated with elevated premature mortality risk (Golia et al., 2014). Psychological stressors can also provoke autonomic nervous system and hypothalamic-pituitary-adrenocortical (HPA) axis activity, and chronic activations of these system incur wear-and-tear that can exact a toll on the cardiovascular, immune, and metabolic systems (McEwen, 2002). While loneliness is associated with both systemic inflammation and neurological wear-and-tear in the existing literature, the direction of causality is unknown and is likely bi-directional.

It also remains unclear whether the health consequences of social isolation and loneliness occur along a single mechanistic pathway, or whether social isolation and loneliness operate in different ways to influence mortality. One possible distinction is that loneliness is more strongly associated with depression than social isolation (Ge et al., 2017). Depression is known to reduce physical activity (FarioliVecchioli et al.,

Table 2
Association between loneliness and all-cause mortality (n = 3975).

Variables	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Loneliness	1.34	(1.22–1.47)	1.31	(1.19–1.44)	1.27	(1.16–1.40)	1.12	(1.01–1.23)	1.11	(1.00–1.23)	1.05	(0.93–1.18)
Male	1.61	(1.35–1.90)	1.70	(1.42–2.02)	1.65	(1.37–1.97)	1.64	(1.36–1.97)	1.58	(1.30–1.91)	1.54	(1.27–1.87)
Race/ethnicity (ref. NH White)												
Non-Hispanic Black	1.30	(0.82–2.06)	1.24	(0.78–1.97)	1.27	(0.79–2.01)	1.12	(0.70–1.79)	1.10	(0.69–1.77)	1.09	(0.68–1.76)
Non-Hispanic other	1.80	(1.19–2.72)	1.76	(1.17–2.66)	1.77	(1.17–2.67)	1.66	(1.10–2.51)	1.62	(1.07–1.46)	1.64	(1.08–2.49)
Hispanic	0.68	(0.35–1.32)	0.68	(0.35–1.31)	0.62	(0.32–1.20)	0.66	(0.34–1.28)	0.66	(0.34–1.28)	0.65	(0.34–1.27)
Education (ref. some grade school)												
High school			0.89	(0.67–1.19)	0.90	(0.68–1.20)	1.11	(0.83–1.48)	1.11	(0.83–1.48)	1.11	(0.83–1.48)
Some college			0.88	(0.66–1.18)	0.91	(0.68–1.21)	1.15	(0.86–1.53)	1.12	(0.83–1.51)	1.12	(0.84–1.51)
Graduated college			0.65	(0.48–0.88)	0.73	(0.54–0.99)	0.99	(0.73–1.35)	0.95	(0.69–1.31)	0.94	(0.69–1.30)
Household income (log)			0.99	(0.96–1.02)	0.99	(0.96–1.02)	0.98	(0.96–1.01)	0.98	(0.96–1.01)	0.99	(0.96–1.01)
Smoking status (ref. never)												
Former					1.31	(1.08–1.59)	1.18	(0.97–1.43)	1.18	(0.97–1.43)	1.19	(0.98–1.44)
Current					2.57	(1.98–3.33)	2.24	(1.72–2.90)	2.21	(1.70–2.89)	2.10	(1.60–2.75)
Physical activity					0.95	(0.90–1.00)	0.99	(0.94–1.05)	0.99	(0.94–1.04)	0.98	(0.93–1.04)
Physical health indicators												
Diabetes							1.46	(1.18–1.71)	1.46	(1.18–1.81)	1.47	(1.19–1.82)
Hypertension							1.10	(0.91–1.24)	1.10	(0.92–1.32)	1.09	(0.90–1.30)
Heart diseases							1.47	(1.12–2.15)	1.47	(1.12–1.93)	1.49	(1.13–1.96)
Cancer							1.28	(1.05–1.59)	1.27	(1.05–1.54)	1.25	(1.03–1.52)
Functional limitation							1.21	(1.10–1.33)	1.21	(1.11–1.32)	1.20	(1.10–1.31)
Self-rated health							0.73	(0.66–0.81)	0.73	(0.66–0.81)	0.74	(0.67–0.83)
Big five personality traits												
Openness									1.01	(0.89–1.33)	1.06	(0.87–1.31)
Conscientiousness									0.93	(0.76–1.13)	0.95	(0.77–1.16)
Extroversion									1.02	(0.84–1.25)	1.05	(0.85–1.28)
Agreeableness									0.86	(0.69–1.08)	0.87	(0.70–1.09)
Neuroticism									0.97	(0.83–1.14)	0.88	(0.73–1.05)
Mental/behavioral problems												
Depression/anhedonia											1.21	(0.88–1.65)
Generalized anxiety disorders											0.55	(0.25–1.21)
K-6 psychological distress											1.28	(1.04–1.58)
Any drug use											0.89	(0.67–1.18)
Number of alcohol problems											1.12	(0.99–1.28)

2018), increase substance use (Boden & Fergusson, 2011), and disrupt sleep (Nutt et al., 2008), which could contribute to poorer health and risk of premature mortality. A prior study of adults in the Longitudinal Aging Study Amsterdam also found that adults who were frail in addition to experiencing loneliness or social isolation were at the highest risk for mortality (Hoogendijk et al., 2020). This may explain why our hazard ratios for loneliness, social isolation, and their combined effects all decreased between our first and later models, in which we introduced adjustment for physical health and functional limitations among other factors.

Another key challenge within this field is the lack of consistent definitions for social isolation and loneliness across the literature. This study makes use of a single-item indicator for the study of loneliness, which may differ from other studies which capture both the emotional and social components of loneliness. The three-item UCLA scale for example asks participants: how often they lack companionship, how often they feel left out, and how often they feel isolated from others. Variations in how loneliness is measured may explain partially why this study's associations between loneliness and mortality differ from others in the literature.

Consistent with previous studies (Patterson & Veenstra, 2010; Steptoe et al., 2013), we made use of progressively adjusted models in which we first adjusted for sociodemographic characteristics and then added health behaviors like smoking and physical activity, personality traits, physical health conditions, and mental/behavioral problems in subsequent models. Across the models, the addition of these covariates attenuated the associations between social isolation/loneliness and mortality. However, social isolation remained statistically significant with adjustment of a comprehensive set of covariates, indicating the robustness of isolation as a risk factor for mortality. Notably, the findings were robust to further adjustment for religiosity (results not shown), which might be

another confounder (VanderWeele et al., 2017). We also found no significant interaction between living alone and loneliness (results not shown); that is, there was no evidence that the effect of loneliness differed for those living alone versus those living with other people.

Some prior studies examining the association between loneliness and isolation and mortality have treated mental health variables as potential mediators rather than confounders and thus have not adjusted for them in their models. Given that the relationship between mental health and loneliness/isolation is likely to be bidirectional, that approach will overestimate the effects of loneliness/isolation unless one can establish that loneliness/isolation preceded any mental health problems. In this study, we use progressively adjusted models, which allow readers to assess the relationship before and after adjustment for mental health factors. Compared with studies that do not control for mental health variables, we find smaller associations between loneliness and isolation and mortality. Such studies might report similarly attenuated estimates if they adjusted for these factors as confounders.

Social isolation has increased in the US over recent decades: between 1985 and 2004, the mean social network size, kin or non-kin, decreased by about a third (McPherson et al., 2006). The conspicuous decline in all forms of in person interaction and its implication on civic engagement across age groups were also discussed by Putnam in his 2001 book, *Bowling Alone* (Putnam, 2000). Decreases in economic security and increases in economic inequality over recent decades have also affected social support systems such as family and community structures (Benach et al., 2014; Chetty et al., 2017; Putnam, 2000). For instance, when young adults are made economically insecure as a result of manufacturing declines, they are less likely to pursue marriage and/or have children (Autor et al., 2019). Declines in marriage and fertility and increases in divorce rates have resulted in a growing number of middle-aged and older adults who have no close family members and are

Table 3
Association between isolation and all-cause mortality (n = 3975).

Variables	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Isolation	1.24	(1.15–1.34)	1.21	(1.12–1.31)	1.16	(1.07–1.26)	1.15	(1.06–1.24)	1.14	(1.05–1.24)	1.13	(1.04–1.23)
Male	1.52	(1.28–1.80)	1.60	(1.35–1.91)	1.55	(1.30–1.86)	1.61	(1.34–1.93)	1.56	(1.29–1.89)	1.55	(1.28–1.88)
Race/ethnicity (ref. NH White)												
Non-Hispanic Black	1.24	(0.78–1.96)	1.18	(0.74–1.87)	1.22	(0.77–1.94)	1.07	(0.67–1.71)	1.06	(0.66–1.71)	1.06	(0.66–1.71)
Non-Hispanic other	1.75	(1.16–2.64)	1.71	(1.13–2.58)	1.72	(1.13–2.59)	1.62	(1.07–2.44)	1.58	(1.04–2.39)	1.62	(1.07–2.45)
Hispanic	0.66	(0.34–1.27)	0.65	(0.34–1.26)	0.60	(0.31–1.17)	0.66	(0.34–1.28)	0.66	(0.34–1.27)	0.65	(0.34–1.27)
Education (ref. some grade school)												
High school			0.88	(0.66–1.17)	0.89	(0.67–1.19)	1.13	(0.85–1.51)	1.14	(0.85–1.52)	1.13	(0.85–1.52)
Some college			0.86	(0.64–1.15)	0.89	(0.67–1.19)	1.62	(0.87–1.56)	1.15	(0.85–1.55)	1.15	(0.85–1.55)
Graduated college			0.66	(0.49–0.89)	0.74	(0.54–1.00)	1.04	(0.76–1.42)	1.02	(0.74–1.41)	1.01	(0.73–1.40)
Household income (log)			0.99	(0.96–1.02)	0.99	(0.96–1.01)	0.98	(0.96–1.01)	0.98	(0.96–1.01)	0.99	(0.96–1.02)
Smoking status (ref. never)												
Former					1.35	(1.11–1.63)	1.19	(0.98–1.44)	1.18	(0.97–1.44)	1.19	(0.98–1.44)
Current					2.53	(1.94–3.29)	2.14	(1.64–2.79)	2.12	(1.62–2.77)	1.99	(1.52–2.62)
Physical activity					0.95	(0.91–1.01)	0.99	(0.94–1.05)	0.99	(0.94–1.04)	0.98	(0.93–1.04)
Physical health indicators												
Diabetes							1.48	(1.20–1.83)	1.49	(1.13–1.84)	1.49	(1.20–1.84)
Hypertension							1.05	(0.92–1.32)	1.11	(1.06–1.33)	1.09	(0.91–1.31)
Heart diseases							1.48	(1.13–1.94)	1.49	(1.11–1.96)	1.50	(1.14–1.97)
Cancer							1.29	(1.07–1.57)	1.29	(0.66–1.56)	1.26	(1.04–1.53)
Functional limitation							1.21	(1.11–1.32)	1.21	(0.86–1.32)	1.20	(1.10–1.31)
Self-rated health							0.73	(0.66–0.81)	0.73	(0.74–0.81)	0.74	(0.67–0.82)
Big five personality traits												
Openness									1.05	(0.86–1.29)	1.03	(0.84–1.27)
Conscientiousness									0.91	(0.74–1.12)	0.94	(0.77–1.15)
Extroversion									1.06	(0.86–1.29)	1.08	(0.88–1.32)
Agreeableness									0.88	(0.70–1.10)	0.89	(0.71–1.12)
Neuroticism									1.00	(0.85–1.16)	0.88	(0.73–1.05)
Mental/behavioral problems												
Depression/anhedonia											1.21	(0.89–1.66)
Generalized anxiety disorders											0.53	0.24–1.16)
K-6 psychological distress											1.30	(1.07–1.57)
Any drug use											0.88	(0.66–1.17)
Number of alcohol problems											1.12	(0.98–1.27)

Table 4
Association between social isolation components and all-cause mortality (n = 3975)^a.

Variables	Model 1		Model 6	
	HR	(95% CI)	HR	(95% CI)
Married/Partnered (ref.)				
Not married/with no partner	1.37	(1.14–1.65)	1.15	(0.95–1.40)
Weekly contact with family/friend (ref.)				
Infrequent contact with family/friend	1.28	(1.08–1.52)	1.22	(1.02–1.45)
Attended church at least sometimes or monthly (ref.)				
Infrequent attendance of religious activity	1.30	(1.09–1.55)	1.15	(0.96–1.38)
Participated in some other social group at least monthly (ref.)				
Infrequent attendance of other social activity	1.33	(1.11–1.60)	1.10	(0.91–1.34)

^a Model 1 adjusted for sex and race/ethnicity; model 6 added education, household income, smoking status (never, former, current), frequency of vigorous leisure physical activity, diabetes, hypertension, heart diseases, cancer, physical functional limitation, self-rated physical health status, openness, conscientiousness, extroversion, agreeableness, neuroticism, general anxiety disorder, depression/anhedonia, Kessler-6 psychological distress, drug abuse, and number of alcohol problems.

therefore at greater risk for loneliness (Verdery & Margolis, 2017). The number of adults living alone has likewise increased from 16.7 percent of the U.S. population in 1970 to 28.4 percent in 2019 (2019US Census Bureau).

While prior studies have investigated the joint effects of loneliness and social isolation, the current study was among the first to identify a

Table 5
Association between social isolation, loneliness and all-cause mortality, adjusted HRs (95%CI)^a.

Variables	HRs (95% CIs)	
	Model 1 ^a	Model 6 ^a
Loneliness		
No loneliness (ref.)		
A little loneliness	2.03 (1.46–2.83)	1.55 (1.11–2.17)
Some or more loneliness	2.49 (1.58–3.94)	1.47 (0.91–2.37)
Isolation ^b		
Low isolation (ref.)		
High isolation	1.80 (1.44–2.26)	1.59 (1.26–2.01)
Loneliness*isolation		
A little loneliness*High isolation	0.59 (0.39–0.89)	0.61 (0.40–0.93)
Some or more loneliness*High isolation	0.62 (0.37–1.96)	0.61 (0.36–1.05)
<i>P for joint tests of two interaction terms</i>	0.022	0.032

^a Model 1 adjusted for sex and race/ethnicity; model 6 added education, household income, smoking status (never, former, current), frequency of vigorous leisure physical activity, diabetes, hypertension, heart diseases, cancer, physical functional limitation, self-rated physical health status, openness, conscientiousness, extroversion, agreeableness, neuroticism, general anxiety disorder, depression/anhedonia, Kessler-6 psychological distress, drug abuse, and number of alcohol problems.

^b High isolation was defined as scoring 2–4 on the social integration index, while low isolation had a score of 0 or 1 on the index.

negative interaction between loneliness and social isolation and their effects on all-cause mortality in the U.S. This study made use of national prospective data to collect detailed assessments of health behaviors, physical and mental health conditions, enabling a comprehensive adjustment for potential confounders. Still, the study has several limitations. First, the cut-off points to define low/moderate/high risk for

loneliness and low/high risk for social isolation were derived on the ground of empirical assessment of elevated risks. Thus, the results from the current study may not be directly comparable to other studies that applied different “high-risk” cut-off points (Step toe et al., 2013). Second, while our analyses indicate that social isolation and loneliness are associated with mortality, we cannot rule out potential residual confounding related to the presence of an illness or condition that simultaneously raises the risk of isolation/loneliness and the risk of mortality. Such omitted variable bias would lead to an over-estimate of the effect size for loneliness/isolation. However, sensitivity analyses excluding participants with poor/fair self-rated health and excluding deaths within 4 years of baseline yielded similar results to those for the entire sample, indicating that confounding by illness is unlikely a serious source of bias. Third, a single item loneliness measure, including the similar item included in the CES-D and other variants, is considered a common way to measure loneliness in epidemiological studies (Shiovitz-Ezra & Ayalon, 2012) and has been used extensively in contemporary research (Holwerda et al., 2014; O’Luanaigh et al., 2012; Routasalo et al., 2006; Savikko et al., 2005; Thurston & Kubzansky, 2009), but this simple measure of loneliness has known limitations including relatively low reliability and may underestimate loneliness (Shiovitz-Ezra & Ayalon, 2012). Fourth, while a comprehensive set of covariates aimed to guard against residual confounding, it was not possible to establish the temporal ordering of our exposures and covariates. Fifth, the current mortality follow-up was censored at December 2016. Given the sensitivity of hazard ratios to length of follow-up (Hernán, 2010), future investigations with extended mortality follow-up (and increased number of events) are warranted.

In this national sample of adults in the United States, we found a significant negative interaction between social isolation and loneliness and the risk for all-cause mortality, adjusting for sociodemographic characteristics and physical and mental health conditions. This result suggests that loneliness and social isolation may partially substitute for one another as risk factors for mortality. Both the emotional aspect (loneliness) and the structural dimension (isolation) are associated with an increased risk of mortality relative to those who express neither loneliness nor isolation, but we find no evidence that the combined effect is worse than experiencing either by itself.

Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ssmmh.2021.100014>.

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